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Tetrahedron Letters 48 (2007) 7354–7357
Tetrahedron Letters

Antimony(III) chloride-catalyzed ring opening of epoxides with anilines

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Received 5 July 2007; revised 3 August 2007; accepted 6 August 2007
Available online 10 August 2007

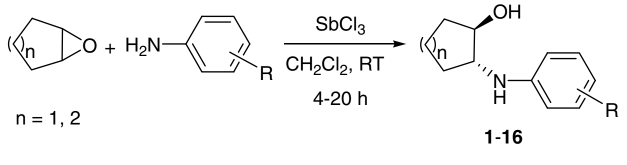
Abstract—A mild and convenient ring opening of epoxides with aniline and its derivatives takes place at room temperature in the presence of antimony trichloride as catalyst to afford the corresponding β-amino alcohols in good yields.

β-Amino alcohols are versatile intermediates for the preparation of natural products and pharmacologically important targets and are used extensively as chiral auxiliaries and ligands.[1–4] The most practical and widely employed strategy for the synthesis of β-amino alcohols is the direct aminolysis of epoxides with an excess of amine at elevated temperature.[5] However, high temperature is detrimental to some functional groups and is also not ideal for control of regioselectivity. To circumvent these problems, a variety of activators such as Lewis acids and metal salts have been introduced for the ring opening of epoxides with amines. These include $Sn(OTf)_2$,[6a] $Cu(OTf)_2$,[6a] $Bi(OTf)_3$,[6b,c] $Al(OTf)_3$,[6d] $TaCl_5$,[7a] $InCl_3$,[7b] $BiCl_3$,[7c] VCl_3,[7d] $ZnCl_4$,[7e] $InBr_3$,[7f] $CoCl_2$,[7g] $Cu(BF_4)_2$,[8] $Zn(ClO_4)_2$,[9] heteropoly acids,[10] ionic liquids,[11] and fluoro alcohols.[12] Limitations such as low yields, failure of deactivated amines and sterically demanding aromatic amines are associated with most of the literature methods. Therefore, the introduction of new and efficient methods are still in demand.

In the course of our investigations on catalytic asymmetric synthesis, we required racemic β-amino alcohols. For this purpose we chose antimony trichloride as a new activator for the aminolysis of epoxides. Herein we disclose our results on the $SbCl_3$-mediated mild and convenient ring opening of *meso*-epoxides with aromatic amines.

At the outset of this work, we studied cyclohexene oxide ring-opening with aniline in the presence of 10 mol % $SbCl_3$ in solvents such as cyclohexane and dichloromethane at room temperature. The reaction in dichloromethane produced *trans*-2-phenylaminocyclohexanol (**1**) in better yield. To optimize the catalyst loading, the reactions were carried out with 2 mol %, 5 mol %, 10 mol %, and 15 mol % catalyst in dichloromethane and the efficiency of the catalyst loading was determined from the time needed for the complete conversion of the starting materials to products by monitoring the reaction by TLC at regular intervals. It was found that at lower catalyst loadings the reaction proceeded slowly (15–20 h for 2 and 5 mol %), whereas the reaction reached completion in 7 h with 10 mol % of catalyst and the product was isolated in 85% yield. There was not much improvement on the rate of reaction with 15 mol % $SbCl_3$.

Encouraged by this result, several structurally diverse aniline derivatives were investigated for the ring-opening reaction with cyclohexene oxide (Scheme 1, Table 1). Thus cyclohexene oxide was treated with 4-bromoaniline, 4-chloroaniline, and *p*-anisidine under catalytic influence of $SbCl_3$ to furnish the corresponding β-amino alcohols **2**–**4** in high yields[13] (entries 2–4). Likewise, 4-trifluoromethylaniline and 3,5-dimethylaniline also



Scheme 1.

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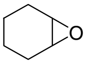
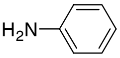
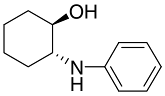
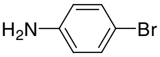
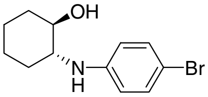
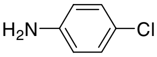
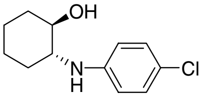
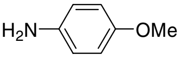
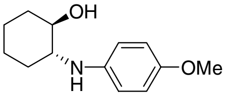
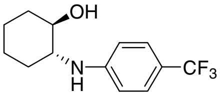
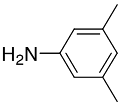
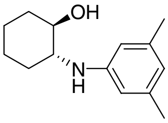
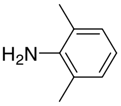
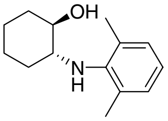
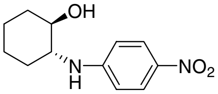
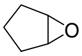
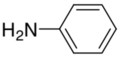
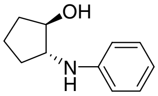
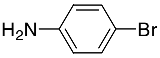
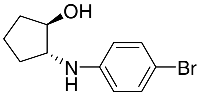
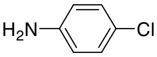
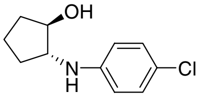
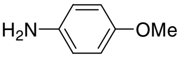
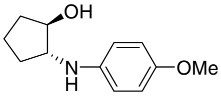
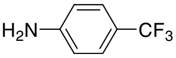
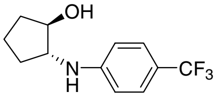
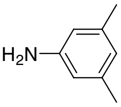
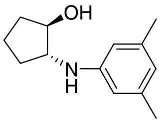
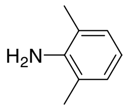
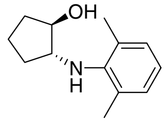
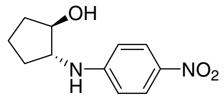
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.08.023

Table 1. Ring opening of epoxides with various anilines at room temperature using antimony trichloride[a]

Entry	Epoxide	Nucleophile	Time (h)	Product		Yield[b] (%)
1			7		**1**	85
2			4		**2**	80
3			4		**3**	85
4			8		**4**	83
5			6		**5**	85
6			8		**6**	75
7			8		**7**	72
8			20		**8**	46
9			12		**9**	82
10			8		**10**	86
11			7		**11**	85
12			10		**12**	83
13			15		**13**	80
14			15		**14**	83

(*continued on next page*)

Table 1 (*continued*)

Entry	Epoxide	Nucleophile	Time (h)	Product	Yield[b] (%)
15			15	 **15**	72
16			20	 **16**	54

[a] The reactions were carried out with 5 mM epoxide, 5 mM of aromatic amine in the presence of 0.5 mM of $SbCl_3$ in 5 mL of dichloromethane.[13]

[b] Yield of pure and isolated products.

underwent facile ring-opening with cyclohexene oxide to afford the desired products **5** and **6** in high yields after 6–8 h (entries 5 and 6). The structurally demanding 2,6-dimethylaniline reacted smoothly offering amino alcohol **7** in good yield (entry 7). The reaction of 4-nitroaniline did not reach completion and therefore, this reaction was stopped at 20 h to produce β-amino alcohol **8** in acceptable yield (entry 8). The decreased reactivity of 4-nitroaniline may be due to the fact that the deactivating nitro functionality diminishes the nucleophilicity of this aniline.

We next turned our focus to extending the epoxide ring-opening reactions with cyclopentene oxide. Several examples illustrating this simple and practical methodology are summarized in Table 1. Again, a very clean reaction was observed in each case studied, albeit with slightly longer reaction times. The nucleophilic opening of cyclopentene oxide with various substituted aniline derivatives proceeded smoothly to provide the corresponding β-amino alcohols **9**–**16** in yields comparable to those of cyclohexene oxide-derived β-amino alcohols **1**–**8**, respectively.

The structures of β-amino alcohols **1**–**16** were assigned on the basis of their IR, ^1H and ^{13}C NMR, and GC–MS spectral analysis. The trans stereochemistry of the amino alcohols was deduced from the coupling constants of the protons on carbons 1 and 2. For example, in the ^1H NMR (500 MHz) spectrum of 2-(phenylamino)cyclohexan-1-ol (**1**) two ^1H signals appeared at δ 3.15 (ddd, $J = 13.0$, 9.5, 4.0 Hz) and δ 3.36 (ddd, $J = 13.5$, 9.5, 4.0 Hz) for the C*H*NH and C*H*OH protons, respectively, which are indicative of trans stereochemistry. Furthermore, the ^1H NMR data of the β-amino alcohols were in accordance with those of the compounds reported in the literature.[6a,7c,12,14]

In conclusion, we have demonstrated a mild and efficient method for the preparation of β-amino alcohols using $SbCl_3$ as a catalyst. To the best of our knowledge, antimony trichloride is not known to catalyze aminolysis of epoxides with aniline and its derivatives. The worthy feature of this transformation is that highly deactivated and sterically demanding anilines also served as nucleophiles for the ring opening of epoxides.

Acknowledgements

We thank the Department of Science and Technology, New Delhi, for providing financial assistance. M.C.S. thanks MHRD, New Delhi, for the award of fellowship.

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13. *General procedure*: To a mixture of epoxide (5 mM) and amine (5 mM) in dichloromethane (5.0 mL) was added anhydrous $SbCl_3$ (0.5 mM) at room temperature and the

reaction contents were stirred for a period of time as indicated in Table 1. Then the reaction mixture was quenched by the addition of aqueous $NaHCO_3$, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate) to furnish pure *trans*-2-arylaminocycloalkanol.

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