Mild and efficient synthesis of β-amino alcohols by bismuthtrichloride catalysed opening of epoxides

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ABSTRACT

Nucleophilic opening of epoxides with aniline derivatives in the presence of catalytic amount of bismuthtrichloride in acetonitrile at room temperature afforded the corresponding β-amino alcohols in excellent to very good yield.

Key words: Epoxide, bismuthtrichloride, nucleophilic opening, aromatic amine, β-aminoalcohols.

INTRODUCTION

Epoxides are having wide application in organic synthesis, due to their ease of generation and wide reactivity with different nucleophiles such as alcohols, thiols, amines etc. β-amino alcohols have remarkable synthetic utility because these are used as intermediates in the synthesis of a vast range of biologically active natural products¹ and synthetic amino acids. Some of these compounds are constantly used as β-blockers, insecticidal agents, chiral auxiliaries for asymmetric synthesis² and precursors for oxazoles which have been widely explored as protecting groups³. The classical synthesis of β-amino alcohols consists of heating of epoxides with an excess of amine at elevated temperature⁴. Since the high temperature may not be ideal condition for certain heat labile functional groups, a number of activators have been introduced in the literature to carry out the reaction at room temperature. Thus, improved procedures have been developed these include the use of alumina⁵, metal amides⁶, metal alkoxides⁷, metal halides⁸, silica under high pressure⁹. However in spite of their potential utility many of these methods involve expensive reagents, strongly acidic conditions and difficulty in handling of chemicals. Hence a better catalyst is still desirable for nucleophilic opening of epoxide rings by aromatic amines to afford the corresponding β-amino alcohol.

In continuation to our constant effort of exploring the applicability of bismuthtrichloride (BiCl₃)¹⁰ as a mild Lewis acid in various organic synthesis, here we report a mild and efficient method for regioselective nucleophilic opening of epoxide rings with amines using this reagent (Scheme 1). As a representative example, we carried out the reaction of styrene oxide (1a) with aniline (2a) in the presence of BiCl₃ at room temperature for 1.00 hr in dry acetonitrile to furnish the β-amino alcohol derivative (3a) in 92% yield.

A Series of epoxides were subjected to BiCl₃ catalyzed nucleophilic ring opening with aromatic amines and the results are summarized in Table1. Regioselective ring cleavage in case of aryl oxiranes with a variety of amines with preferential opening from the benzylic position led to single product (1-3). Epichlorohydrin (6-9), glycicyl aryl ethers (10-13) were underwent cleavage with a variety of amines in a regioselective way at the terminal position to give only one product in each case. Stereochemistry of the ring opening product was find to be trans in case of cyclohexylepoxides (4 and 5) as evident from the coupling constant of the methyine protons of the cyclohexane ring in ¹H NMR spectra.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Expoxide</th>
<th>Nucleophile</th>
<th>Productb</th>
<th>Time (h)</th>
<th>Yield (%)c</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a Ar = Ph</td>
<td>1.2</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ar = 4-Me-C₆H₄</td>
<td>1.0</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>Ar = 4-Cl-C₆H₄</td>
<td>1.10</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2a</td>
<td>3d</td>
<td>3.0</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>2d</td>
<td>3e</td>
<td>3.15</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>2a</td>
<td>4a</td>
<td>3.0</td>
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<tr>
<td>7</td>
<td>1c</td>
<td>2d</td>
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<td>8</td>
<td>1c</td>
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<td>4c</td>
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<tr>
<td>9</td>
<td>1c</td>
<td>2e</td>
<td>4d</td>
<td>4.5</td>
<td>91</td>
</tr>
</tbody>
</table>
All reactions were conducted at room temperature using 15 mol% BiCl₃ in acetonitrile.

All products were characterized by m.p. 1H NMR and 13C NMR and Mass spectroscopy.

Yield refers to isolated pure products and melting points are uncorrected.

**EXPERIMENTAL**

Synthetic procedure: to a magnetically stirred solution of epichlorohydrin 1c (185 mg, 2 mmol) and m-nitroaniline 2c (276 mg, 2 mmol) in acetonitrile (1.5 mL) was added BiCl₃ (94.2 mg, 0.3 mmol) and the mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC) the reaction was quenched with water (4 mL) and the resulting mixture was extracted with CH₂Cl₂ (3×20 mL). The extract is washed with water (2×5 mL) and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (60-120 mesh) using 20% ethylacetate-petroleum ether (60-80 °C) as eluent to afford 4d as crystalline solid (4.52 mg, 92%); m.p.61 °C; ¹H NMR (CDCl₃, 200 MHz) δ 3.29 (1H,dd, J=6.9, 12.8Hz), 3.40 (1H,dd, J=3.0, 12.9 Hz), 3.66 (1H,dd, J=6.3, 11.5 Hz), 3.73 (1H,dd, J=4.5, 11.5 Hz), 4.08-4.17 (1H,m), 4.40 (1H,brs), 6.93 (1H, dd, J=2.0, 8.1 Hz), 7.30 (1H,t,J=8.2 Hz), 7.44-7.45 (1H,m), 7.57 (1H,dd, J=14.8, 0 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 46.6, 55.7, 66.8, 70.9, 113.2(2), 114.7(2), 115(2), 117.9, 129.3(2), 148.0, 152.5, 154.2; HRMS calcd. For \([C_{16}H_{19}O_3N+Na]^+\) 274.1438, found 274.139.

Spectral data of 4e: m.p.59 °C ¹H NMR (CDCl₃,200 MHz) δ 3030(1H, dd, J=7.1, 129.9 Hz), 3.44 (1H,dd, J=4.1, 9.4 Hz), 3.78 (3H,s), 4.00 (1H, dd, J=5.9, 9.4 Hz), 4.06 (1H, dd, J=4.0, 9.4 Hz), 4.23-4.25 (1H,m), 6.69 (2H,d, J=7.9 Hz), 6.75 (1H, t, J =7.7 Hz), 6.68-6.89 (4H,m). 7.20 (2H,t, J=7.8 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 46.6, 55.7, 66.8, 70.9, 113.2(2), 114.7(2), 115(2), 117.9, 129.3(2), 148.0, 152.5, 154.2; HRMS calcd. For \([C_{16}H_{19}O_3N+Na]^+\) 274.1438, found 274.139.

Spectral data of 4g: m.p. 75°C; ¹H NMR (CDCl₃,200 MHz) δ 3.27 (1H,dd, J=6.9, 12.8Hz), 3.40 (1H, dd, J=4.0, 12.8Hz), 3.75 (3H,s), 3.98 (1H, dd, J=6.4, 9.2), 4.04 (1H, dd, J=3.9, 9.3 Hz), 7.30-7.35 (2H,m), 7.45 (4H,m), 7.60-7.70 (4H,m). 7.80 (3H,s); ¹³C NMR (CDCl₃, 75 MHz) δ 46.6, 55.7, 66.8, 70.9, 113.2(2), 114.7(2), 115(2), 117.9, 129.3(2), 148.0, 152.5, 154.2; HRMS calcd. For \([C_{16}H_{19}O_3N+Na]^+\) 274.1438, found 274.139.

**Scheme 1**
4.20-4.26 (1H, m), 6.54 (1H, d, J=1.7, 8.0 Hz), 6.65 (1H, d, J=1.7 Hz), 6.69 (1H, d, J=7.8 Hz), 6.82-6.91 (4H, m), 7.08 (1H, t, J=8.1 Hz); 13C NMR (CDCl₃, 75 MHz) δ 46.3, 55.7, 68.7, 70.8, 115.6(2), 117.7, 130.2, 135.0, 149.2, 152.4, 154.3; HRMS calcd. for [C₁₆H₁₈O₃ NCl+H+] 308.1048, found 308.1046.

CONCLUSION

We have developed a mild and efficient method for opening of epoxides with various aromatic amines to afford β-amino alcohol. Bismuthtrichloride was found to be the catalyst of choice in terms of cost, handling, operational simplicity and ease of isolation of products. Moreover, it does not require any promoter or activator such as microwave irradiation. The reactions were very clear and products were obtained in excellent yields without formation of any undesired side product.

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