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Stereoselective Synthesis of Erythro α-Amino Epoxides

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Abstract: The stereoselective reduction of bromomethyl ketones derived from leucine, phenylalanine, alanine and valine is described using borohydride reagents. The Boc-amino alcohol product has erythro stereochemistry at the carbinol center as deduced by conversion to Boc-amino epoxides. These oxiranes are useful for the preparation of hydroxyethylene peptide isosteres.

The hydroxyethylene amide isostere 1 is widely employed in aspartic protease inhibitors\(^1\) and is frequently accessed by nucleophilic opening of an amino epoxide (figure 1). The threo oxirane 2 is selectively obtained by epoxidation of an allylic amine 3\(^2\), while the erythro isomer 4 is less specifically generated by reduction of an α-haloketone 5, followed by base induced ring closure.\(^3\) The objective of this study was to survey reducing agent, solvent and temperature variables in an effort to identify a more stereoselective and potentially general route to 4 from 5, thereby improving the efficiency of this route for elaboration of hydroxyethylene based enzyme inhibitors.\(^1\)\(^;\)\(^3\)

Figure 1:

\[
\begin{align*}
&\text{R}_2\text{HN} &\text{R}_2\text{HN} \\
&\text{R}_1 &\text{R}_1 \\
&2 &1 \\
\Rightarrow &\text{R}_2\text{HN} &\text{R}_2\text{HN} \\
&\text{O} &\text{O} \\
&\text{Nu} &\text{Nu} \\
&\text{R}_1 &\text{R}_1 \\
&3 &5 \\
&\text{R}_2\text{HN} &\text{R}_2\text{HN} \\
&\text{R}_1 &\text{R}_1 \\
&4 &\text{X}
\end{align*}
\]

The preparation of bromomethyl ketones 5 derived from leucine, phenylalanine, valine and alanine was carried out by treatment of the corresponding diazoketones with concentrated (48%) aqueous HBr in ether at -20°C (Scheme 1). This biphasic reaction is quite clean and rapid\(^3\)\(^a\) and the product can be conveniently isolated by crystallization from the reaction mixture. This sequence has been successfully and reproducibly carried out on up to a 30 mmol scale and can be easily completed in less than one day.
Scheme 1:

\[
\text{BocHN} \overset{-\text{CO}_2\text{H}}{-\text{R}} \text{ \ (1) isobutyl chloroformate, NMM, THF, 0°C, 20 min} \rightarrow \text{BocHN} \overset{-\text{Br}}{-\text{R}}
\]

1) isobutyl chloroformate,
2) CH\text{2N}2, Et\text{2O}, 0°C, 3h
3) 48% HBr, Et\text{2O}, -20°C,

6a) R=isobutyl
b) R=CH\text{2Ph}
c) R=isopropyl
d) R=Me

15-30 min.

The reduction of 5a (Scheme 2) was surveyed using the reagents, solvents and conditions listed in Table 1. For each entry in Table 1, the crude reaction mixture was examined following workup by NMR to determine the stereoselectivity of the reduction by integration of the NH proton signals which were clearly resolved at 4.6 and 4.7 ppm in CDCl\text{3} solution. In those cases where diastereomers were produced, they could not be distinguished by analytical tlc. It was possible to separate a sample of the major isomer 7e (mp 93-94°C) from the mixture by crystallization from hexanes. When a single isomer was indicated by NMR, simple recrystallization from hexanes provided the yield indicated in the Table. The NMR data was supported by HPLC analysis\textsuperscript{4} of the reaction mixture which indicated that a trace amount (\leq 3\%) of the \textit{threo} isomer 7t was present. In those cases where substantial amounts of the \textit{threo} diastereomer were produced, the ratio determined by NMR was consistent with that measured by HPLC.

Scheme 2:

\[
\text{BocHN} \overset{-\text{CO}_2\text{Br}}{-\text{R}} \rightarrow \text{BocHN} \overset{-\text{OH}}{-\text{R}} + \text{BocHN} \overset{-\text{Br}}{-\text{R}}
\]

Table 1: Reduction of 2a by Hydride Reagents

<table>
<thead>
<tr>
<th>reagent</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>7e:7t</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH\textsubscript{4}</td>
<td>EtOH</td>
<td>-78</td>
<td>97:3</td>
<td>71</td>
</tr>
<tr>
<td>NaBH\textsubscript{4}</td>
<td>THF</td>
<td>-78</td>
<td>1:1</td>
<td>75</td>
</tr>
<tr>
<td>NaBH\textsubscript{4}</td>
<td>THF</td>
<td>0</td>
<td>1:1</td>
<td>a</td>
</tr>
<tr>
<td>LiBH\textsubscript{4}</td>
<td>THF</td>
<td>-78</td>
<td>4:1</td>
<td>a</td>
</tr>
<tr>
<td>Zn(BH\textsubscript{4})\textsubscript{2}</td>
<td>THF</td>
<td>-78</td>
<td>2:1</td>
<td>a</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>THF</td>
<td>-78</td>
<td>97:3</td>
<td>60</td>
</tr>
<tr>
<td>LiAIH(OtBu)\textsubscript{3}</td>
<td>Et\text{2O}</td>
<td>0</td>
<td>1:2</td>
<td>a</td>
</tr>
<tr>
<td>LiAIH(OtBu)\textsubscript{3}</td>
<td>THF</td>
<td>-78</td>
<td>2:1</td>
<td>65</td>
</tr>
<tr>
<td>DiBAL-H</td>
<td>CH\text{2Cl}2</td>
<td>-78</td>
<td>8:1</td>
<td>65</td>
</tr>
<tr>
<td>DiBAL-H</td>
<td>PhCH\text{3}</td>
<td>-78</td>
<td>5:1</td>
<td>a</td>
</tr>
</tbody>
</table>

a) product alcohols not isolated; isomer ratio determined as described in text
Two different reagent/solvent combinations, NaBH₄ in ethanol and L-Selectride in THF, led nearly exclusively to generation of the *erythro* isomer. For comparison, Dufour and coworkers⁵ reported that reduction of the chloromethyl analog of 5a with NaBH₄ in methanol at 0°C gave a 6:1 ratio of 7e:7t. As observed previously⁵, NaBH₄ in THF at 0°C gave a 1:1 ratio of alcohols. Interestingly, lowering the reaction temperature to -78°C did not improve stereoselectivity. At -78°C, DiBAL-H furnished an 8:1 mixture of *erythro:* *threo* diastereomers in methylene chloride and a 5:1 ratio in toluene.

The stereochemistry of the major amino alcohol 7e was established by conversion (KOH/EtOH) to the corresponding epoxide, 8 (Scheme 3). Luly et al.²ᵃ have previously reported that the oxirane methine of the *erythro* compound was observed at 2.84 ppm, while in the *threo* diastereomer it resonates at 2.99 ppm. In compound 8, the oxirane methine was seen at 2.84 ppm and none of the isomeric material was detected by ¹H, ¹³C NMR or HPLC.

The generality of the stereoselective reduction of 5a was extended first to 5b, a precursor to a medicinally important¹⁻³ hydroxyethylene isostere found in HIV-1 protease inhibitors. (Scheme 4). Using NaBH₄ in EtOH at -78°C, only one product could be observed in the crude reaction mixture by HPLC and NMR and the product alcohol 9b was isolated in good yield by crystallization of the reaction mixture. Product stereochemistry was confirmed by conversion to epoxide 10b, followed by comparison to published NMR data.²ᵃ,³ᵃ Analogous treatment of bromomethyl ketones 5c and 5d with NaBH₄ afforded single amino alcohols (NMR and HPLC) 9c (72%) and 9d (87%). It was possible to carry out the reduction of 5c at 0°C and retain exclusive *erythro* reduction. This is most likely a direct result of the steric effect of the isopropyl group.³ᵃ,⁵ Valine derivative 9e was converted to 10e as described for 9b. In this compound, the epoxide methine was observed at 2.85 ppm, suggestive of the *erythro* orientation, by analogy with 8.

The stereochemical outcome of the reduction of 5a-d by the reducing agents employed in this study is consistent with the model proposed by Dufour et al.⁵ The stereospecificity observed with NaBH₄ in ethanol is dependent on the substrate (e.g. 5c), and on a combination of temperature and solvent. Among the metal borohydride reagents, solvent makes an important contribution, possibly by affecting the nature of the species which delivers hydride.⁹ Others have reported highly stereocontrolled reduction of 5b, but the outcome could
not be generalized to other systems, as seen here. A comparison of these results with others\textsuperscript{2-3,5} indicates that with NaBH\textsubscript{4} in alcoholic solvents, lower temperature improves the stereoselectivity. It is not necessary to carry out the reaction at -78\textdegree, identical results have been obtained with 5a at -45\textdegree. Temperatures between 0\textdegree and -45\textdegree have not been investigated.

In summary, NaBH\textsubscript{4} in ethanol and L-Selectride in THF at subzero temperatures stereospecifically reduce N-Boc bromomethyl ketones to the \textit{erythro} diastereomer in good yield in four different substrates. This appears to represent a general approach that does not rely solely on steric factors in the ketone. These results nicely complement the \textit{threo} selective epoxidation route\textsuperscript{2}, and allows more efficient preparation of \textit{erythro} hydroxyethylene peptide isosteres\textsuperscript{11}.

\textbf{Acknowledgments:} The suggestions of Drs. John Mallamo, Sankar Chatterjee and Chakrapani Subramanyam were instrumental in the completion of this research.

\textbf{References:}
7) Reference 3a claims preparation of valine chlorohydrin, but no data were given.
10) Boc-amino alcohol 9b: mp 100-103\textdegree(C hexanes), NMR: 0.89 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H), 1.44 (s, 9H), 2.15-2.22 (m, 1H), 2.67 (br s, 1H), 3.42-3.72 (m, 4H), 4.45 (d, J=9.6 Hz, 1H). IR (KBr) 3450, 2940, 1670, 1505, 1300, 1165, 1030, 1005. Anal. calc. C 44.60, H 7.49 N 4.73. obs. C 44.95, H 7.51, N 4.76.
Boc-amino epoxide 10c: mp 70-72\textdegree(C hexanes), NMR: 0.98 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.8 Hz, 3H), 1.44 (s, 9H), 1.94 (dd, J=6.8, 12.9 Hz, 1H), 2.74-2.77 (m, 2H), 2.87 (dd, J=3.2, 5.2, 7.1 Hz, 1H), 3.19-3.22 (m, 1H), 4.51 (d, J=8.9 Hz, 1H). \textsuperscript{13}C: 17.5, 19.2, 28.4, 31.6, 45.8, 53.2, 56.0, 156.2. IR (KBr): 3315, 2920, 1670, 1510, 1300, 1265, 1155. anal. calc. C 61.39 H 9.83 N 6.51. obs. C 61.69 H 9.99 N 6.49.
11) After this work was completed, a report describing an alternative, stereospecific approach to N-Boc amino epoxides was published: Castejon, P.; Fasto, M.; Moyano, A.; Pericas, M. A.; Riera, A. \textit{Tet. Letters} \textbf{1995}, \textit{36}, 3019.

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