Synthesis of heterocyclic compounds

Tapio Nevalainen
Drug synthesis II
2010

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

Heterocyclic compounds

- Heterocycles contain one or more heteroatoms in a ring

\[ \text{X, Y, Z are usually N, O, S} \]
Heterocycles

• Aromatic five-membered heterocycles

\[
\begin{array}{cccc}
\text{1H-pyrrole} & \text{1H-pyrazole} & \text{1H-thiazole} & \text{1H-indole} \\
\text{2} & \text{3} & \text{4} & \text{5} \\
\text{1} & \text{2} & \text{3} & \text{4} \\
\end{array}
\]

furan isoxazole oxazole 1H+1,2,4-triazole 1H+1,2,3-triazole 1H-benzimidazole

thiophene isothiazole thiazole benzofuran benzothiophene benzoxazole

Heterocycles

• Aromatic six-membered heterocycles

\[
\begin{array}{cccc}
\text{pyridine} & \text{pyridazine} & \text{pyrimidine} & \text{pyrazine} \\
\text{1} & \text{2} & \text{3} & \text{4} \\
\text{5} & \text{6} & \text{7} & \text{8} \\
\end{array}
\]

quinoline isoquinoline quinazoline quinoxaline
Heterocycles

• Aliphatic heterocycles

Heterocycles

• Tautomerism

2-pyridine

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.

\[
\text{H}_2\text{NCH}_3 + \text{POCl}_3 \rightarrow \text{H}_2\text{NCH}_3\text{Cl} + \text{POCl}_3
\]

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

**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.

\[
\text{Friedel–Crafts reaction: } \text{X}_2 + \text{H}_2\text{NCH}_3 \rightarrow \text{X}_2\text{NCH}_3
\]
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.

\[
\begin{align*}
\text{HN} & \quad \text{CH}_3 \\
\text{CH}_2=\text{O} & \quad \text{Mannich reaction} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\end{align*}
\]

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

\[
\begin{align*}
\text{HN} & \quad \text{CH}_3 \\
\text{CH}_2=\text{O} & \quad \text{Mannich reaction} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{CH}_3 \\
\end{align*}
\]

Common building-blocks for heterocyclic compounds

- Amide
- Sulfide
- Guanidine
- Urea
General strategies for heterocycle synthesis

- "1+4" strategy

\[ \text{Diagram showing the reaction of two molecules to form a heterocyclic structure.} \]

- "1+5" strategy

\[ \text{Diagram showing the reaction of a cyclohexane ring with another molecule to form a heterocyclic structure.} \]

- "2+3" strategy

\[ \text{Diagram showing the reaction of two molecules to form a heterocyclic structure.} \]

- "3+3" strategy

\[ \text{Diagram showing the reaction of three molecules to form a heterocyclic structure.} \]

Examples:

- \( X = \text{Cl, Br, I} \)
Reactions used in heterocyclic ring synthesis

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

\[
\text{R}_4\text{C}=\text{O} + \text{R}_3\text{H} \rightarrow \text{R}_4\text{C}OH + \text{R}_3\text{H}^+.
\]

- Imine/enamine formation

\[
\text{R}_1\text{C}+\text{R}_2\text{H} + \text{H}_2\text{N}-\text{R}_3 \rightarrow \text{R}_1\text{C}=\text{N}+\text{R}_2\text{H}-\text{R}_3.
\]

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

\[
\text{R}_2\text{H} + \text{R}_4\text{H} \rightarrow \text{R}_2\text{C}=\text{N}+\text{R}_4\text{H}.
\]

- Enamines can function as enolates

\[
\text{R}_1\text{C}=\text{N}+\text{R}_2\text{H} \rightarrow \text{R}_1\text{C}=\text{N}+\text{R}_2\text{H}^+ + \text{H}_2\text{O}.
\]
Reactions used in heterocyclic ring synthesis

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

Furans

- **Paal Knorr**

- **Feist-Benary**
**Thiophenes**

- **Paal Knorr**

- **Hinsberg Synthesis of Thiophene Derivatives**

- **Gewald reaction**

---

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

\[
\begin{align*}
\text{Hantzsch Pyrrole Synthesis}\quad &\quad \text{From Amino acids and alkynes. Example: atorvastatin}
\end{align*}
\]

Huisgen Pyrrole Synthesis

1,2-Azoles
- Pyrazoles can be synthesized from 1,3-dicarbonyls with hydrazine

\[
\begin{align*}
\text{Pyrazoles:} &\quad \text{from 1,3-dicarbonyls with hydrazine}
\end{align*}
\]

- Isoxazoles can be made from 1,3-dicarbonyl compounds or β-ketoesters with hydroxylamine
1,2-Azoles

Example of pyrazole synthesis: Rimonabant

The synthesis of sildenafil (Viagra)

Retrosynthesis
**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.

- 2-acylamino-ketones reacts with phosphorus pentasulfide to form thiazoles
1,3-Azoles

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

![Chemical reaction diagram]

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

Example: synthesis of nizatidine

![Chemical reaction diagram]
1,3-Azoles: Synthesis of imidazoles

- From amidines and hydroxy or halocarbonyl compounds

\[ R_3\text{NH}_2 + \xrightarrow{X} R_1\text{O}R_2 \rightarrow \xrightarrow{X=\text{Br, Cl, OH}} R_3N\text{N}R_1R_2 \]

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

For more imidazole syntheses, look:

---

1,3-Azoles: Imidazoles from isocyanides


\[
\begin{align*}
R_1\text{NH}_2 + & \xrightarrow{\text{H}_2\text{O}} R_1\text{N}R_2 & \xrightarrow{\text{TOSMIC}} & R_1N\text{N}R_2 & \xrightarrow{\text{Ts, Base}} & R_1N\text{N}R_2 \\
R_1 & \xrightarrow{\text{Base}} & R_3 & \xrightarrow{\text{Ts, Base}} & R_1N\text{N}R_2 \\
\end{align*}
\]

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

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

\[
\begin{align*}
\text{EtO} & \quad \text{+} \quad \text{piperidine} \quad \text{EtOH} \quad \text{heat} \\
\text{NH_2} & \quad \text{+} \quad \text{EIO} \\
\text{H_2C} & \quad \text{+} \quad \text{NO_2} \quad \text{Ac_2O} \\
\text{H_3C} & \quad \text{+} \quad \text{PCl_3} \quad \text{PCl_3}
\end{align*}
\]

pyridoxine

Glutarimides

- Thalidomide

\[
\begin{align*}
\text{H_2N} & \quad \text{+} \quad \text{OH} \\
\text{H_2C} & \quad \text{+} \quad \text{N_2H_5} \quad \text{NH_2} \\
\text{H_2C} & \quad \text{+} \quad \text{H_2C} \\
\text{H_2C} & \quad \text{+} \quad \text{H_2C}
\end{align*}
\]

2-phthalimido-D-glutaric acid

\[
\begin{align*}
\text{H_2N} & \quad \text{+} \quad \text{OH} \\
\text{H_2C} & \quad \text{+} \quad \text{N_2H_5} \quad \text{NH_2} \\
\text{H_2C} & \quad \text{+} \quad \text{H_2C} \\
\text{H_2C} & \quad \text{+} \quad \text{H_2C}
\end{align*}
\]

(R)-Thalidomide

Thalidomide

HOBt = N-hydroxybenzotriazole

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

- Aminoglutethimide

\[
\begin{align*}
\text{H_2N} & \quad \text{+} \quad \text{OH} \\
\text{H_2C} & \quad \text{+} \quad \text{N_2H_5} \quad \text{NH_2} \\
\text{H_2C} & \quad \text{+} \quad \text{H_2C} \\
\text{H_2C} & \quad \text{+} \quad \text{H_2C}
\end{align*}
\]

Aminoglutethimide

(Prohormone: H2R, 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, \( \alpha,\beta \)-ketoester and urea constitutes a rapid and facile synthesis of tetrahydropyrimidones.

\[
\text{BiOAc}C=\text{CH}_{\text{R}} + \text{HAc} + \text{EtOH} \xrightarrow{\Delta} \text{BiOAc}C=\text{C}N_{\text{Ph}} + \text{HAc}
\]

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

\[
\text{BiOAc}C=\text{CH}_{\text{R}} + \text{Yb(OH)$_3$} \xrightarrow{\text{THF, reflux, 12h}} \text{BiOAc}C=\text{C}N_{\text{Ph}}\text{HAc}
\]

Tetrazoles

- Carboxylic acid isostere

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

- Synthesis

\[
\text{NaNH}_2\text{NH}_3\text{Cl} \xrightarrow{\text{LiCl, DMF, 100°C}} \text{R-C=N} \rightarrow \text{R-C=N} + \text{H}^+
\]

- Synthesis of Losartan (antihypertensive)

\[
\text{Br-CN} \xrightarrow{\text{NaH}, \text{ZnBr$_2$}} \text{Br-N}+\text{H}\text{Br} \xrightarrow{\text{Pd/C}} \text{Ph-N}+\text{H}\text{Br} \xrightarrow{\text{DMA}} \text{Losartan}
\]
**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**

  ![Synthesis of Sumatriptan](image)

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

---

**Quinolines**

- Quinoline nucleus is usually formed in one of two ways
  - Skraup, Dißner von Miller and Conradi impach syntheses
  - Friedländer and Pflüger synthesis

- **Skraup-reaction**

  ![Skraup-reaction](image)

  **Mechanism:**

  ![Mechanism](image)
Quinolines

- **Doebner-Miller reaction**: $\alpha,\beta$-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:

- 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.

\[
\text{A. Pictet and T. Spengler, Ber. 44, 2030 (1911)}
\]

**Synthesis of Tadalafil**

\[
\text{(Diagram showing the synthesis of Tadalafil)}
\]

---

**Isoquinolines**

- Pomeranz-Fritsch Reaction

\[
\text{C. Pomeranz, Monatsh. 14, 116 (1893)}
\]
\[
\text{P. Fritsch, Ber. 26, 419 (1893)}
\]

- Schlittler-Müller Reaction

\[
\]
Quinolones

• Retrosynthesis

Synthesis

Thiadiazoles

• Synthesis of Timolol (β-blocker)
Benzodiazepines

- The retrosynthesis of diazepam

\[ \text{Diazepam} \rightarrow \text{NH} + \text{Cl} + \text{Cl} \]

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

\[ \text{Cl} + \text{NH} + \text{CH}_3 \rightarrow \text{Cl} + \text{N} + \text{O} + \text{CH}_3 \]

\[ \text{C} + \text{H} + \text{C} + \text{H} \]

\[ \text{Ac}_2\text{O} \]

\[ \text{Cl} + \text{Cl} \]

\[ \text{NH}_3 \]

\[ \text{Cl} + \text{N} + \text{O} + \text{C} + \text{H} + \text{3} + \text{O} \]

\[ \text{Cl} + \text{N} + \text{O} + \text{C} + \text{H} + \text{3} + \text{O} \]

\[ \text{Diazepam} \]

---

Benzodiazepines

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

\[ \text{R}_3\text{CO} + \text{H}_2\text{NN}_2 + \text{R}_2\text{H}_\text{O} + \text{CN}_\text{R}_4 \rightarrow \text{R}_3\text{N}_2\text{R}_2\text{O}_\text{R}_4 \]


\[ \text{R}_3\text{N}_2\text{R}_2\text{O}_\text{R}_4 \]

\[ \text{R}_3\text{N}_2\text{R}_2\text{O}_\text{R}_4 \]

\[ \text{AcMe}\text{MeCH}_3 \]

\[ \Delta \]

---