Synthesis of Substituted Imidazoles via Organocatalysis

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Imidazoles as Targets in Medicinal Chemistry

Imidazole CSAID Ligands -- SKB

Orally available Angiotensin II inhibitor -- Lilly

Losartan

Eprosartan

p38 MAP kinase inhibitors
Debus Reaction

**Debus imidazole synthesis**

\[ \text{Reaction provides 2-monosubstituted, and 2,(3,4 homo)trisubstituted imidazoles} \]

Proposed Mechanism of the Debus Reaction

\[ \text{R}-\text{NH} \quad \text{H} \quad \text{H} \quad \text{NH} \quad \text{R} \]

\[ \text{R} \quad \text{H} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{R} \]

\[ \text{R} \quad \text{NH}_3 \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{R} \]

Michael Rishel @ Wipf Group 4 3/27/04
Wallach Reaction

Wallach chloroimidazole synthesis

\[
\begin{align*}
R & \quad \text{II} \\
\text{O} & \quad \text{PCl}_5, \text{POCl}_3 \\
\text{heat} & \quad \\
\text{Provides 1,2 disubstituted chloroimidazoles} \\
\end{align*}
\]

Proposed Mechanism of the Wallach Reaction

TosMIC Based Imidazole Synthesis

Synthesis from TosMIC

1. NaH, DME
2. H2O
3. K2CO3, MeOH

Process regioselectively provides 1,5-di and a limited number of 1,4,5-trisubstituted imidazoles

TosMIC = tosylmethyl isocyanide

Mechanism of TosMIC based Imidazole Synthesis

\[
\text{O=S} \quad | \quad \text{N=C} \quad | \quad \text{R''} \quad + \quad \text{R'N} \quad \rightarrow \quad [3+2] \quad \rightarrow \quad \text{R''R} \quad \rightarrow \quad \text{R''R} \quad + \quad \text{SO}_3^- 
\]
An Extension of the TosMIC chemistry

R' = H or Alk
R" = H or Alk
R and R' cannot both = Alk

Process regioselectively provides 4, 1,4, and 4,5 mono- and disubstituted imidazoles
1,4,5 trisubstituted imidazoles are not easily made with this methodology as a regioisomeric mixture of products results.

Modified TosMIC Imidazole Mechanism
Synthesis of Imidazoles from Amidines

Selective synthesis of 1,2,5 substituted imidazoles

\[
\text{NH} \quad \text{R}^' \quad \text{NHR}' + \quad \overrightarrow{\text{OR}''} \quad \text{Br} \quad \overrightarrow{\text{X}} \quad \text{K}_2\text{CO}_3 \quad \text{CHCl}_3, \text{H}_2\text{O} \quad \text{R} \quad \text{N} \quad \text{R}^' \quad \text{X} \quad \text{major} + \quad \text{R} \quad \text{N} \quad \text{R}^' \quad \text{X} \quad \text{minor}
\]

\( X = \text{CHO}, \text{CN} \)

modest yields, good selectivity amenable to the synthesis of multikilogram quantities of pharmaceutical intermediates

Imidazoles from Amidines -- Mechanism
Imidazole carboxylates from BICAs

1,5 imidazole carboxylates from amines and 3-bromo-2-isocyanoacrylates (BICAs)


Complementary to the amidine methodology
BICA Mechanism

\[ R'NH_2 + Br\text{NC}
\text{COOMe} \rightarrow R\text{NHR'}\text{NC}
\text{COOMe} \]

\[ \text{A} \]

\[ \text{B} \]

\[ \text{R'HN} \text{NC}
\text{COOMe} \]

\[ \text{C} \]
Hetero Cope Rearrangement -- A Strategy to Highly Substituted Imidazoles

Hetero-Cope Rearrangements to regioselectively provide highly Substituted imidazoles

Mechanism of the Hetero Cope Rearrangement Approach
Highly Substituted Imidazoles From ketoamides

Regioselective synthesis of tetrasubstituted imidazoles from ketoamides under neutral reaction conditions

\[
\begin{align*}
\text{ammonium trifluoroacetate} \\
\implies \\
\text{Methodology tolerates variance at positions 1,2 and 5 quite well.} \\
\text{Position 4 usually, but not always, aromatic.}
\end{align*}
\]

Synthesis of \(-\)-Ketoamides… Nontrivial??
A Traceless Synthesis of \( \alpha \)-Ketoamides

A traceless entry into \( \alpha \)-ketoamides -- and tetrasubstituted imidazoles

Thiazolium Catalyzed Synthesis of \(-\)-Ketoamides

\[
\begin{align*}
R_1 \text{CHO} + \text{R}_2\text{N} + \text{R}_3\text{NH}_2 \rightarrow \text{R}_2\text{N} + \text{R}_3\text{NH}_2
\end{align*}
\]

Mechanism of \(-\)-Ketoamide Synthesis by Organocatalysis

Regioselective, “One Pot” Synthesis of Substituted Imidazole

\[
\text{PyCHO} + \text{PhSO}_2\text{NH} + \text{PhSO}_2\text{NH} \xrightarrow{(5 \text{ mol\%} \text{ Et}_3\text{N}, \text{5 equiv} \text{ THF, 50 }^\circ\text{C})} \text{Imidazole}
\]

\[
\text{NH}_4\text{OAc} \xrightarrow{(15 \text{ equiv}) \text{ reflux 12 h}} \text{product 4 (76\%)}
\]
One-Pot Synthesis of Di- and Trisubstituted Imidazoles

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>47%&lt;sup&gt;b&lt;/sup&gt; 68%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>82%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>78%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>55%&lt;sup&gt;b&lt;/sup&gt; 82%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>35%&lt;sup&gt;b&lt;/sup&gt; 58%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>42%&lt;sup&gt;b&lt;/sup&gt; 61%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Image" /></td>
<td>83%&lt;sup&gt;c&lt;/sup&gt; &gt;98% ee</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Image" /></td>
<td>48%&lt;sup&gt;b&lt;/sup&gt; 73%&lt;sup&gt;c&lt;/sup&gt; &gt;98% ee</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction yields and isolations were not optimized and represent the result of a single experiment. <sup>b</sup> Product isolated by crystallization from the crude product mixture. <sup>c</sup> Product isolated by SiO<sub>2</sub> chromatography.
Synthesis of Tetrasubstituted Imidazoles

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>isolated yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Chemical Structure 1]</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>![Chemical Structure 2]</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>![Chemical Structure 3]</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>![Chemical Structure 4]</td>
<td>75%</td>
</tr>
</tbody>
</table>

* Reaction yields were not optimized and represent the result of a single experiment. Products isolated by SiO₂ chromatography.
Application to the Synthesis of Substituted Oxazoles and Thiazoles

Scheme 3

\[
\text{CHO} + \text{Tol-SO}_2\text{O} \xrightarrow{\text{Et}_3\text{N}, \text{Toluene}, 50^\circ\text{C}} \text{N} \text{ \text{OH}} (5\text{ mol}\%)
\]

1) \[ \xrightarrow{\text{PPh}_3, \text{I}_2} \]

2) Lawesson's reagent

\[
\begin{align*}
\text{17} & \quad 77\% \\
\text{18} & \quad 50\%
\end{align*}
\]
Conclusions

- A rapid, one-pot, regioselective, organocatalyzed synthesis of highly functionalized imidazoles from \( β \)-ketoamides has been described.

- The methodology has been extended to the synthesis of substituted oxazoles and thiazoles.