

## Mild and efficient synthesis of $\beta$ -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  $\beta$ -amino alcohols in excellent to very good yield.

**Key words:** Epoxide, bismuthtrichloride, nucleophilic opening, aromatic amine,  $\beta$ -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.  $\beta$ -amino alcohols have remarkable synthetic utility because these are used as intermediates in the synthesis of a vast range of biologically active natural products<sup>1</sup> and synthetic amino acids. Some of these compounds are constantly used as  $\beta$ -blockers, insecticidal agents, chiral auxiliaries for asymmetric synthesis<sup>2</sup> and precursors for oxazoles which have been widely explored as protecting groups<sup>3</sup>. The classical synthesis of  $\beta$ -amino alcohols consists of heating of epoxides with an excess of amine at elevated temperature<sup>4</sup>. 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 alumina<sup>5</sup>, metal amides<sup>6</sup>, metal alkoxides<sup>7</sup>, metal halides<sup>8</sup>, silica under high pressure<sup>9</sup>. 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  $\beta$ -amino alcohol.

In continuation to our constant effort of exploring the applicability of bismuthtrichloride ( $\text{BiCl}_3$ )<sup>10</sup> as a mild Lewis acid in various organic synthesis, here in 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  $\text{BiCl}_3$  at room temperature for 1.00 hr in dry acetonitrile to furnish the  $\beta$ -amino alcohol derivative (3a) in 92% yield.

A Series of epoxides were subjected to  $\text{BiCl}_3$  catalyzed nucleophilic ring opening with aromatic amines and the results are summarized in Table 1. Regioselective ring cleavage in case of aryl oxiranes by a variety of amines with preferential opening from the benzylic position led to single product (1-3). Epichlorohydrin (6-9), glycidyl 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 found to be trans in case of cyclohexylepoxides (4 and 5) as evident from the coupling constant of the methylene protons of the cyclohexane ring in <sup>1</sup>H NMR spectra.

**Table 1: Bismutrichloride mediated regioselective ring opening of epoxides by aromatic aminesa**


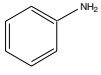
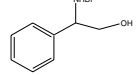
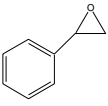
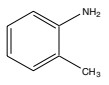
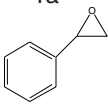
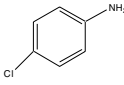

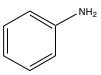
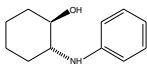

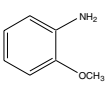

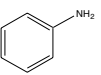
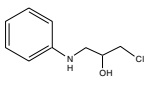

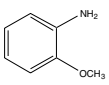

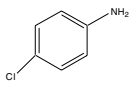


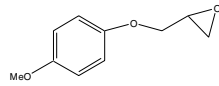
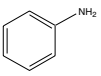
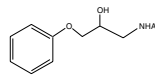
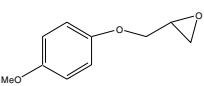
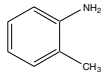
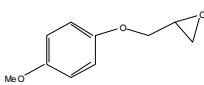

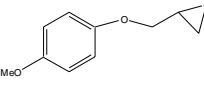
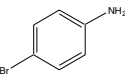
Entry	Epoxide	Nucleophile	Productb	Time (h)	Yield (%)c
1				1.2	92
2			Ar = 4-Me-C <sub>6</sub> H <sub>4</sub> 3b	1.0	87
3			Ar = 4-Cl-C <sub>6</sub> H <sub>4</sub> 3c	1.10	90
4				3.0	83
5			3e	3.15	85
6				3.0	85
7			4b	3.0	84
8			4c	2.15	89
9			4d	4.5	91

Table 1. Cont .....

10				4.5	80
11			Ar = 2-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> f	4.0	78
12			Ar = 3-Cl-C <sub>6</sub> H <sub>4</sub> g	4.0	83
13			Ar = 4-Br-C <sub>6</sub> H <sub>4</sub> h	3.5	71

<sup>a</sup>All reactions were conducted at room temperature using 15 mol% BiCl<sub>3</sub> in acetonitrile.

<sup>b</sup>All products were characterized by m.p. <sup>1</sup>H NMR and <sup>13</sup>C NMR and Mass spectroscopy.

<sup>c</sup>Yield refers to isolated pure products and melting points are uncorrected.

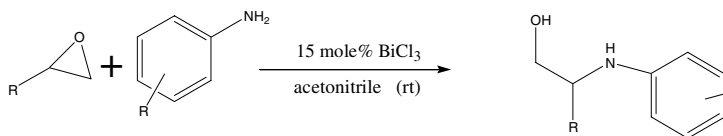
## EXPERIMENTAL

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 BiCl<sub>3</sub> (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 CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL). The extract is washed with water (2x5 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. 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) was eluent to afford 4d as crystalline solid (4.52 mg, 92%); m.p. 61 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 3.29 (1H, dd, *J*=7.2, 12.9 Hz), 3.45 (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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 46.6, 47.4, 69.8, 106.6, 112.4, 119.3, 129.9, 148.8, 149.2; HRMS calcd. for (C<sub>9</sub>H<sub>11</sub>N<sub>2</sub>ClO<sub>3</sub>+Na<sup>+</sup>) 253.0356, found 253.0357.

Spectral data of 4e : m.p. 59 °C <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 3.030 (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); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 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<sub>16</sub>H<sub>19</sub>O<sub>3</sub>N+H<sup>+</sup>] 274.1438, found 274.139.

Spectral data of 4g: m.p. 75 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 3.27 (1H, dd, *J*=6.9, 12.8 Hz), 3.40 (1H, dd, *J*=4.0, 12.8 Hz), 3.75 (3H, s), 3.98 (1H, dd, *J*=6.4, 9.2), 4.04 (1H, dd, *J*=3.9, 9.3 Hz),



Scheme 1

4.20-4.26 (1H,m), 6.54 (1H,dd,  $J=1.7,8.0$  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);  $^{13}\text{C}$  NMR( $\text{CDCl}_3$ ,75 MHz)  $\delta$  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  $[\text{C}_{16}\text{H}_{18}\text{O}_3\text{NCl}+\text{H}^+]$  308.1048, found 308.1046.

Spectral data of 4h: m.p. 111 °C;  $^1\text{H}$  NMR( $\text{CDCl}_3$ , 200 Hz)  $\delta$  2.51(1H, brs.), 3.25(1H, dd,  $J=7.1, 12.8$  Hz), 3.39 (1H,dd,  $J=4.3,12.8$  Hz), 3.78 (3H,s), 3.98 (1H, dd,  $J=6.6, 9.5$  Hz), 4.05 (1H,dd,  $J=5.4, 9.3$  Hz), 4.22(2H,m), 6.55 (2H,d, $J=8.8$  Hz), 6.83-6.88 (4H,m), 7.26 (2H,d,  $J=8.7$ Hz);  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ , 75MHz)  $\delta$  46.5, 55.7, 68.7, 70.7, 109.5, 114.7 (4), 115.5 (2), 132.0 (2), 147.1, 152.4, 154.3; HRMS calcd. for  $[\text{C}_{16}\text{H}_{18}\text{BrNO}_3+\text{H}^+]$  352.0543, found 352.052.

## CONCLUSION

We have developed a mild and efficient method for opening of epoxides with various aromatic amines to afford  $\beta$ -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.

## ACKNOWLEDGEMENTS

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## REFERENCES

- (a) E .J. Corey and F. Zhang, *Angew. chem.*, Int.Ed, **38**: 1931 (1999).  
(b) G. A. Rogers, S. M. Parsons, D. C. Anderson, R. S. Jacobs and B.Kirtman, *J. Med, chem.*, **32**: 1217 (1989).  
(c) B. L. Chang and A. Ganesan, *Bioolg. Med. Chem. Lett.*, **7**: 1511 (1997).
- (a) D. J. Ager, I. Prakash and D. R. Schaad, *Chem,Rev.*, **96**: 835 (1996).  
(b) C. Auvin-Guette, S. Rebuffat, Y. Prigent and B. Bodo *J. am. Chem. Soc.*, **114**: 2170 (1992).  
(c) S.Wu, R. takeya, M.Eto and C. Tomizawa, *J.Pestic.Sci.*, **12**,221(1987).  
(d) J.takchara, S. Hashiguchi, A. Fujii, S.I.Inoue, T. Ikaria and R. Nayori, *J. Chem. Soc., Chem. Commun*; 233 (1996).  
(e) E.J.Corey, R.K. Bakshi, S. Shibata,C.P. Chen and V.K.Singh, *J. Am. Chem. Soc.*, **109**: 7925 (1987)
- (a) R.Gupta, S.Paul, A.K.Gupta, P.L.Kachroo and A.Dandia, *Indian. J. Chem.*,Sect. B, **36**: 281 (1997).  
(b) J.S. Yadav, B.V.S. Reddy, A.K.Basak and A.V. Narasaiah, *Tetrahedron Lett.*, **44**:1047 (2003).  
(c) J.S.Yadav, B.V.S.reddy, K.Sadashiv, K.Harikishan and A.V.Narasaiah, *J.Mol.Catal. A*, **200**: 153 (2004)
- J.A. Deyrup and C.L. Moyer, *J.Org.Chem*, **34**: 175 (1969).
- G.H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.*, **99**: 8208 (1977).
- (a) L.E. Overman and L.A. Flippin, *Tetrahedron Lett.*, **22**:195 (1981).  
(b) A.papini, I. Riuci, M. Taddei, G. Weconi and P. Dembach, *J. Chem. Soc, Perkin Trans,1*: 2261 (1984).  
(c). M.C. Carre, J. P. Houmounou and P. Caubeae, *Tetrahedron Lett.*, **26**: 3107 (1985).
- (a) S. Sagava, H. Abe, H. Hase and T. Inaba, *J. Org. Chem.*, **64**: 4962 (1999).  
(b).S. Rampalli, S .S. Chaudhari and K.G. Akamanchi, *Synthesis*, **78** (2000)
- (a)J.Iqbal and A. Pandey, *Tetrahedron Lett*, **31**: 575 (1990);  
(b). S. ChendraShekar, T. Ramachandar and S. J. Prakash, *Synthesis*, 1817 (2000).
- (a) H. Kotsuki, T. shimanouchi, M. Teraguchi, M.Kataoka, A. Tatsukawa and H. Nishizawa, *Chem.Lett.*, 2159 (1994).  
(b) H.Kotsuki, K. Hayashida, T.Shinanouchi and H. Nishizawa, *J. Org. Chem.*, **61**: 984 (1996)
- (a) T. Ollevier and T. Ba *Tetrahedron Lett.*, **44**,9003 (2003).  
(b)H.Suzuki,T. Ikegami and Y. Matano, *Synthesis*, 2491 (1997).  
(c) H. Suzukli and Y. Matano, *Organo Bismuth Chemistry*, (Edited by Elsevier Amsterdam), (2001).  
(d) N.M.Leonard L. C. Wieland and R. Mohan, *Tetrahedron*, **58**: 8373 (2002)