Stereoselective synthesis of 1,3-oxazolines by the reaction of steroidal oxiranes with acetamide

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The reaction of 3~-acetoxy-5,6a-epoxy-5a-cholestane 1, 3~-chloro-5,6a-epoxy-5a-cholestane 2 and 5,6a-epoxy-5a-cholestane 3 with acetamide in THF at room temperature in the presence of LiBr as catalyst afford selectively the corresponding steroidal, cis-1,3-oxazolines 4-6 in high yields. The structures of these compounds 4-6 have been established on the basis of their elemental analyses and spectral data.

Keywords: Stereoselective synthesis, oxazolines, steroidal oxiranes, acetamide

IPC: Int.C1.8 C 07 D

Oxazolines are used in the development of chiral ligands used for asymmetric catalysis1-12, are used in synthesis13-14 and provide a useful means for the protection of amino alcohols or carboxylic acids. Many methods for the synthesis of oxazolines have been reported15-19 and some of them were found to possess anti HIV activities20. Oxazolines have been proved to be quite valuable in the synthesis of structurally interesting and biologically active natural products including Podophyllotoxin21 and Schizandrin22. Kihara et al.13 have reported a selective method for the preparation of trans- 1,3-oxathiolane-2-thiones by using alkali metal halides. Lee et al.9 have recently reported trans-oxazolines as the major product in the presence of base in Pd (O) catalysed reaction.

Recently we have reported a selective method for the preparation of steroidal cis-1,3-oxathiolane by the reaction of steroidal 5α,6α-epoxide with thioacetamide in the presence of LiBr as a catalyst14.

In continuation to our earlier studies14-16, herein we report a novel and convenient method for preparation of steroidal cis-1,3-oxazolines 4-6 at room temperature in high yields by the reaction of steroidal 5α, 6α-epoxides 1-3 with acetamide in THF using lithium bromide as catalyst (Scheme I). The cis-products were obtained selectively as the single product.

It is proposed that this reaction proceeds via nucleophilic attack of bromide ion at less substituted C-6 position of steroidal epoxide (Scheme II), the reaction of epoxide with lithium bromide is rate determining step15. Nitrogen being a better nucleophile than oxygen, nitrogen can attack on less substituted C-6 position since there is considerable amount of steric hindrance to ring closure from one side of the ring at C-6. These cis-oxazolines 4-6 were obtained selectively from the reaction of epoxides 1-3 with acetamide by double SN2 inversion on epoxide ring at C-6.

The structures of compounds 4-6 have been established on the basis of their physical and spectral data (Table I).

Experimental Section

All the melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 782 infrared spectrophotometer; 1H NMR spectra in CDCl3 at 200 MHz on a Jeol PMX-60/Brucker BZH-200 instrument using TMS as internal standard (chemical shifts in ppm); and mass spectra on a JMS D-300 mass spectrometer at 70 eV.

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane17 1 with acetamide in the presence of LiBr. A solution of LiBr (0.099 g, 0.111 mmoles) and 1 (1.0 g, 2.249 mmoles) in THF (25 mL) was stirred at room temperature for 5 min. Then acetamide (0.14 g, 2.4 mmoles) was added to the solution and the resulting mixture was stirred at room temperature for 3-4 hr. Progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified on a silica gel column (pet. ether-diethyl ether; 25:1) to give steroidal 3β-acetoxy-5α-cholestan-2'-methyl-1,3-oxazoline 4. It was recrystallized from methanol, yield 91%, m.p. 102°C. Its characterization data are given in Table I.

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestan17 2 with acetamide in the presence of LiBr. A similar reaction of 22 (1.0 g, 2.375 mmoles) with acetamide (0.15 g, 2.5 mmoles) in the presence of LiBr (0.01 g, 0.118 mmoles) in THF (25 mL) and stirring at room temperature for 5 hr afforded...
Scheme I

Scheme II
Table I—The characterization data of compounds 4-6

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (Calcd.)%</th>
<th>( ^1H ) NMR (CDCl(_3))</th>
<th>Mass ( m/z )</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C(<em>{31})H(</em>{31})N(_O_3)</td>
<td>76.63 (76.65)</td>
<td>10.61 (10.58)</td>
<td>2.92 (2.88)</td>
</tr>
<tr>
<td>4</td>
<td>102</td>
<td>91</td>
<td>C(<em>{29})H(</em>{48})NOCl</td>
<td>74.9 (75.0)</td>
<td>10.42 (10.46)</td>
<td>3.02 (3.03)</td>
</tr>
<tr>
<td>5</td>
<td>92</td>
<td>85</td>
<td>C(<em>{29})H(</em>{49})NO</td>
<td>81.46 (81.44)</td>
<td>11.58 (11.55)</td>
<td>3.30 (3.27)</td>
</tr>
</tbody>
</table>

3\(\beta\)-acetoxy-5\(\alpha\)-cholestan-2'-methyl-1', 3' -oxazoline 5. It was recrystallized from methanol, yield 85%, m.p. 92°C. Its characterization data are given in Table I.

Reaction of 5,6\(\alpha\)-epoxy-5\(\alpha\)-cholestan18 3 with acetamide in the presence of LiBr, A solution of LiBr (0.11 g, 0.128 mmole) and 3\(^{18}\) (1.0 g, 2.587 mmoles) in THF (25 mL) was similarly treated with acetamide (0.16 g, 2.75 mmoles) for 5-6 hr at room temperature to afford 5\(\alpha\)-cholestan-2'-methyl-1',3'-oxazoline 6. It was recrystallized from methanol, yield 82%, m.p. 72°C. Its characterization data are given in Table I.

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References