# Synthesis of heterocyclic compounds

Tapio Nevalainen
Drug synthesis II
2012

http://www.scripps.edu/chem/baran/heterocycles/

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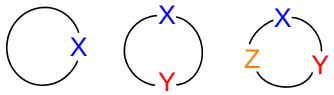
## Heterocyclic compounds

- Heterocycles contain one or more hereroatoms in a ring




X,Y,Z are usually N,O,S

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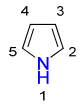
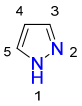
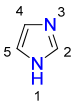
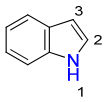
# Heterocycles

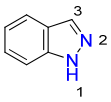
- Aromatic five-membered heterocycles

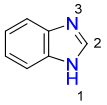

1*H*-pyrrole


1*H*-pyrazole


1*H*-imidazole


1*H*-indole

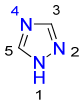

1*H*-indazole

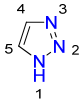

1*H*-benzo[*d*]imidazole

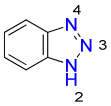

furan

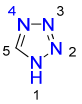

isoxazole


oxazole


1*H*-1,2,4-triazole


1*H*-1,2,3-triazole

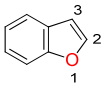

1*H*-benzo[*d*][1,2,3]triazole

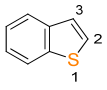

1*H*-tetrazole

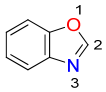

thiophene


isothiazole


thiazole


benzofuran

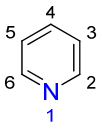

benzo[*b*]thiophene

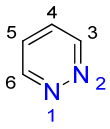

benzo[*d*]oxazole

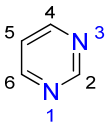


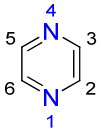
# Heterocycles

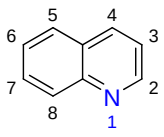
- Aromatic six-membered heterocycles

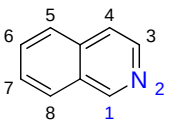

pyridine

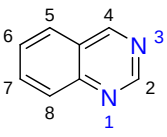

pyridazine

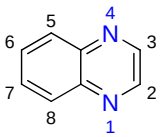

pyrimidine


pyrazine


quinoline

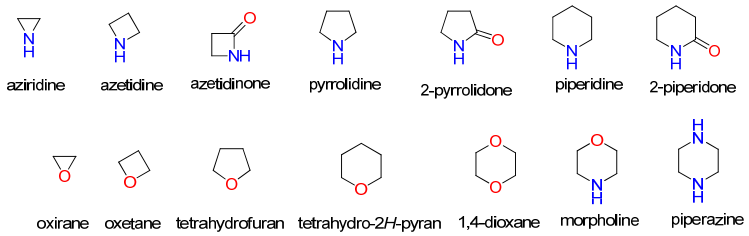

isoquinoline


quinazoline


quinoxaline

## Heterocycles

- Aliphatic heterocycles

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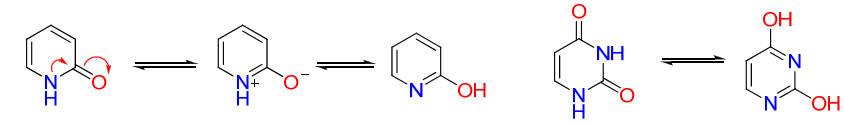
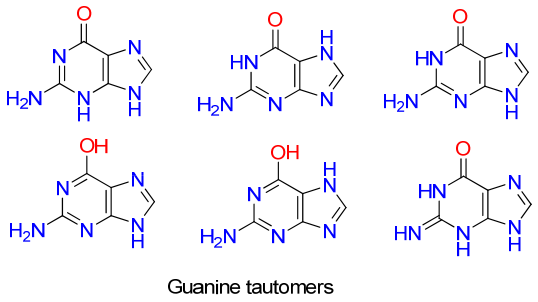
## Heterocycles

- Tautomerism



Guanine tautomers

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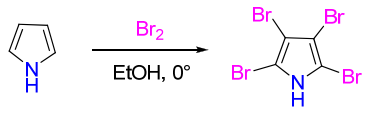
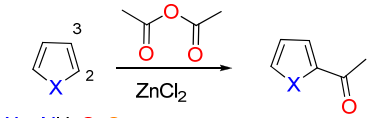
# Reactions of heterocycles

## Five-membered heterocycles are good nucleophiles

- Reaction with bromine requires no Lewis acid and leads to substitution at all four free positions.




- In Friedel–Crafts reactions the 2-position is more reactive than the 3-position




X = NH, O, S

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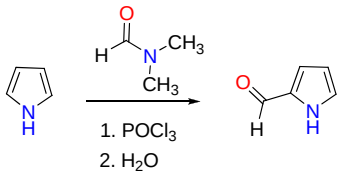
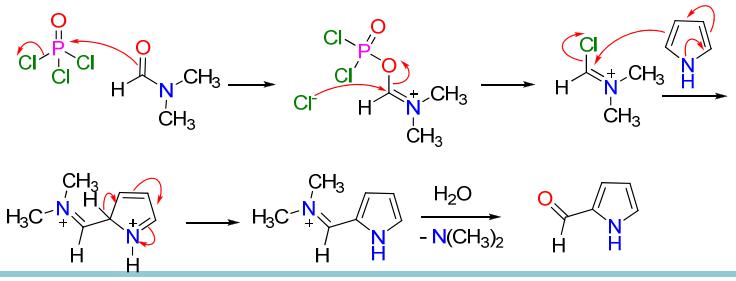
# Reactions of heterocycles

- Vilsmeier reaction (Vilsmeier-Haack reaction) allows the formylation of heterocyclic and electron-rich arenes. The formylating agent, chloroiminium ion, is formed in situ from N,N-dimethylamide and $POCl_3$

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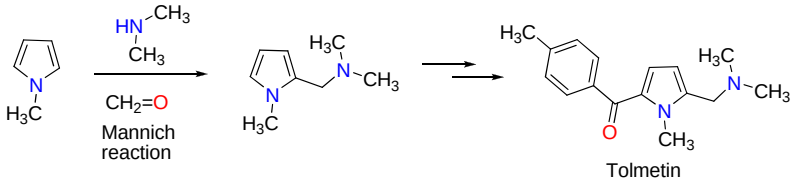
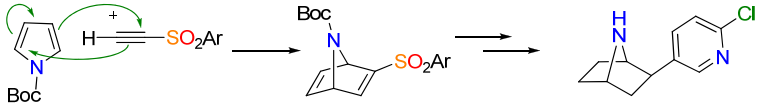
## Reactions of heterocycles

- Aromatic heterocycles undergoes aminoalkylation (Mannich reaction)
- For example N-methylpyrrole reacts at the 2-position . Reaction is used in the manufacture of the nonsteroidal anti-inflammatory compound, tolmetin.




- Five-membered heterocycles act as dienes in Diels–Alder reactions

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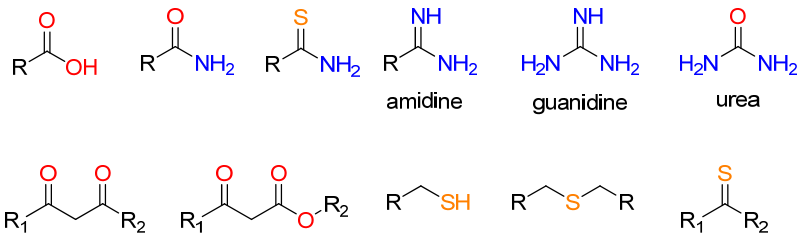
## Common building-blocks for heterocyclic compounds

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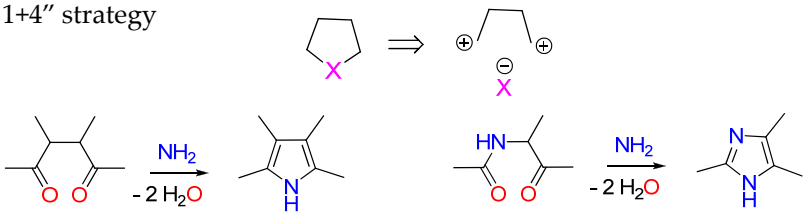
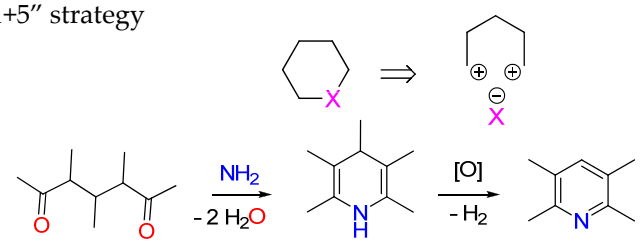
## General strategies for heterocycle synthesis

- ”1+4” strategy




- ”1+5” strategy

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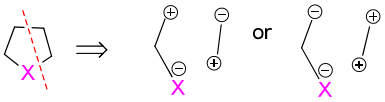
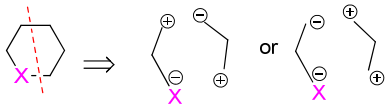
## General strategies for heterocycle synthesis

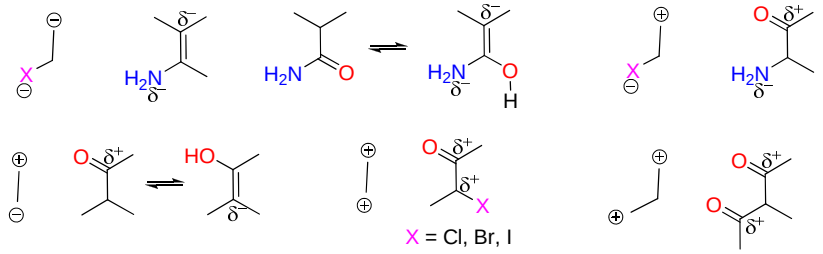
- ”2+3” strategy




- ”3+3” strategy




- Examples

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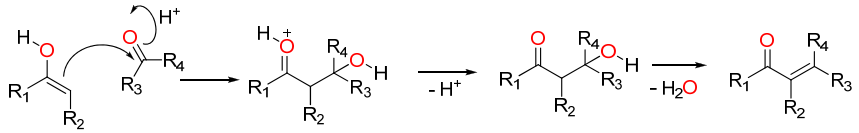
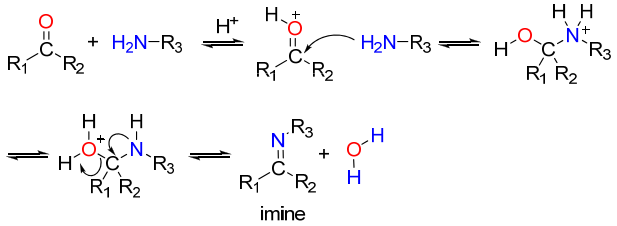
## Reactions used in heterocyclic ring synthesis

- Aldol-type reactions of enols or enolate anions with electrophiles.



- Imine/enamine formation

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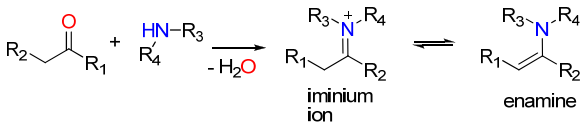
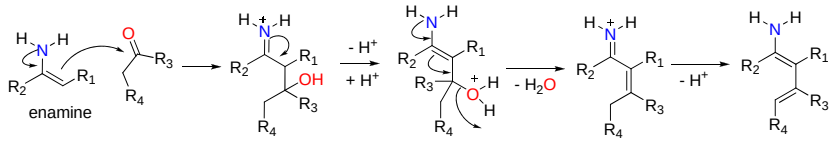
## Reactions used in heterocyclic ring synthesis

- Enamine is tautomeric form of imine. If dialkylamine is used, enamine is formed




- Enamines can function as enolates

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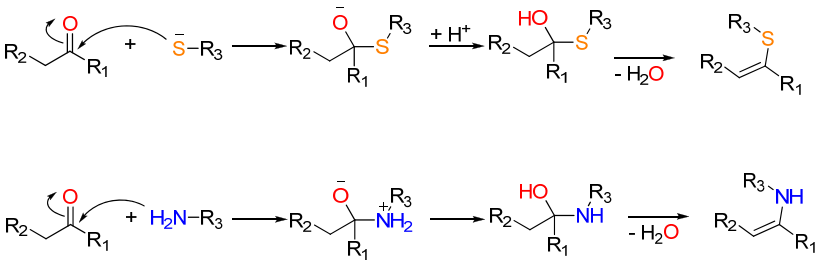
## Reactions used in heterocyclic ring synthesis

- When the process leads to C-heteroatom bond formation, then the nucleophile is an appropriate heteroatom.



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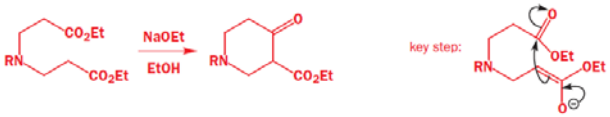
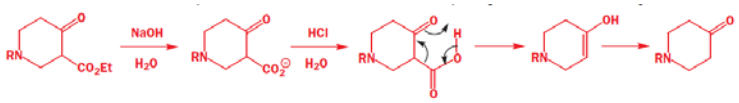
## Synthesis of heterocyclic ketones

- Michael additions to conjugated esters

- Intramolecular Claisen ester condensation give The β keto-esters ketone




- The β keto-esters can be easily hydrolysed and decarboxylated to give the symmetrical cyclic ketone.



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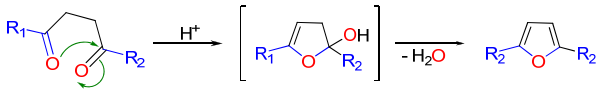
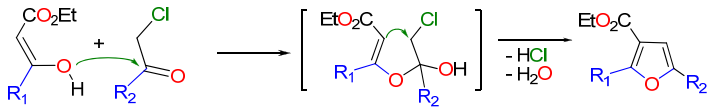
## Furans

- **Paal Knorr**




- **Feist-Benary**

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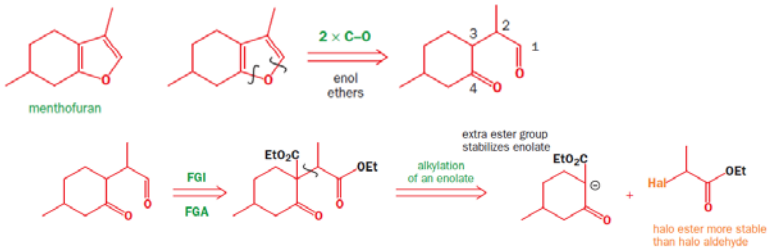
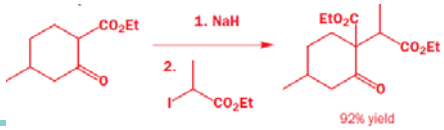
## Furans

- An example of furan synthesis: menthofuran, which contributes to the flavour of mint.




- Aldehyde is displaced by an ester to make it more stable.
- The alkylation step goes well with the α-iodo-ester.

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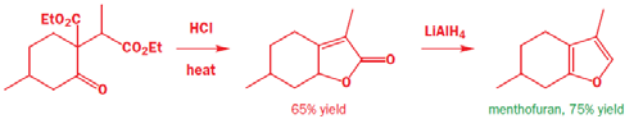
## Furans: synthesis of menthofuran

- The 1,4-dicarbonyl compound cyclizes to a lactone, and the redundant ester group is lost by hydrolysis and decarboxylation.
- The double bond moves into conjugation with the lactone carbonyl group. Finally, the reduction gives the furan.

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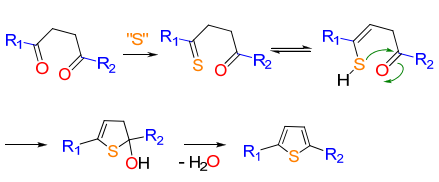
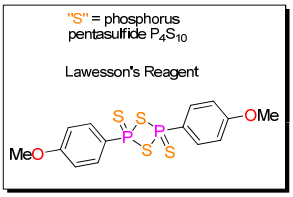
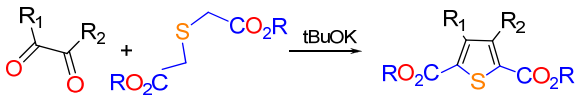
## Thiophenes

- **Paal Knorr**

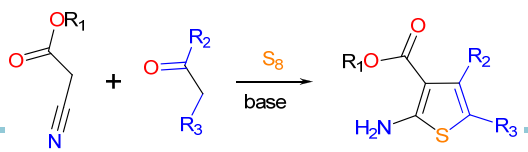



- **Hinsberg Synthesis of Thiophene Derivatives**




- **Gewald reaction**

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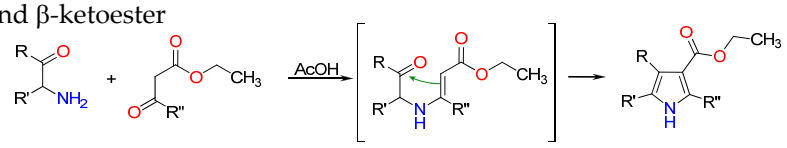
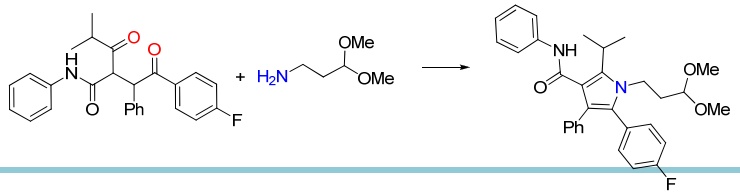
# Pyrroles

- **Knorr pyrrole synthesis**: Condensation of α-aminoketone and β-ketoester




- **Paal-Knorr Pyrrole-Synthesis**: condensation amine and 1,4-ketone
  - Example: Synthesis of atorvastatin (Lipitor)



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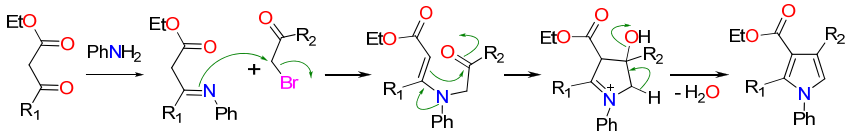
# Pyrroles

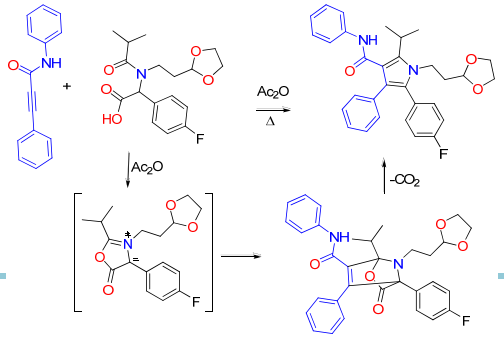
- Hantzsch pyrrole synthesis: from α-halomethyl ketones, β-keto esters and ammonia or amines



A. Hantzsch, *Ber.* **23,** 1474 (1890)

- Huisgen Pyrrole Synthesis

From Amino acids and alkynes. Example: atorvastatin



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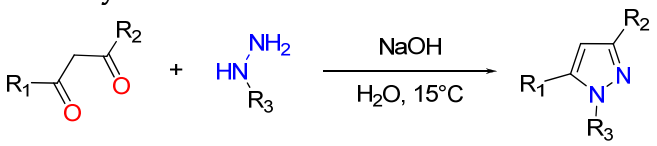
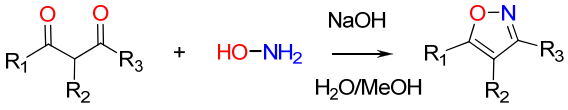
## 1,2-Azoles

- Pyrazoles can be synthesized from 1,3-dicarbonyls with hydrazine




- Isoxazoles can be made from 1,3-dicarbonyl compounds or β-ketoesters with hydroxylamine

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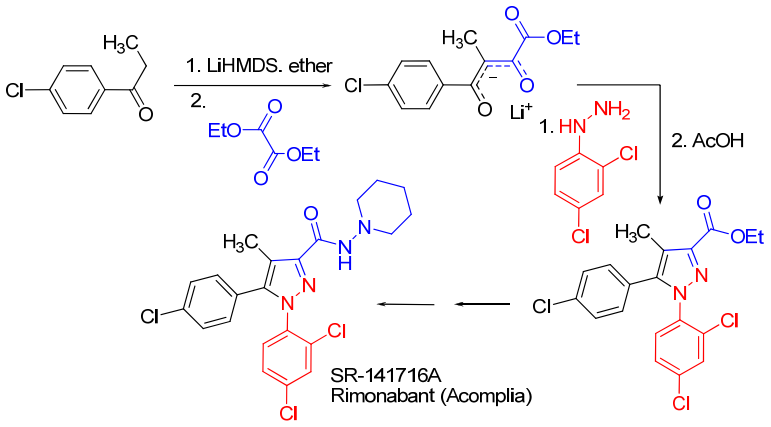
## 1,2-Azoles

**Example of pyrazole synthesis: Rimonabant**




Org. Process Res. Dev., 2007, 11 (5), 910–912

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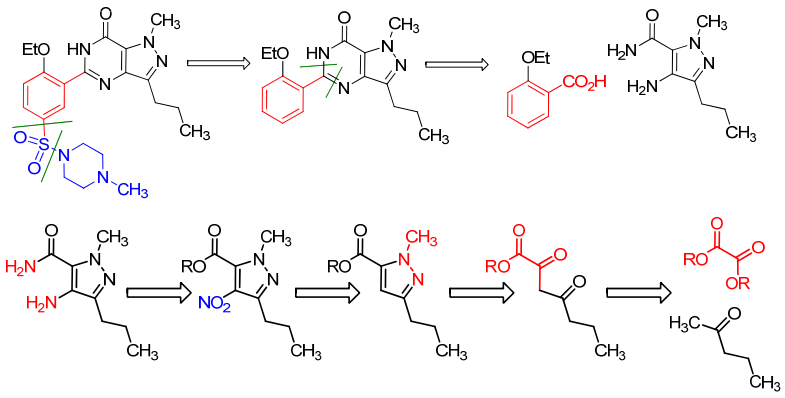
# 1,2-Azoles

**The synthesis of sildenafil (Viagra)**

- Retrosynthesis



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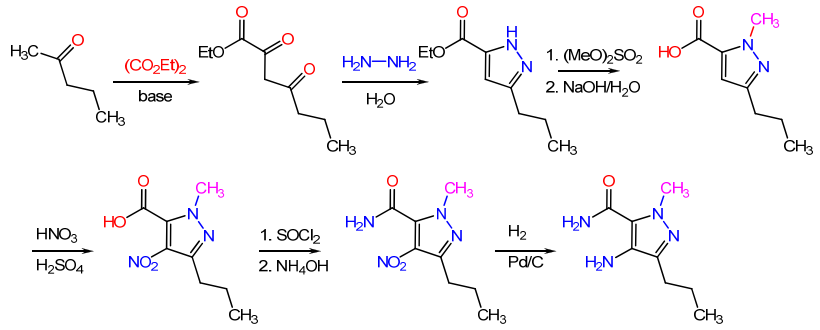
# 1,2-Azoles

**The synthesis of sildenafil (Viagra)**



Bioorg. Med. Chem. Lett. 6, pp. 1819, 1996

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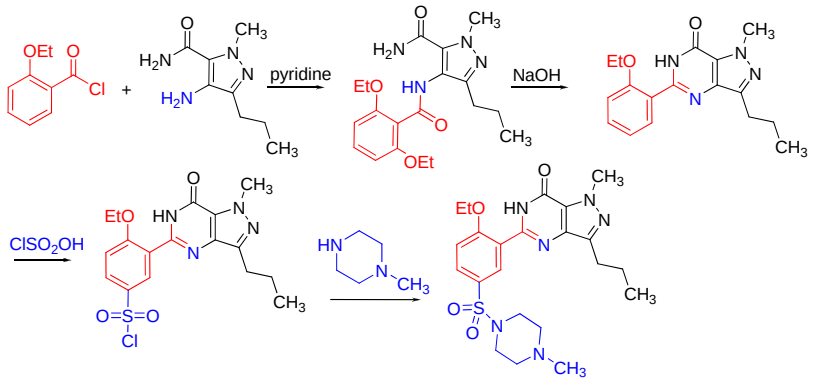
# 1,2-Azoles

**The synthesis of sildenafil (Viagra)**



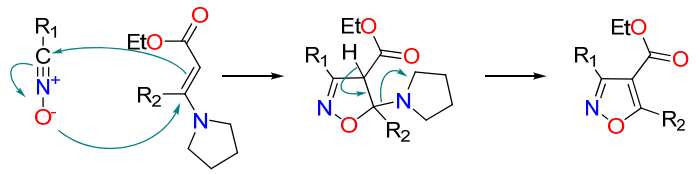

Bioorg. Med. Chem. Lett. 6, pp. 1819, 1996



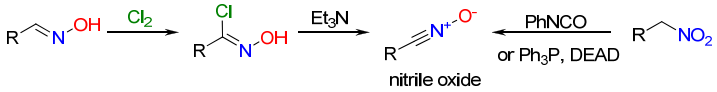
# 1,2-Azoles

**synthesis of isoxazoles**

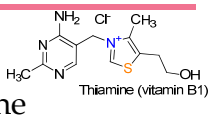
- By 1,3-cycloaddition from nitrile oxides and unsaturated compounds



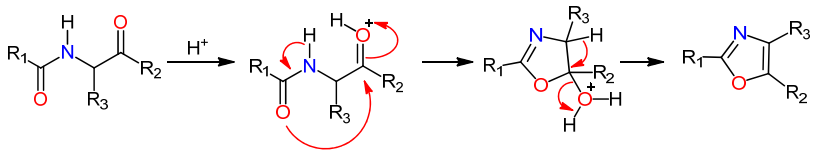

- Nitrile oxides can be prepared by the γ-elimination of chlorooximes or the dehydration of nitroalkanes



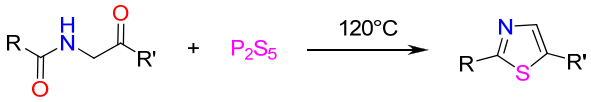
## 1,3-Azoles




- Oxazoles and thiazoles can be obtained by the Robinson-Gabriel synthesis from 2-acylamino-ketones.



- 2-acylamino-ketones reacts with phosphorus pentasulfide to form thiazoles

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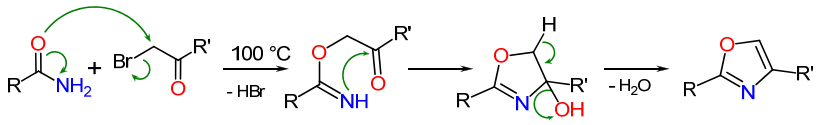
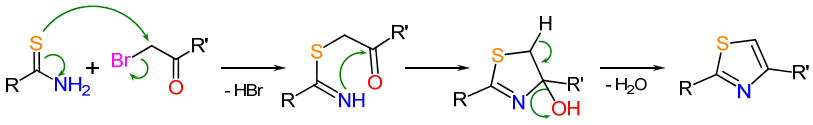
## 1,3-Azoles

- Oxazoles can be made by Blümlein-Lewy Synthesis: heating an α–haloketone with amide




- Most important method for thiazoles is Hantzsch thiazole synthesis from thioamides and a-halocarbonyl compounds

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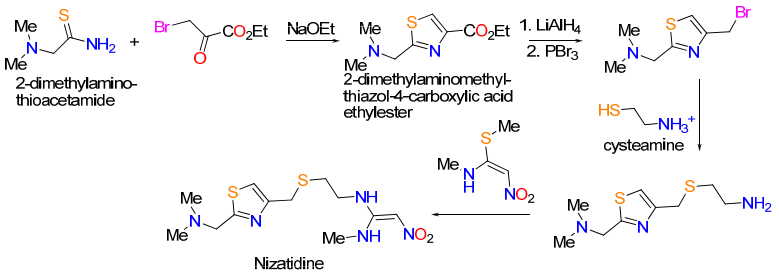
## 1,3-Azoles

- Example: synthesis of nizatidine

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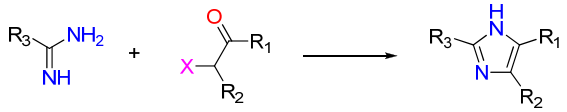
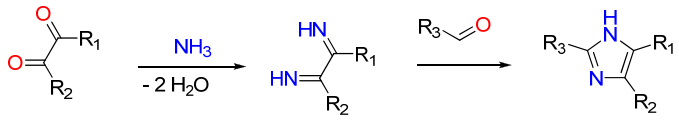
## 1,3-Azoles: Synthesis of imidazoles

- From amidines and hydroxy or halocarbonyl compounds



X = Br, Cl, OH

- **Debus-Radziszewski imidazole synthesis:** diketone and ammonia form an diimine, which condenses with the aldehyde




For more imidazole syntheses, look:
http://www.scripps.edu/chem/baran/images/grpmtgpdf/Zografos_Feb_04.pdf

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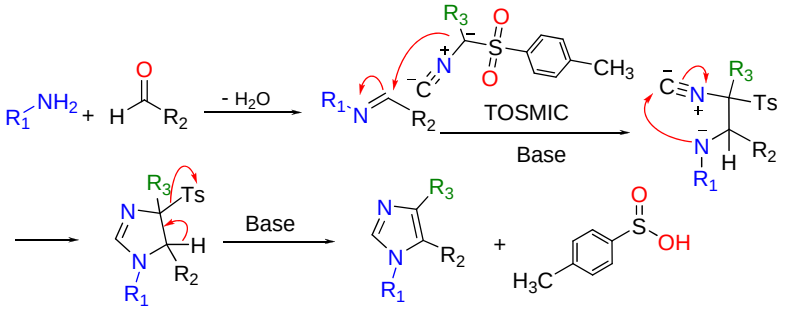
## 1,3-Azoles: Imidazoles from isocyanides

- The reaction of aldehydes, primary amines and toluenesulphonylmethyl isocyanide (TOSMIC) yield 1,4,5-trisubstituted imidazoles (van Leusen et al. *J. Org. Chem.* **1977**, *42*, 1153).

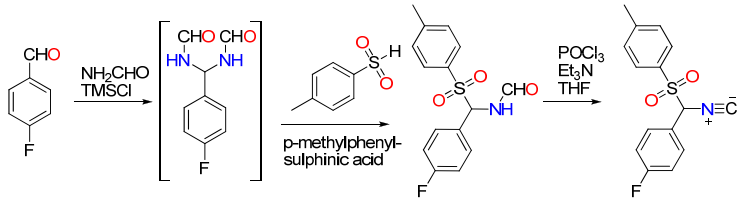



http://www.organic-chemistry.org/Highlights/2005/05May.shtm

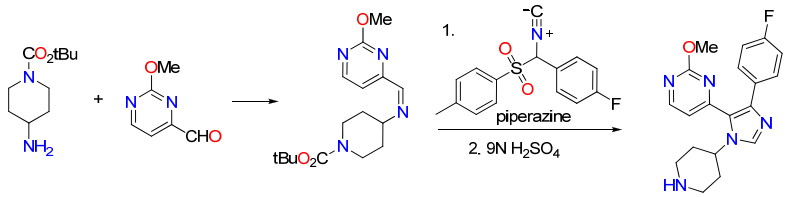


## 1,3-Azoles: Imidazoles from isocyanides

- Substituted tosylmethyl isocyanides (TosMICs) are synthesized from tosylmethyl formamides and *p*-methylphenylsulphinic acid.

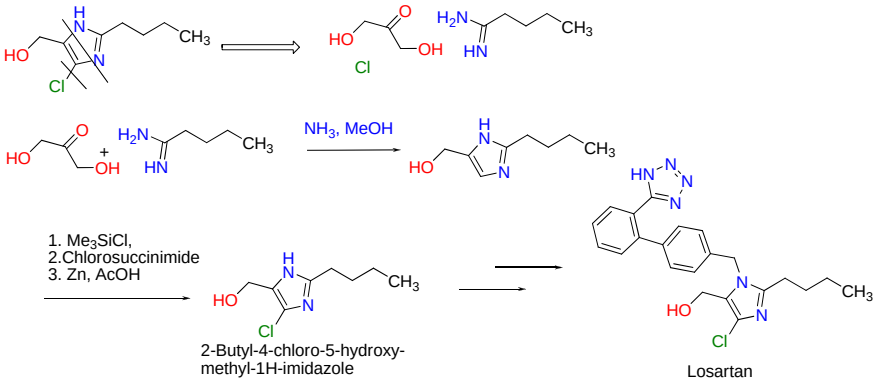



- Synthesis of the GSK p38 kinase inhibitor



# 1,3-Azoles

- Synthesis of 2-Butyl-4-chloro-5-hydroxymethyl-1H-imidazole




Synthetic Communications (1993), 23(18), 2623-30.

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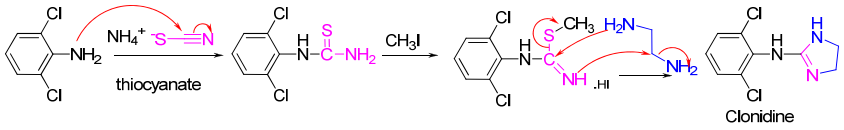
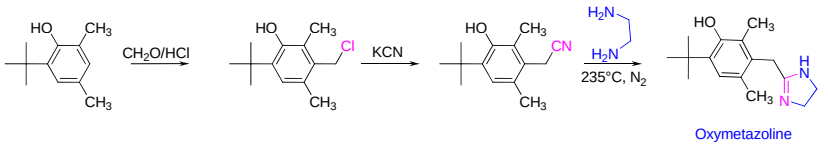
# Dihydroimidazoles

Clonidine (anti-hypertensive agent)




Oxymetazoline (topical decongestant)

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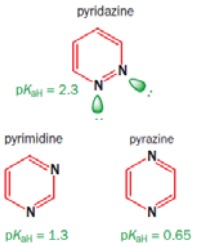
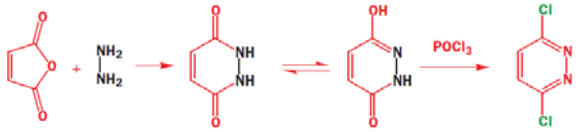
## Six-membered aromatic heterocycles with two N-atoms

- Pyridazine, pyrimidine, and pyrazine are very weak bases. Pyridazine is slightly more basic than the other two because the two adjacent lone pairs repel each other and make the molecule more nucleophilic
- Pyrimidine is important because of its involvement in DNA and RNA.
- Synthesis:
  - Maleic hydrazide is formed when hydrazine is acylated twice by maleic anhydride.
  - The compound prefers to exist as tautomers. Reaction with POCl3 gives aromatic pyridazine dichloride.

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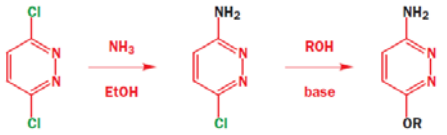
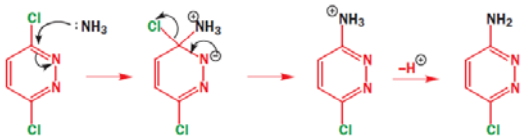
## Six-membered aromatic heterocycles with two N-atoms

- Each of these chlorides can be displaced in turn with an oxygen or nitrogen nucleophile.




- The mechanism of the reactions is addition to the pyridazine ring followed by loss of the leaving group.

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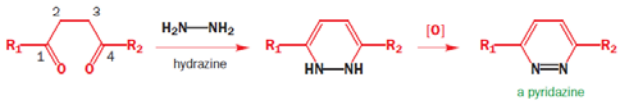
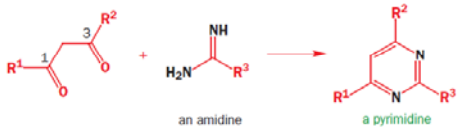
## Six-membered aromatic heterocycles with two N-atoms

- In general, pyridazines can be made by reacting a 1,4-diketone with hydrazine ($NH_2NH_2$)




- If an amidine is combined with the 1,3-diketone we get pyrimidine

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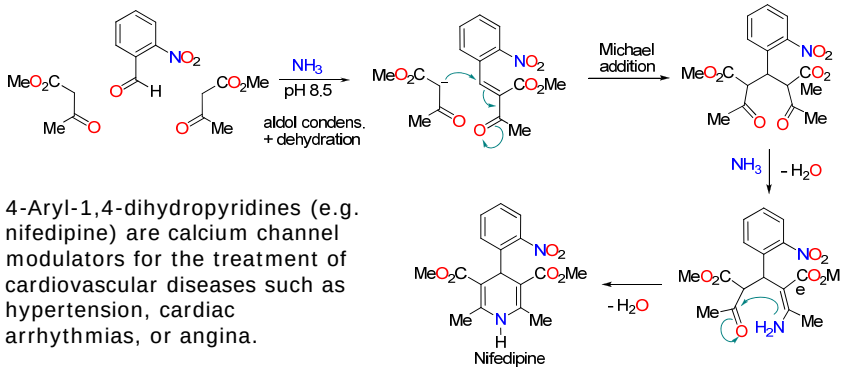
## Six-membered aromatic heterocycles: 1,4-Dihydropyridines

- 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.

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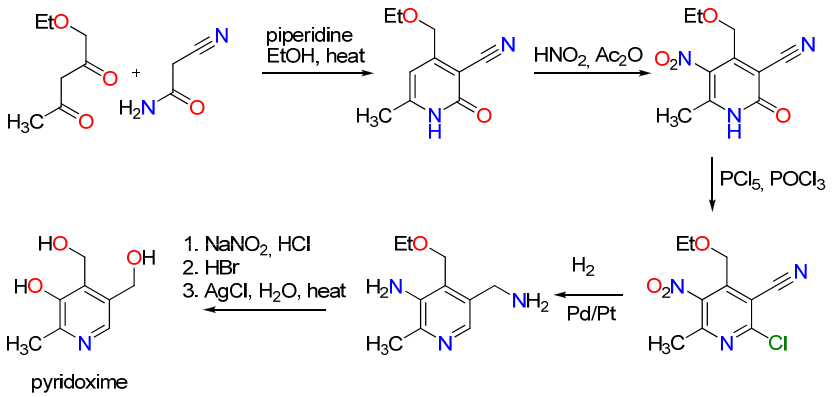
## Six-membered aromatic heterocycles: Pyridines

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

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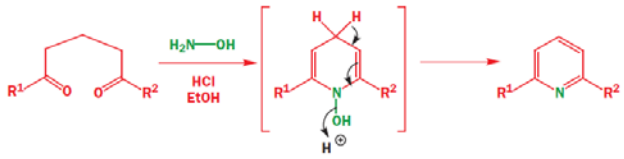
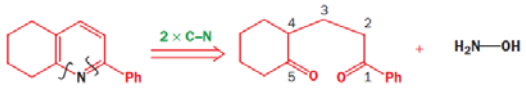
## Six-membered aromatic heterocycles: Pyridines

- If hydroxylamine ($NH_2OH$) is used instead of ammonia as the nucleophile, reaction with a 1,5-diketone gives a dihydropyridine but then water is lost and no oxidation is needed.




- 1,5-diketones may be quickly made by the Mannich and Michael reactions.
- For example the pyridine shown above can be disconnected to the 1,5-diketone.

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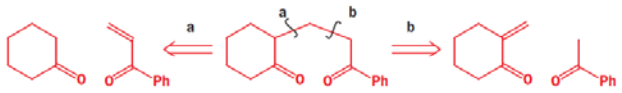
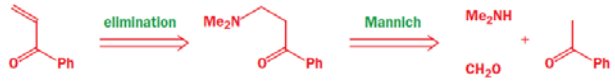
## Six-membered aromatic heterocycles: Pyridines

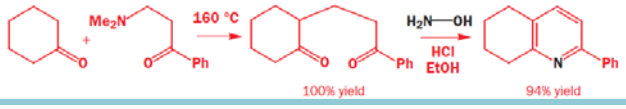
- Further disconnection reveals a ketone and an enone.




- Enone can be made by elimination from Mannich base




- The stable Mannich base is simply heated with the ketone to give a 1,5-diketone. Treatment of that with the HCl salt of NH2OH in EtOH gives the pyridine directly in good yield.

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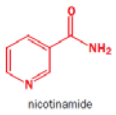
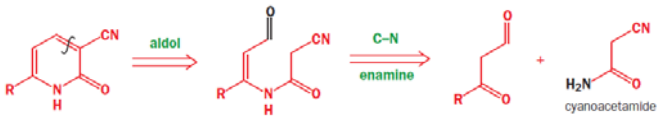
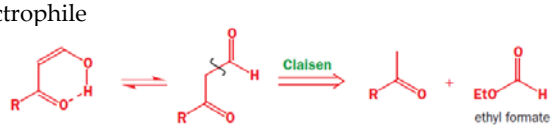
## Six-membered aromatic heterocycles: pyridones

- 3-Substituted pyridones are useful compounds, because they can be used to synthezise nicotinamide and related derivatives
- 3-Cyano pyridone is disconnection to aldol product, which is further disconnected from C–N bond forming the keto-aldehyde and cyanoacetamide




- The keto-aldehyde can be made by a Claisen condensation using the enolate of the methyl ketone with ethyl formate as the electrophile

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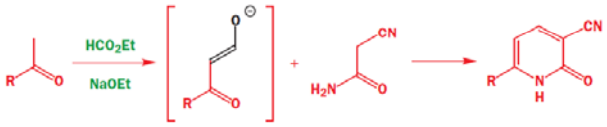
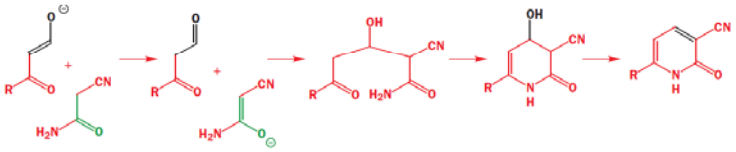
## Six-membered aromatic heterocycles: pyridones

- The enolate anion of the keto-aldehyde can be combined directly without isolation with cyanoacetamide to give the pyridone




- Cyclization probably occurs next through C–N bond formation and, finally, dehydration is forced to give the *Z*-alkene.



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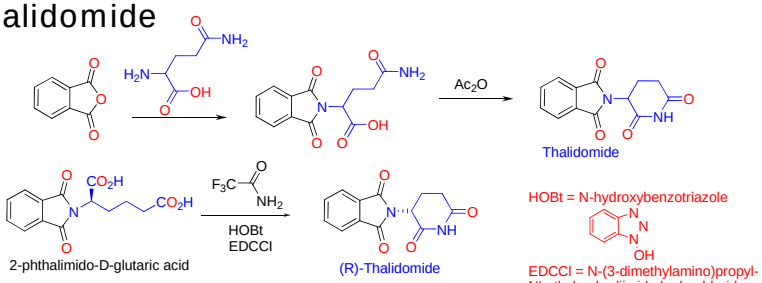
## Glutarimides

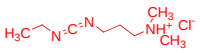
- Thalidomide




HOBt = N-hydroxybenzotriazole

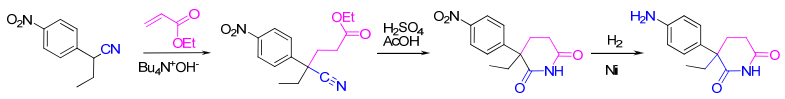


EDCCI = N-(3-dimethylamino)propyl-N'-ethylcarbodiimide hydrochloride



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

- Aminoglutethimide




Aminoglutethimide (Aromatase Inhibitor, breast cancer)

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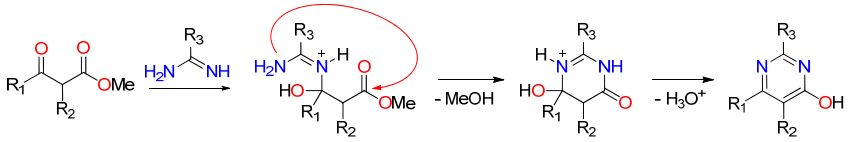
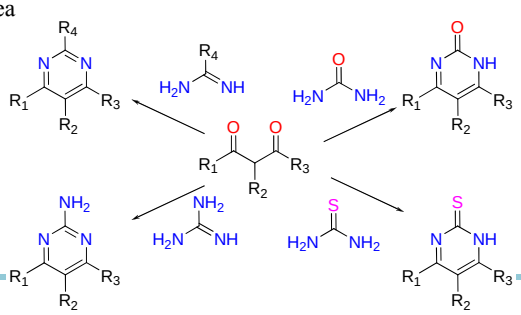
# Pyrimidines

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




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



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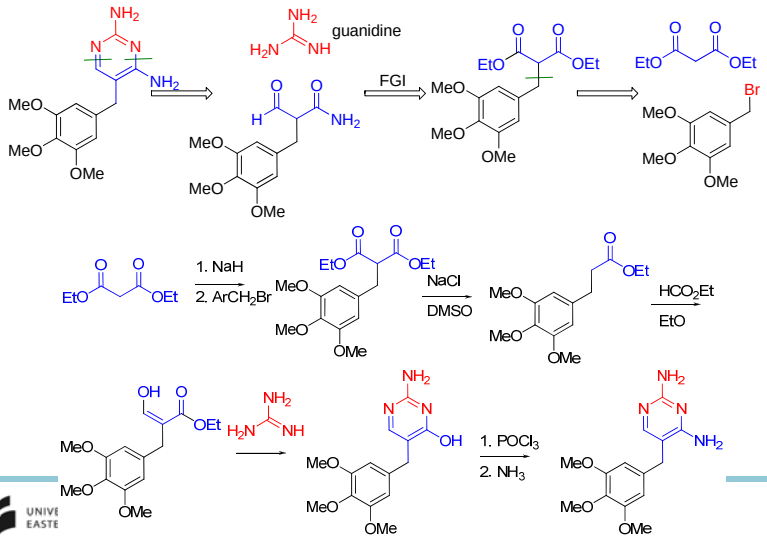
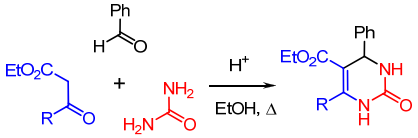
# Pyrimidines

- Example: trimethoprim (bacteriostatic antibiotic)



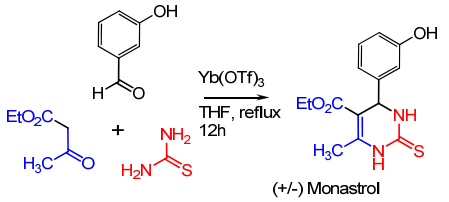
## Pyrimidines

- 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)




(+/-) Monastrol

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

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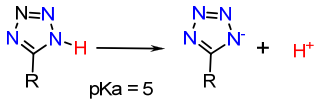
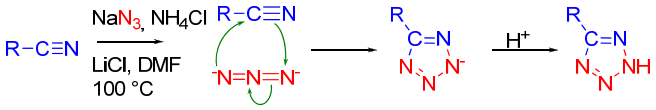
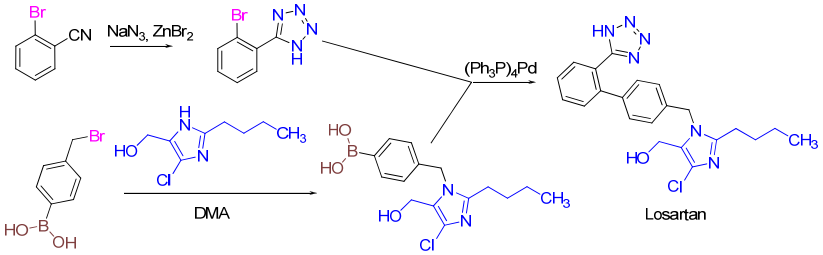
## Tetrazoles

- Carboxylic acid isostere
- Synthesis




- Synthesis of Losartan (antihypertensive)

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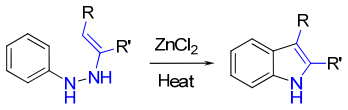
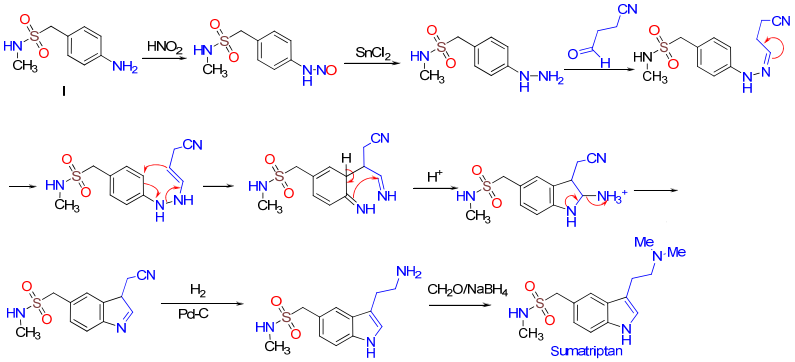
# Indoles

- 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)

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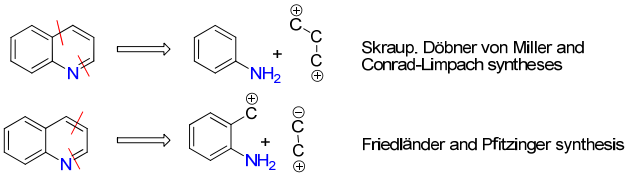
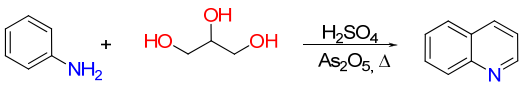
# Quinolines

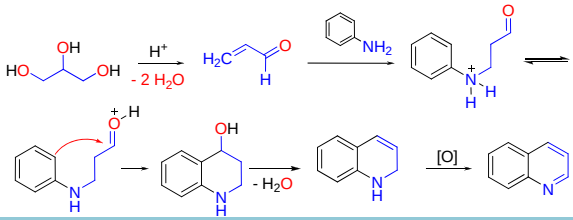
- Quinoline nucleus is usually formed in one of two ways




- Skraup-reaction




- Mechanism:

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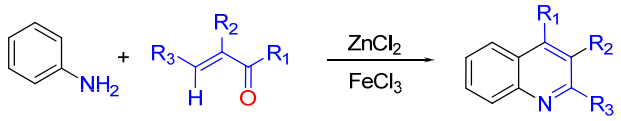
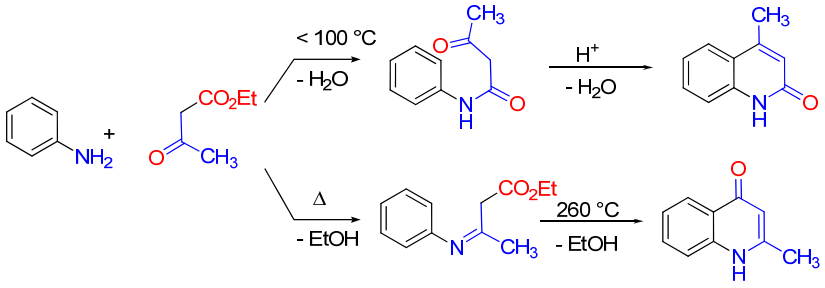
## Quinolines

- **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

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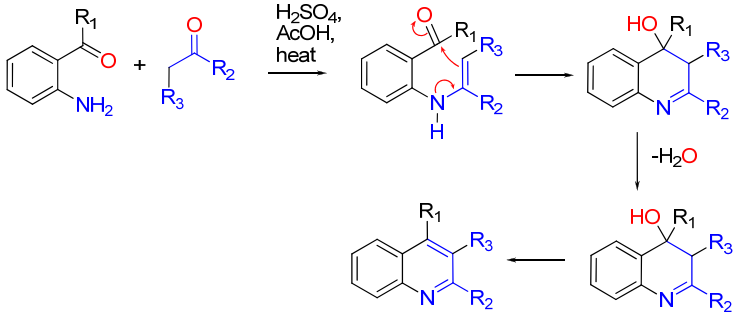
## Quinolines

- Friedländer-quinoline synthesis

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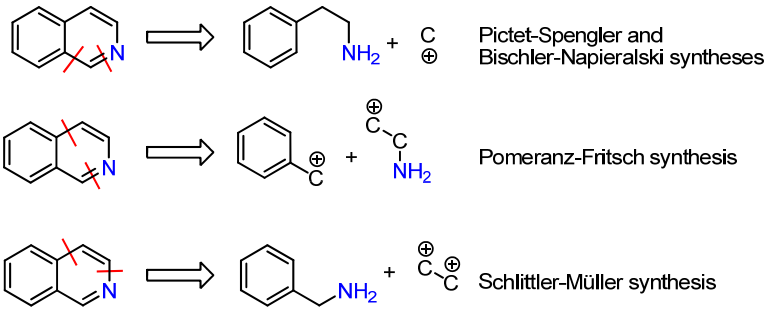
## Isoquinolines

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

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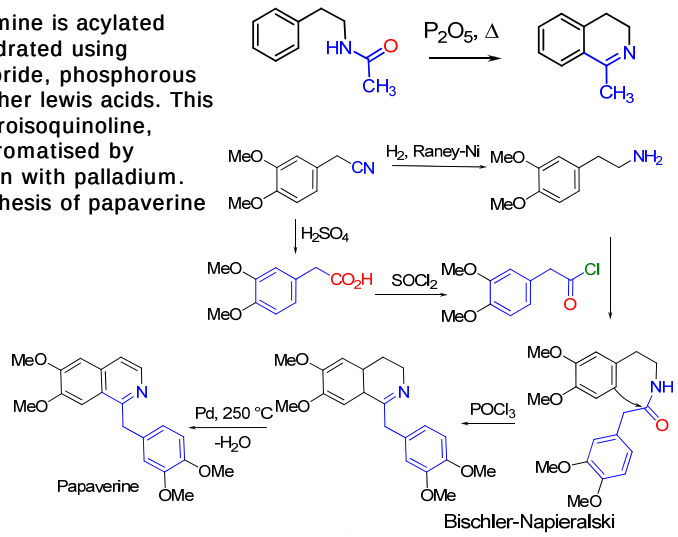
## Isoquinolines

### •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

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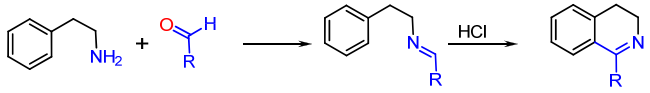
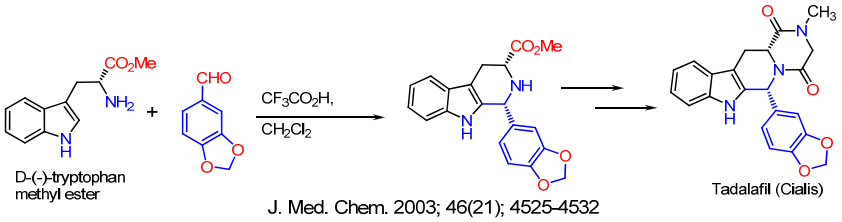
# Isoquinolines

- 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




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

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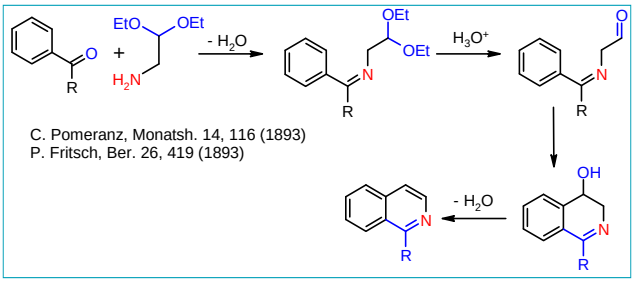
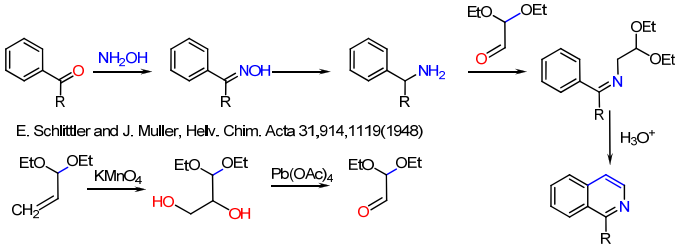
# Isoquinolines

- Pomeranz-Fritsch Reaction




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

- Schlittler-Müller Reaction

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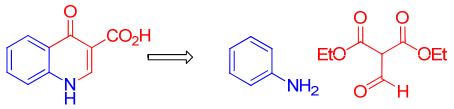
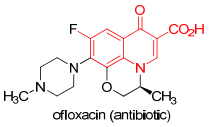
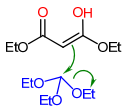
# Quinolones

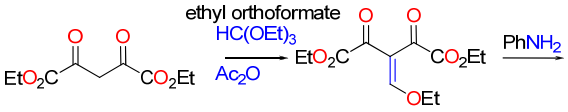
- **Retrosynthesis**

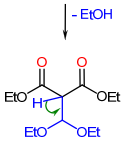


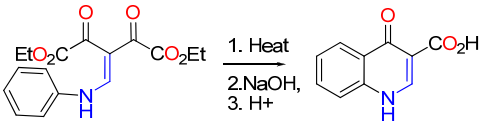


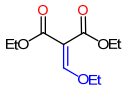



- **Synthesis**



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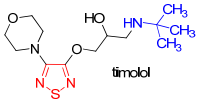
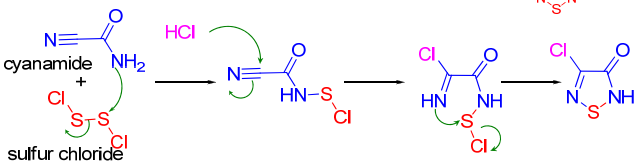
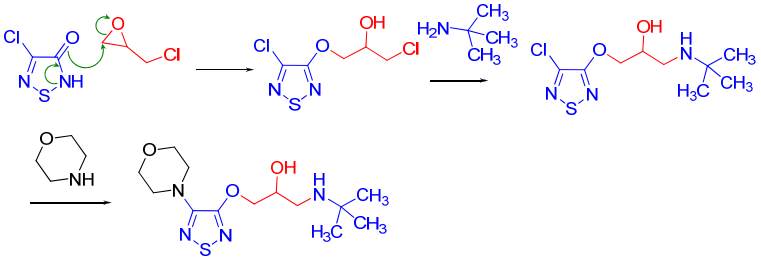
# Thiadiazoles

- Synthesis of Timolol (β-blocker)



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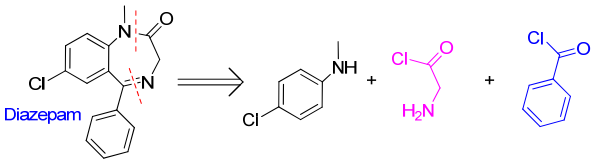
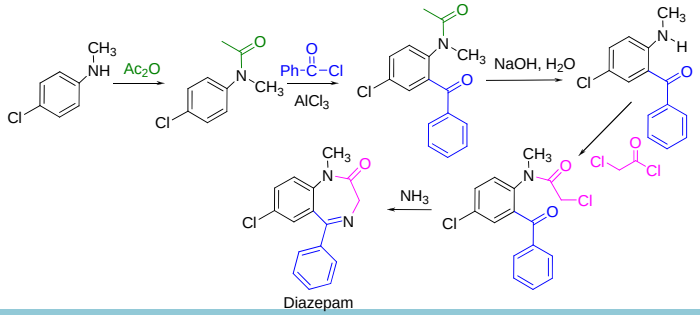
# Benzodiazepines

- The retrosynthesis of diazepam




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

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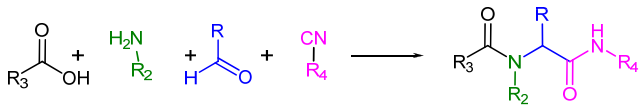
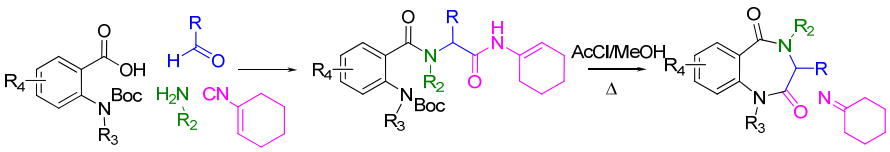
# Benzodiazepines

- **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)

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