A SYNTHESIS OF 3-(α,β-EPOXY)-2-AZETIDINONES DERIVATIVES

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Abstract Condensation of 1-phenyl-2-azetidinone with α-methylthio ketones yielded the corresponding β-hydroxy sulfides, which were converted to 3-(α,β-epoxy)-1-phenyl-2-azetidinones through two steps involving desulfurization of the sulfonium iodides. In a similar fashion, condensation of 1-phenyl-2-azetidinone with ethyl α-methylthioacetates gave the corresponding sulfenyl ketones, which were also converted to the 3-(α,β-epoxy)-2-azetidinone derivatives. These 2-azetidinones were further lead to α-anilinomethyl-1,2-butenolides by treatment with methanesulfonic acid.

In our continuing efforts aimed at the synthetic utility of 2-azetidinones as a source of heterocyclic compounds, we found that the epoxides of 1-phenyl-3-vinyl-2-azetidinones were easily converted to α-anilinomethyl-1,2-butenolides by treatment with methanesulfonic acid in benzene. (See Scheme 1).

\[ R_2 \rightarrow \text{LDA} \rightarrow R_2 \]

\[ i) \text{LDA} \rightarrow \text{m-CPBA} \]

\[ R_2 \rightarrow R_1 \rightarrow R_2 \rightarrow \text{NHCO}_{2} \text{H}_{5} \]

Scheme 1
Since those 1,2-butenolides were found to be useful intermediates leading to \( \alpha \)-methylene-\( \gamma \)-butyrolactones and 3-methylfuran derivatives, we have further investigated the alternative facile approach to the 3-(\( \alpha \),\( \beta \)-epoxy)-2-azetidinone derivatives by an application of desulfurization of \( \beta \)-hydroxy sulfonium iodides in the formation of oxirane moiety. These results were described in this paper. Condensation of lithium salt of 1-phenyl-2-azetidinone (1) with \( \alpha \)-methylthioacetone (2a) at \(-78^\circ \text{C}\) afforded the \( \beta \)-hydroxy sulfide (3a) as a mixture of stereoisomers in 70\% yield, mp 68-79 °C, m/e 251 (M\(^+\)), 233 (M\(^+\)-18). Methylation of 3a with methyl iodide in methanol for 2 hr under reflux, followed by treatment of the resulting methylsulfonium iodide, without purification, with one equivalent of potassium \( t \)-butoxide in ethanol at room temperature for 0.5 hr gave the desired 3-(\( \alpha \),\( \beta \)-epoxy)-2-azetidinone (4a) as a mixture of stereoisomers in 53\% yield. In a similar fashion, 1 was condensed with \( \alpha \)-methylthioacetophenone (2b)\(^9\) and \( \alpha \)-methylthiopropionophenone (2c)\(^9\), to give the corresponding alcohols (3b, 68\%, oil) and (3c, 70\%, mp 76-83 °C), respectively. 3b and 3c were converted to the corresponding epoxides (4b, 48\%) and (4c, 50\%) through the same manner as above as outlined in the Scheme 2. These 2-azetidinones (3b), (3c), (4b) and (4c) should be considered to be a mixture of diastereomers according to their \(^1\)HNMR spectra (CDCl\(_3\)). Although the over all yields of the epoxides (4) were not improved comparing with those in the previous method, this approach might be useful when one wishes to prepare 4 and related compounds without using oxidative conditions.

\[ \text{Scheme 2} \]

Successively, we examined the condensation of 1 with ethyl methylthioacetate (5a) at \(-78^\circ \text{C}\) to give 3-methylthioacetyl-1-phenyl-2-azetidinone (6a), reduction of which with sodium borohydride in methanol at \(-78^\circ \text{C}\) afforded the diastereo-
isomeric mixture of the 6-hydroxy sulfide (7a) in nearly quantitative yield.

Methylation of 7a with methyl iodide in methanol under reflux for 2 hr, followed by treatment of the resulting sulfonium iodide, without purification, with potassium t-butoxide yielded the corresponding epoxide (8a) as a mixture of diastereomers in 30 % yield accompanied by the formation of 1 (20 %) and 7a (25 %). These were separated by column chromatography on silica gel. Elution with benzene-chloroform (1:1) gave 1 and elution with benzene-chloroform (2:3) afforded 8a. 7a was obtained from the benzene-chloroform (1:2) fraction. In a similar fashion, the reaction of lithium salt of 1 with the ester (5b) and (5c) yielded the corresponding 3-acyl-1-phenyl-2-azetidinones (6b) and (6c) as diastereoisomeric mixtures. These were smoothly converted to the diastereoisomeric mixtures of the epoxides (8b) and (8c), respectively, via 6-hydroxy sulfides (7b) and (7c) as shown in the Scheme 3. Treatment of 8a-8c with methanesulfonic acid in benzene under reflux gave the a-anilinomethyl-1,2-butenolides (9a) and (9c), respectively, in 70-75 % yield.

\[
\begin{align*}
1 & \xrightarrow{1) \text{LDA}} 1 \xrightarrow{2) \text{R-CH-COOEt}} 6 \xrightarrow{3) \text{CH}_3I} 8 \\
& \xrightarrow{2) \text{t-BuOK}} 7 \xrightarrow{3) \text{t-BuOK}} 9
\end{align*}
\]

a: R=H; b: R=CH₃; c: R=CH₃CH₂

Scheme 3

-591-
Table 1. Physical Data of 6, 7, 8 and 9

<table>
<thead>
<tr>
<th>Compd</th>
<th>Yield (%)</th>
<th>mp °C</th>
<th>m/c (M+</th>
<th>1H NMR (CDCl3) δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>75</td>
<td>80-83</td>
<td>235</td>
<td>2.11 (s, 3H), 3.30 (d, J=14 Hz, 1H), 3.66 (d, J=14 Hz, 1H), 3.68 (t, J=6.0 Hz, 1H), 4.08 (d, J=3 and 6 Hz, 1H), 4.79 (d, d, J=3 and 6 Hz, 1H), 6.93-7.47 (m, 5H)</td>
</tr>
<tr>
<td>6b</td>
<td>72</td>
<td>98-100</td>
<td>249</td>
<td>1.42 (d, J=6.5 Hz, 3H), 1.96 (s, 3H), 3.56-4.17 (m, 3H), 4.96 (d, d, J=3 and 5 Hz, 1H), 6.93-7.40 (m, 5H)</td>
</tr>
<tr>
<td>6c</td>
<td>73</td>
<td>80-82</td>
<td>263</td>
<td>0.80-1.18 (m, 3H), 1.48-2.03 (m, 2H), 1.92 (s, 3H), 3.53 (t, J=7 Hz, 1H), 3.66 (t, J=5.5 Hz, 1H), 4.10 (d, d, J=3 and 5.5 Hz, 1H), 4.95 (d, d, J=3 and 5.5 Hz, 1H), 6.95-7.43 (m, 5H)</td>
</tr>
<tr>
<td>7a</td>
<td>96</td>
<td>106-108</td>
<td>237</td>
<td>2.13 (s, 3H), 2.60-4.34 (m, 6H), 6.88-7.48 (m, 5H)</td>
</tr>
<tr>
<td>7b</td>
<td>95</td>
<td>104-106</td>
<td>251</td>
<td>1.36 (d, J=6 Hz, 3H), 2.13 (s, 3H), 2.63-4.18 (m, 5H), 6.93-7.45 (m, 5H)</td>
</tr>
<tr>
<td>7c</td>
<td>95</td>
<td>102-106</td>
<td>265</td>
<td>1.09 (t, J=7.5 Hz, 3H), 1.34-1.94 (m, 2H), 2.14 (s, 3H), 2.58 (d, t, J=9.5 and 5.5 Hz, 1H), 3.52-3.82 (m, 2H), 3.98-4.14 (m, 1H), 6.91-7.36 (m, 5H)</td>
</tr>
<tr>
<td>8a</td>
<td>30</td>
<td>oil</td>
<td>189</td>
<td>2.58-3.81 (m, 6H), 6.92-7.43 (m, 5H)</td>
</tr>
<tr>
<td>8b</td>
<td>68</td>
<td>109-120</td>
<td>203</td>
<td>1.41 (broad d, J=5 Hz, 3H), 2.98-3.90 (m, 5H), 6.90-7.47 (m, 5H)</td>
</tr>
<tr>
<td>8c</td>
<td>70</td>
<td>69-79</td>
<td>217</td>
<td>1.16 (t, J=7 Hz, 3H), 1.65 (d, t, J=7 and 14 Hz, 2H), 2.93-3.85 (m, 5H), 6.85-7.39 (m, 5H)</td>
</tr>
<tr>
<td>9a</td>
<td>83</td>
<td>73-75</td>
<td>189</td>
<td>4.03 (d, J=2 Hz, 1H), 4.10 (d, J=2 Hz, 1H), 4.73 (d, 2 Hz, 1H), 4.80 (d, J=2 Hz, 1H), 6.48-7.35 (m, 6H)</td>
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<tr>
<td>9b</td>
<td>75</td>
<td>oil</td>
<td>203</td>
<td>1.38 (J=7 Hz, 3H), 4.04 (broad s, 2H), 4.78-5.23 (m, 1H), 6.43-7.37 (m, 6H)</td>
</tr>
<tr>
<td>9c</td>
<td>75</td>
<td>oil</td>
<td>217</td>
<td>0.94 (t, J=7 Hz, 3H), 1.23-2.35 (m, 2H), 4.07 (broad s, 2H), 4.73-5.07 (m, 1H), 6.44-7.42 (m, 6H)</td>
</tr>
</tbody>
</table>

References

10. All new compounds gave satisfactory microanalysis or high resolution mass spectral data.

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