Synthesis of heterocyclic compounds

Tapio Nevalainen
Drug synthesis II
2012

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

Heterocyclic compounds

- Heterocycles contain one or more heteroatoms in a ring

\[
\begin{array}{c}
  X \\
  \ 
  Y \\
  Z
\end{array}
\]

\[X,Y,Z\] are usually \(N,O,S\)
Heterocycles

• Aromatic five-membered heterocycles

1H-pyrrole 1H-pyrazole 1H-imidazole

1H-indole 1H-indazole 1H-benzo[d]imidazole

furan isoxazole oxazole

1H-1,2,4-triazole 1H-1,2,3-triazole 1H-benzotriazole

thiophene isothiazole thiazole

benzofuran benzo[b]thiophene benzo[b]thiazole

Heterocycles

• Aromatic six-membered heterocycles

pyridine pyridazine pyrimidine pyrazine

quinoline isoquinoline quinazoline quinoxaline
Heterocycles

• Aliphatic heterocycles

- Asparagine
- Aspartic acid
- Azetidine
- Pyrrolidine
- 2-Pyrrolidine
- Piperidine
- 2-Piperidone
- Cysteine
- Cystine
- Tetrahydrofuran
- Tetrahydro-2H-pyran
- 1,4-Dioxane
- Morpholine
- Piperazine

Heterocycles

• Tautomerism

- 2-Pyridone
- Uracil
- Guanine tautomers
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.

\[
\text{H}_2\text{N}_2\text{O}_2\text{S} \quad \xrightarrow{\text{EtOH, } 0^\circ} \quad \text{Br}_4
\]

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

\[
\text{X} = \text{NH, O, S}
\]

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 POCl₃

\[
\text{H}_2\text{N}_2\text{O}_2\text{S} \quad \xrightarrow{\text{1. POCl₃}} \quad \text{H}_2\text{O} \quad \xrightarrow{\text{2. H₂O}} \quad \text{CH₃O}_2\text{NCH₃}
\]
Reactions of heterocycles

• Aromatic heterocycles undergo aminoalkylation (Mannich reaction)
• For example N-methylpyrrrole 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

Common building-blocks for heterocyclic compounds
General strategies for heterocycle synthesis

- "1+4" strategy

- "1+5" strategy

Examples

X = Cl, Br, I
Reactions used in heterocyclic ring synthesis

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

\[
\begin{align*}
R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}
&\xrightarrow{R_3} R_4
\rightarrow R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}R_3
\rightarrow R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}R_3\rightarrow R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}R_3
\end{align*}
\]

- Imine/enamine formation

\[
\begin{align*}
R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}
&\xrightarrow{R_3} R_4
\rightarrow R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}R_3
\rightarrow R_1\overset{\text{H}^+}{\underset{\text{H}^-}{\text{O}}}R_3
\end{align*}
\]

Enamines can function as enolates
Reactions used in heterocyclic ring synthesis

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

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.
Furans

- **Paal Knorr**

  \[ R_1\text{CO}_2\text{Et} + R_2\text{H} \xrightarrow{\text{H}^+} R_1\text{CO}_2\text{Et} + R_2\text{H} \xrightarrow{-\text{H}_2\text{O}} R_1\text{CO}_2\text{Et} + R_2\text{H} \]

- **Feist-Benary**

  \[ R_1\text{CO}_2\text{Et} + R_2\text{H} \xrightarrow{\text{H}^+} R_1\text{CO}_2\text{Et} + R_2\text{H} \xrightarrow{-\text{H}_2\text{O}} R_1\text{CO}_2\text{Et} + R_2\text{H} \]

---

**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 \( \alpha \)-iodo-ester.
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.

Thiophenes

- Paal Knorr

- Hinsberg Synthesis of Thiophene Derivatives

- Gewald reaction
**Pyrroles**

- **Knorr pyrrole synthesis**: Condensation of \(\alpha\)-aminoketone and \(\beta\)-ketoester

\[
\begin{align*}
R'\text{C}O_2H + \text{R''NH}_2 + \text{AcOH} &\rightarrow R'\text{C}O_2\text{R''NHCH}_3 \\
&\rightarrow \text{R'RCOCH}_3
\end{align*}
\]

- **Paal-Knorr Pyrrole-Synthesis**: Condensation amine and 1,4-ketone

  - Example: Synthesis of atorvastatin (Lipitor)

  ![Paal-Knorr Pyrrole-Synthesis](image)

- **Hantzsch pyrrole synthesis**: From \(\alpha\)-halomethyl ketones, \(\beta\)-keto esters and ammonia or amines

  ![Hantzsch Pyrrole Synthesis](image)

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

- **Huisgen Pyrrole Synthesis**

  From Amino acids and alkynes. Example: atorvastatin

  ![Huisgen Pyrrole Synthesis](image)
1,2-Azoles

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

\[
\begin{align*}
R_1\overset{\text{O}}{\underset{\text{C}}{\overset{\text{O}}{\text{R_2}}}} + H_N^2 R_3 \xrightarrow{\text{NaOH}} \overset{\text{N}}{\underset{\text{R_1}}{\text{R_2}}} & \quad \text{H}_2\text{O}, 15^\circ\text{C} \\
\end{align*}
\]

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

\[
\begin{align*}
\overset{\text{O}}{\underset{\text{C}}{\overset{\text{O}}{\text{R_1}}} R_2} + \overset{\text{O}}{\underset{\text{N}}{\overset{\text{O}}{\text{R_1}}} R_3} \xrightarrow{\text{NaOH}} \overset{\text{N}}{\underset{\text{R_1}}{\text{R_2}}} & \quad \text{H}_2\text{O/MeOH} \\
\end{align*}
\]

Example of pyrazole synthesis: Rimonabant
1,2-Azoles
The synthesis of sildenafil (Viagra)

Retro synthesis

1,2-Azoles
The synthesis of sildenafil (Viagra)


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.

\[
\begin{align*}
R_1NHCO \quad R_4 & \quad H^+ \\
\rightarrow & \quad R_1NR_2CO \quad R_4
\end{align*}
\]

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

\[
\begin{align*}
R_1NHCO \quad R_4 & \quad P_2S_5 \\
& \quad 120^\circ C \\
\rightarrow & \quad R_1NR_2S
\end{align*}
\]

1,3-Azoles

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

\[
\begin{align*}
R_1NHCO \quad R_4 & \quad Br \\
& \quad 100^\circ C \\
& \quad R_1NHCO \quad R_4
\end{align*}
\]

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

\[
\begin{align*}
R_1NHCO \quad R_4 & \quad Br \\
& \quad R_1NHCO \quad R_4
\end{align*}
\]
1,3-Azoles

- Example: synthesis of nizatidine

![Chemical structure of nizatidine synthesis]

Debus–Radziszewski imidazole synthesis: diketone and ammonia form an imine, which condenses with the aldehyde.

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).

\[
\begin{align*}
R_1NH_2 + H_2C &= R_1NHR_2 \quad \xrightarrow{H_2O} \quad R_1N^+ \quad \xrightarrow{\text{Base}} \quad 1,4,5-
\end{align*}
\]

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

Dihydroimidazoles

Clonidine (anti-hypertensive agent)

Oxymetazoline (topical decongestant)
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.

\[
\text{Maleic hydrazide} \rightarrow \text{Pyridazine dichloride}
\]

\[\text{POCl}_3 + \text{Pyridazine} \rightarrow \text{Pyridazine dichloride}\]

Six-membered aromatic heterocycles with two N-atoms

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

\[
\text{Pyridazine dichloride} + \text{Nucleophile} \rightarrow \text{Pyridazine nucleophile}
\]

- The mechanism of the reactions is addition to the pyridazine ring followed by loss of the leaving group.
Six-membered aromatic heterocycles with two N-atoms

- In general, pyridazines can be made by reacting a 1,4-diketone with hydrazine (NH$_2$NH$_2$)

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

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.
Six-membered aromatic heterocycles: Pyridines

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

![Chemical structure of pyridoxine, vitamin B6, and pyridine synthesis]

- If hydroxylamine (NH₂OH) 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.
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 NH$_2$OH in EtOH gives the pyridine directly in good yield.

Six-membered aromatic heterocycles: pyridones

- 3-Substituted pyridones are useful compounds, because they can be used to synthesize nicotinamide and related derivatives.

- 3-Cyano pyridone is disconnection to aldol product, which is further disconnected from C−N bond forming the ketoaldehyde 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.
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.

Glutarimides

- Thalidomide

  2-phthalimido-D-glutaric acid

  \[
  \text{HOBt = N-hydroxybenzotriazole} \\
  \text{EDCCI = N-(3-dimethylamino)propyl-N-ethylcarbodiimide hydrochloride}
  \]


- Aminoglutethimide

  Aminoglutethimide (Arimidex inhibitor, breast cancer)
Pyrimidines

- Pinner pyrimidine synthesis: 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, α,β-ketoester and urea constitutes a rapid and facile synthesis of tetrahydropyrimidones.

\[
\text{BacillioC} + \text{H}^+ + \text{EtOH}, \Delta \rightarrow \text{BacillioC} + \text{EtOH}
\]

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

Tetrazoles

• Carboxylic acid isostere

\[
\text{R-C} = \text{N} + \text{H}^+ \rightarrow \text{R-C} = \text{N} + \text{H}_2\text{N} + \text{H}_2\text{O}
\]

• 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

  ![Fischer Indole Synthesis Diagram](image)

- Synthesis of Sumatriptan

  ![Synthesis of Sumatriptan Diagram](image)

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

**Quinolines**

- Quinoline nucleus is usually formed in one of two ways

  ![Quinoline Nucleus Diagram](image)

  - Skraup-reaction

  - Mechanism:

    ![Skraup-reaction Mechanism Diagram](image)
Quinolines

- **Doebner-Miller reaction**: $\alpha,\beta$-unsaturated ketone or aldehyde can be used instead of glycerol to form a quinoline

\[
\begin{align*}
\text{C}_6\text{H}_4\text{NH}_2 + \text{R}_1\text{C} = \text{O} & \xrightarrow{\text{ZnCl}_2, \text{FeCl}_3} \text{R}_1\text{R}_2\text{R}_3 \\
\end{align*}
\]

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

\[
\begin{align*}
\text{C}_6\text{H}_4\text{NH}_2 + \text{CO}_2\text{Et} & \xrightarrow{< 100 \degree C} \xrightarrow{\Delta \text{EtOH}} \text{R}_1\text{R}_2\text{R}_3 \\
\text{R}_1\text{R}_2\text{R}_3 & \xrightarrow{\text{H}^+ - \text{H}_2\text{O}} \\
\text{R}_1\text{R}_2\text{R}_3 & \xrightarrow{260 \degree C \text{EtOH}} \\
\end{align*}
\]

Quinolines

- **Friedländer-quinoline synthesis**

\[
\begin{align*}
\text{R}_1\text{R}_2\text{R}_3 & \xrightarrow{\text{H}_2\text{SO}_4, \text{AcOH}, \text{heat}} \xrightarrow{\text{H}_2\text{O}} \text{R}_1\text{R}_2\text{R}_3 \\
\end{align*}
\]
Isoquinolines

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

  - **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

- Pfitz-Spengler and Bischler-Napieralski syntheses
- Pomeranz-Fritsch synthesis
- Schiltler-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: \( \beta \)-Arylethylamine is heated in the presence of an aldehyde and acid.
- A special case of the Mannich reaction.

\[
\text{ArNH}_2 + \text{CHO} + \text{HCl} \rightarrow \text{ArN} + \text{H}_2\text{O}
\]

A. Pictet and T. Spengler, Ber. 44, 2030 (1911)

**Synthesis of Tadalafil**

\[
\text{D-}\text{Arylpropion amine methyl ester} + \text{CHOCH}_2\text{Cl} \rightarrow \text{Tadalafil (Cialis)}
\]

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

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**Isoquinolines**

- Pomeranz-Fritsch Reaction

\[
\begin{align*}
\text{Ph} & \text{NH} + \text{CHO} + \text{H}_2\text{O} \rightarrow \text{PhN} + \text{H}_2\text{O} \\
\text{PhN} & \rightarrow \text{PhN}
\end{align*}
\]

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

- Schlittler-Müller Reaction

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Quinolones

• Retrosynthesis

Synthesis

Thiadiazoles

• Synthesis of Timolol (β-blocker)
Benzodiazepines

- The retrosynthesis of diazepam

\[
\begin{align*}
\text{Diazepam} & \quad \text{NH} + \text{H}_2\text{N-C-} + \text{PhCl} \\
\text{Cl} & \quad \text{Cl} & \quad \text{O} \\
\text{Cl} & \quad \text{Cl} & \quad \text{O}
\end{align*}
\]

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

\[
\begin{align*}
\text{Diazepam} & \quad \text{NH} + \text{H}_2\text{N-C-} + \text{PhCl} \\
\text{Cl} & \quad \text{Cl} & \quad \text{O} \\
\text{Cl} & \quad \text{Cl} & \quad \text{O}
\end{align*}
\]

Benzodiazepines

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

\[
\begin{align*}
\text{R}_3\text{C}=\text{O} & \quad \text{H}_2\text{N} & \quad \text{H}_2\text{O} & \quad \text{CN} & \quad \text{I}_4 \\
\text{R}_2 & \quad & & & \text{R}_4
\end{align*}
\]


\[
\begin{align*}
\text{R}_3\text{N} & \quad \text{R}_2 \\
\text{R}_2 & \quad & \text{R}_3 \\
\text{R}_3 & \quad & \text{R}_2
\end{align*}
\]