Facile preparation of $\alpha$-amino ketones from oxidative ring-opening of aziridines by pyridine $N$-oxide


{[Chemical structure image]}

John Maciejewski

*Current literature*

01/05/08
**α-Amino ketones**

Shown to treat symptoms assoc. with common cold


Rupintrivir

Natural product found in leaves of *Catha edulis* Forsk


Active against brucellosis (Malta fever)

*AAC* **2007**, *51*, 3752

*K*<sub>i</sub> values

<table>
<thead>
<tr>
<th>Caspase-3</th>
<th>Caspase-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 nM</td>
<td>4.0 nM</td>
</tr>
</tbody>
</table>

Potent caspase inhibitors

*Org. Lett.* **2005**, *7*, 3529
α-Amino ketone preparation

Often important synthetic intermediates

(-)-aphanorphin

key synthetic intermediate

Begin from chiral pool

Synthesis 2007, 1, 55

Other methodologies include the following:

J. Het. Chem. 1984, 21, 1509

Org. Lett. 2007, 9, 3671

Cinchona alkaloids afford α–amino ketones in high enantioselectivity
Preparation of $N$-oxides

*Mild oxidants, easily prepared*

\[
\begin{align*}
\text{MMPP}^* & \quad \rightarrow & \quad \text{(Product)} \\
\text{RuCl}_3 \text{(cat.)} & \quad \rightarrow & \quad \text{(Product)} \\
\end{align*}
\]

$magnesium\ monoperoxyphthalate$

*J. Org. Chem.*, 2007, 72, 6653

Other methods of $N$-oxide preparation include use of peracids, $\text{H}_2\text{O}_2$, and $\text{O}_2$ with catalysts

\[
R^1\text{N}^+\text{R}^3 \quad \xrightarrow{\text{conditions}} \quad R^1\text{O}^-\text{R}^3
\]

*Synthesis* 1993, 3, 263 (and references therein)

\[
\begin{align*}
\text{N}^+\text{O}^- & \\
\text{~71 kcal/mol} & \\
\text{J. Chem. Thermodynamics} \textbf{1995}, 27, 391
\end{align*}
\]
Applications for \(N\)-oxides

\[
\begin{align*}
\text{\(N\)-oxide (TMANO)} & \quad \text{and} \quad \text{\(N\)-oxide (NMO)} & \quad \text{not to be confused with} \quad \text{nitrooxyl free radical (TEMPO)}
\end{align*}
\]

\[
\begin{align*}
\text{Upjohn dihydroxylation} & : \quad \text{R} - \xrightarrow{\text{OsO}_4/NMO} \text{R} - \text{OH} - \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{Ley oxidation} & : \quad \text{R} - \text{OH} \xrightarrow{\text{TPAP/NMO}} \text{R} - \text{CO}
\end{align*}
\]

\[
\begin{align*}
\text{Ganem oxidation} & : \quad \text{R} - \text{Br} \xrightarrow{\text{DMSO/TMANO}} \text{R} - \text{CO}
\end{align*}
\]

\(N\)-oxides used to regenerate transition metal catalysts
Applications for oxides of sulfur

\[
\begin{align*}
\text{R-Br} & \xrightarrow{\text{DMSO, } B} \text{R-O} \\
\text{O-S} & \xrightarrow{\text{[2,3]}} \text{R-O-S}^{+} \\
\end{align*}
\]

*Kornblum oxidation*

*J. Am. Chem. Soc., 1957, 79, 6562*

Applications with aziridines

\[
\begin{align*}
\text{R}^{1}\text{R}^{2} & \xrightarrow{\text{DMSO}} \text{NCO}^{2}\text{R}^{3} \\
\end{align*}
\]

*Tetrahedron 1970, 26, 4347*

Aziridine opened with DMSO, followed by loss of SMe\(_2\) to afford amino ketone

Drawbacks: DMSO is often difficult to remove, in addition to noxious byproduct (SMe\(_2\))
Oxidative ring-opening of aziridines

Recent advances

\[
\begin{align*}
\text{IBX promotes amino ketone formation, which is facilitated by } \beta-\text{CD}
\end{align*}
\]

\[J. \text{ Org. Chem.}, \textbf{2003}, \textit{68}, 9119\]

\[\text{Tetrahedron Lett.}, \textbf{2005}, \textit{46}, 4111\]

The CAN/NBS system allows selective oxidation to the amino ketone
Oxidative ring-opening of aziridines


Initial investigations tested 1-10 equiv. of DMSO in CH$_2$Cl$_2$, THF, MeCN, benzene, EtOAc, and Et$_2$O

Investigations using pyridine $N$-oxide (1.2 equiv.) DMF at 80°C provided the desired $\alpha$-amino ketone in 60% yield

Toluene at 80°C proved to give best results (70-80% yields)

Increasing oxidant loading to 2-3 equiv. did not improve yields
Oxidative ring-opening of aziridines

Table 1  Oxidative ring opening of aziridine 1b with different amine oxides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine N-oxide 2</th>
<th>Time/h</th>
<th>Yield of 3b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyridine N-oxide</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>4-Methoxypyridine N-oxide</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>4-Acetylpyridine N-oxide</td>
<td>40</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>3-Methylpyridine N-oxide</td>
<td>15</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Collidine N-oxide</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>Quinoline N-oxide</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>Me₃N N-oxide</td>
<td>4</td>
<td>22ᵇ</td>
</tr>
<tr>
<td>8</td>
<td>N-Morpholine N-oxide</td>
<td>5</td>
<td>14ᵇ</td>
</tr>
</tbody>
</table>

* Run at 80 °C in toluene using 1.2 eq. of amine oxide.ᵇ 60% yield of product 4 was also separated.

Electron donating pyridines accelerated reaction, but did not increase yield

Electron withdrawing pyridines resulted in trace product after 40 h

Sterically hindered substrates such as collidine gave low yields

Aliphatic amines gave low yields of α-amino ketones, with undesired amino alcohol in moderate yields
Oxidative ring-opening of aziridines

Table 2  Oxidative ring-opening of aziridines using pyridine N-oxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aziridine</th>
<th>Time/h</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>24</td>
<td>3a</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>48</td>
<td>3b</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>64</td>
<td>3c</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>12</td>
<td>3d</td>
<td>80</td>
</tr>
</tbody>
</table>

Oxidation proceeds in good yields with 5- and 6-membered rings
### Oxidative ring-opening of aziridines

**Table 2** Oxidative ring-opening of aziridines using pyridine N-oxide

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<tr>
<th>Entry</th>
<th>Aziridine</th>
<th>Time/h</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image1.png" alt="Image" /></td>
<td>10</td>
<td><img src="image2.png" alt="Image" /></td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3.png" alt="Image" /></td>
<td>10</td>
<td><img src="image4.png" alt="Image" /></td>
<td>55</td>
</tr>
<tr>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image5.png" alt="Image" /></td>
<td>20</td>
<td><img src="image6.png" alt="Image" /></td>
<td>74</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image7.png" alt="Image" /></td>
<td>24</td>
<td><img src="image8.png" alt="Image" /></td>
<td>20</td>
</tr>
<tr>
<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image9.png" alt="Image" /></td>
<td>24</td>
<td><img src="image10.png" alt="Image" /></td>
<td>82</td>
</tr>
</tbody>
</table>
Oxidative ring-opening of aziridines

Mechanism of oxidation

Mechanism explains formation of amino ketone, but not amino alcohol.

Aliphatic amine oxides provide low yields of desired amino ketone, but moderate yields of amino alcohol

<table>
<thead>
<tr>
<th></th>
<th>Me₃N N-oxide</th>
<th>4</th>
<th>22ᵇ</th>
</tr>
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<tr>
<td>8</td>
<td>N-Morpholine N-oxide</td>
<td>5</td>
<td>14ᵇ</td>
</tr>
</tbody>
</table>

*a Run at 80 °C in toluene using 1.2 eq. of amine oxide. b60% yield of product 4 was also separated.*
Oxidative ring-opening of aziridines

Proposed mechanism of oxidation

Aliphatic amine oxides have acidic hydrogen, where pyridine $N$-oxides do not

Authors did not address (or reference) the mechanism for the formation of amino alcohols

Interesting method for preparing amino alcohols
Summary and Conclusions

*Oxidative ring-opening of aziridines*

Pyridine $N$-oxides are efficient reagents for the oxidative ring-opening of aziridines. The desired $\alpha$-amino ketones were obtained in good yields on various substrates. Aliphatic $N$-oxides primarily afford the amino alcohol over the $\alpha$-amino ketone. Future work includes the development of an asymmetric version (chiral amines?)