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Sulfamic Acid Catalyzed Ring Opening of Epoxides with Amines under Solvent-Free Conditions

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Sulfamic acid (SA) catalyses the nucleophilic opening of epoxide rings by amines leading to the efficient synthesis of *β*–amino alcohols. The reaction works well with aromatic and aliphatic amines in short reaction times and in the absence of solvent. Exclusive *trans* stereoselectivity is observed for the ring opening of cyclohexene oxide. This method exhibits excellent regioselectivity for preferential nucleophilic attack at the less hindered position during the reaction with unsymmetrical epoxides.

Keywords: Sulfamic acid, Epoxide, Amines, β–Amino alcohols

INTRODUCTION

Epoxides are versatile synthetic intermediates and a variety of reagents are known for the ring opening [1]. The resulting products of epoxide aminolysis are important bioisosteres, which appeared in several FDA approved drugs [2]. Opening of epoxides with amines developed in the past few years mainly involve monohaptic nucleophiles and the use different catalysts such as metal triflates [3], metal halides [4] polymer supported [5], montmorillonite K10 [6], metal salt [7], and different reaction media such as fluoro alcohols [8a], ionic liquids [8b] and water [3b,8c] or solvent free conditions (SFC) [4c,9]. Even though these procedures have considerably improved the scope of this reaction, they are associated with certain limitation.

For example, metal triflates and halides either deactivated the Lewis acid catalyst as a consequence of formation of a stable complex between the metal ion and the amine or require prolonged reaction times of about 12 h. Only Zn(II) salts in acetonitrile [4b] are in some cases truly effective catalyst but they completely failed with bihaptic nucleophiles such as 2-picolylamine because the highly azaphilic Zn(II) cation forms a stable complex with the amine. Work-up with such Lewis acids, which are often used in stoichiometric quantities, is difficult due to the formation of emulsions. Furthermore these catalysts are of use with deactivated amines, and are inconvenient in handling. In some cases, reagents are also expensive. Finally, hexafluoro 2-propanol and [bimim]BF_4 were not effective in the aminolysis with alkyl amines [8a,b].

Sulfamic acid (NH_2SO_3H, SA) is a dry, non-volatile, non-hydroscopic, odorless and white stable crystalline solid. It is commercially available as a very cheap chemical. Recently, it has been shown that SA has been used as an efficient heterogeneous acid catalyst for functional group protections and deprotections [10a-c], synthesis for isoamyl acetate [10d], synthesis of polymeric ethers [10e], Beckmann rearrangement [10f], imino Diels-Alder reaction [10g], Pechamnn [10h] and Biginelli condensation [10i,j] and synthesis of sulfonyl imines [10k].

In this pursuit, and during the course of our studies aimed at developing solvent-free procedures [11], in this work, we report the sulfamic acid catalyzed ring opening of epoxides under solvent-free conditions by amines.

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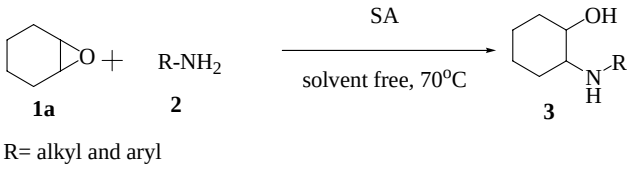


Scheme 1

EXPERIMENTAL

All chemicals were obtained from Merck or Fluka chemical companies. The known compounds were identified by the comparison of their melting points and ^{1}H NMR with the authentic samples. The progress of the reactions was followed by TLC using silica-gel SILG/UV 254 plates. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.9 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

General Procedure for Ring Opening of Epoxides

A mixture of sulfamic acid (0.5 mmol, 0.05 g) amine (5 mmol) and 1,2-epoxide (5 mmol) were heated and stirred in an oil bath at 70 ºC. The progress of the reaction was monitored by TLC (eluent: *n*-hexane-EtOAc 80:20). After the completion of reaction, diethyl ether (3 × 10 ml) was added to the reaction mixture and SA was removed by filtration. The organic solvent was then evaporated and the product was obtained. This was further purified by column chromatography. The structure of the products was confirmed by ^{1}H NMR, ^{13}C NMR and comparison with authentic samples obtained commercially or prepared by reported methods.

2-[(2-Pyridylmethyl)amino]-1-cyclohexanol (3a). ^{1}H NMR ($CDCl_3$): ppm 8.55 (1H, d, *J* = 4.8 Hz), 7.76 (1H, t, *J* = 5.8 Hz), 7.40 (1H, d, *J* = 2.9 Hz), 7.18-7.26 (1H, m), 5.20 (2H, brs, -NH, -OH), 4.34 (1H, d, *J* = 14.5 Hz), 4.10 (1H, d, *J* = 14.5 Hz), 3.60-3.62 (1H, m), 2.56-2.57 (1H, m), 2.01-2.08 (2H, m), 1.67-1.74 (2H, m), 1.18-1.43 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.0, 24.6, 28.8, 33.7, 50.0, 63.3, 72.0, 122.9, 137.1, 149.2, 156.0.

2-Anilinio-1-cyclohexanol (3b). ^{1}H NMR ($CDCl_3$): ppm 7.13 (2H, t, *J* = 7.5 Hz), 6.65-6.89 (3H, m), 3.45 (2H, brs, NH, OH), 3.30-3.39 (1H, m), 3.10-3.14 (1H, m), 2.05-2.10 (2H, m), 1.66-1.76 (2H, m), 1.05-1.35 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.9, 24.2, 31.3, 33.2, 60.3, 74.2, 115.2, 121.9, 129.3, 147.2.

2-(4-Toluidino)cyclohexanol (3c). ^{1}H NMR ($CDCl_3$): ppm 6.78 (2H, d, *J* = 2.27 Hz), 6.48 (2H, d, *J* = 2.5 Hz), 3.09-3.14 (1H, m), 3.98 (2H, brs, NH, OH), 2.87-2.93 (1H, m), 3.89 (3H, s), 1.86-1.89 (2H, m), 1.40-1.56 (2H, m), 1.06-1.18 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 20.4, 24.5, 25.0, 31.5, 33.1, 60.5, 74.3, 115.3, 127.5, 129.3, 145.5.

2-(3-Toluidino)cyclohexanol (3d). ^{1}H NMR ($CDCl_3$): ppm 7.02 (1H, s), 6.39-6.60 (3H, m), 3.46 (2H, brs, NH, OH), 3.19-3.27 (1H, m), 3.02-3.08 (1H, m), 2.21 (3H, s), 2.00-2.05 (2H, m), 1.61-1.69 (2H, m), 1.17-1.35 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 21.5, 23.7, 25.0, 31.0, 33.4, 59.9, 75.6, 111.5, 115.6, 118.5, 128.7, 139.0, 148.0.

2-(3-Methoxyanilino)cyclohexanol (3e). ^{1}H NMR ($CDCl_3$): ppm 7.06 (1H, s), 6.21-6.31 (3H, m), 3.73 (3H, s), 3.33 (2H, brs, NH, OH), 3.27 (1H, ddd, *J* = 3.83, 5.65 and 4.4 Hz), 3.08 (1H, ddd, *J* = 4, 7.42, and 3.90 Hz), 2.05-2.11 (2H, m), 1.65-1.73 (2H, m), 1.02-1.65 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.9, 24.9, 30.9, 32.6, 55.1, 59.9, 73.1, 100.3, 103.1, 107.2, 130.0, 149.3, 160.7.

2-(3-Chloroanilino)cyclohexanol (3f). ^{1}H NMR ($CDCl_3$): ppm 6.98-7.02 (1H, m) 6.50-6.65 (3H, m), 3.81 (brs, 2H, NH, OH), 3.31 (1H, m), 2.85-2.91 (1H, m), 2.01-2.07 (2H, m), 1.62-1.70 (2H, m), 0.87-1.33 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.9, 24.7, 31.1, 32.8, 59.6, 74.0, 112.2, 113.2, 114.8, 130.1, 134.8, 149.6.

2-(2-Bromoanilino)cyclohexanol (3g). ^{1}H NMR ($CDCl_3$): ppm 7.40-7.46 (1H, m), 7.16-7.18 (1H, m), 6.74-6.85 (1H, m), 6.56-6.60 (1H,m) 3.20 (2H, brs, NH, OH), 4.19-4.35 (1H, m), 3.38-3.41 (1H, m), 2.04-2.10 (2H, m), 1.67-1.74 (2H, m), 1.13-1.43 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.0, 24.4, 31.5, 32.7, 59.7, 74.1, 112.9, 118.3, 128.3, 132.5, 144.9.

2-(3-Bromoanilino)cyclohexanol (3h). ^{1}H NMR ($CDCl_3$): ppm 6.93-6.99 (1H, m), 6.75-6.79 (2H, m), 6.53-6.58 (1H, m), 4.15 (2H, brs, NH, OH), 3.42 (1H, m), 3.25-3.30 (1H, m), 2.98-3.03 (2H, m), 1.64-1.73 (2H, m), 1.01-1.31 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.4, 24.6, 31.6, 33.1, 56.9, 73.9, 115.7, 117.8, 120.4, 129.8, 148.4.

2-(4-Fluoroanilino)cyclohexanol (3i). ^{1}H NMR ($CDCl_3$): ppm 6.84-6.91 (2H, m), 6.63-6.69 (2H, m), 3.67 (2H, brs, NH, OH), 3.30-3.34 (1H, m), 2.88-3.01 (1H, m), 2.07-2.10 (2H,

m), 1.70-1.75 (2H, m), 1.04-1.35 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.9, 24.5, 31.2, 33.3, 58.4, 73.0, 115.4, 116.4, 143.4, 158.3.

2-(4-Bromoanilino)cyclohexanol (3j). ^{1}H NMR ($CDCl_3$): ppm 7.11 (2H, m), 6.45 (2H, m), 3.45 (2H, brs, NH, OH), 3.18-3.25 (1H, m), 2.93-2.99 (1H, m), 1.94-1.99 (2H, m), 1.58-1.67 (2H, m), 1.09-1.25 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.4, 24.8, 31.4, 33.4, 59.9, 74.3, 115.7, 116.7, 131.8, 147.0.

2-(3-Hydroxyanilino)cyclohexanol (3k). ^{1}H NMR ($CDCl_3$): ppm 7.06 (1H, s), 6.18-6.27 (3H, m), 4.68 (2H, brs, NH, OH), 3.26-3.29 (1H, m), 3.01-3.04 (1H, m), 1.99-2.02 (2H, m), 1.59-1.65 (2H, m), 1.18-1.26 ppm (4H, m).

1-{4-[(2-Hydroxycyclohexyl)amino]phenyl}-1-ethenone (3l). ^{1}H NMR ($CDCl_3$): ppm 7.76 (2H, d, J = 2.07 Hz), 6.56 (2H, d, J = 3.10 Hz), 4.30 (2H, brs, NH, OH), 3.43-3.55 (1H, m), 3.24-3.28 (1H, m), 2.48 (3H, s), 2.07-2.12 (2H, m), 1.69-1.79 (2H, m), 1.18-1.34 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.9, 24.2, 24.6, 31.4, 33.5, 58.9, 74.2, 112.1, 113.6, 130.6, 130.8, 152.3, 196.6.

4-[(2-Hydroxycyclohexyl)amino]benzoic acid (3m). ^{1}H NMR ($CDCl_3$): ppm 7.85 (2H, d, J = 2.32 Hz), 6.62 (2H, d, J = 2.12 Hz), 4.94 (2H, brs, NH, OH), 3.23-3.43 (2H, m), 1.95-2.10 (2H, m), 1.69-1.85 (2H, m), 1.02-1.47 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.2, 24.4, 30.3, 32.9, 74.2, 113.7, 118.3, 132.2, 151.5, 171.1.

2-(3-Nitroanilino)cyclohexanol (3n). ^{1}H NMR ($CDCl_3$): ppm 7.48-7.54 (2H, m), 7.27 (1H, t, J = 8.04 Hz), 6.95 (1H, d, J = 5.04 Hz), 3.41 (2H, brs, NH, OH), 3.35-3.50 (1H, m), 3.19-3.20 (1H, m), 2.09-2.14 (2H, m), 1.73-1.82 (2H, m), 1.13-1.42 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.1, 24.7, 31.4, 33.5, 59.7, 74.5, 107.5, 112.5, 119.7, 129.8, 148.8.

2-(3-Cyanoanilino)cyclohexanol (3o). ^{1}H NMR ($CDCl_3$): ppm 6.96 (1H, m), 6.80 (2H, d, J = 1.40), 6.54-6.59 (1H, m), 3.32 (2H, brs, NH, OH), 3.30-3.32 (1H, m), 3.05-3.07 (1H, m), 2.06-2.07 (2H, m), 1.66-1.72 (2H, m), 1.16-1.33 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.7, 24.7, 31.3, 33.5, 59.5, 74.3, 116.0, 118.2, 121.1, 129.9, 148.3.

2-(2-Trifluoroanilino)cyclohexanol (3p). ^{1}H NMR ($CDCl_3$): ppm 7.16-7.35 (2H, m), 6.52-6.81 (2H, m) 4.10-4.27 (1H, m), 3.23-3.30 (1H, m), 3.19 (2H, brs, -NH, -OH), 1.88-1.92 (2H, m), 1.52-1.57 (2H, m), 1.07-1.15 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.2, 24.5, 33.4, 55.9, 59.5, 112.4, 113.0, 113.6, 114.6, 115.7, 116.5, 116.8, 117.0, 117.2, 126.2, 126.4, 126.5, 132.9, 144.9, 145.8.

2-({6-[(2-Hydroxycyclohexyl)amino]-2-pyridyl}amino)-cyclohexanol (3q). ^{1}H NMR (DMSO): ppm 7.24-7.41 (2H, m), 6.97 (1H, t, J = 1.45 Hz), 5.50-5.70 (4H, m), 5.36 (4H, brs, NH, OH), 2.30-2.48 (4H, m), 1.42-1.55 (4H, m), 104-1.27 ppm (8H, m); ^{13}C NMR: ppm ($CDCl_3$) 23.7, 24.2, 31.1, 34.1, 56.0, 73.3, 95.1, 138.4, 158.3.

2-(Diphenylamino)cyclohexanol (3r). ^{1}H NMR ($CDCl_3$): ppm 6.67-7-32 (10H, m), 4.13-4.54 (1H, m), 3.02-3.23 (1H, m), 3.01 (2H, brs, -NH, -OH), 2.34-2.48 (2H, m), 1.72-1.84 (2H, m), 1.12-1.34 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.4, 25.9, 32.1, 33.4, 60.2, 74.1, 119.2, 120.6, 126.2, 146.4.

2-(Diisopropylamino)cyclohexanol (3s). ^{1}H NMR ($CDCl_3$): ppm 3.56-3.73 (1H, m), 3.42-3.60 (2H, m), 3.34-3.39 (1H, m), 3.37 (2H, brs, -NH, -OH), 1.14-2.25 ppm (20H, m); ^{13}C NMR: ppm ($CDCl_3$) 19.3, 23.7, 23.8, 29.9, 32.9, 46.5, 67.5, 72.8.

2-(Propylamino)cyclohexanol (3t). ^{1}H NMR ($CDCl_3$): ppm 4.56 (2H, brs, -NH, -OH), 4.31-4.33 (1H, m), 4.13 (2H, dd, J = 7.15, 7.15 Hz), 3.60-3.61 (1H, m), 2.18-2.27 (2H, m), 2.04-2.08 (3H, s), 1.22-1.33 ppm (6H, m); ^{13}C NMR: ppm ($CDCl_3$) 14.1, 21.0, 24.1, 24.5, 30.9, 33.1, 60.4, 72.7, 87.0.

2-Morpholino-1-cyclohexanol (3u). ^{1}H NMR ($CDCl_3$): ppm 3.72 (4H, t, J = 4.9 Hz), 3.35-3.50 (1H, m), 2.72 (2H, t, J = 5.4 Hz), 2.41 (2H, t, J = 4.0 Hz), 2.15-2.30 (1H, m), 1.79-1.84 (2H, m), 1.70-1.71 (2H, m), 1.08-1.27 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 22.2, 23.9, 25.4, 33.1, 48.7, 67.4, 68.3, 70.5.

2-(4-{4-[(2-Hydroxycyclohexyl)amino]phenoxy} anilino)-cyclohexanol (3v). ^{1}H NMR ($CDCl_3$): ppm 6.78 (4H, d, J = 8.77 Hz), 6.59 (4H, d, J = 8.85 Hz), 3.44 (4H, brs, NH, OH), 3.29 (2H, ddd, J = 9.20, 3.57, and 9.77 Hz), 2.99 (2H, ddd, 8.95, 3.60 and 8.97 Hz), 2.01-2.03 (4H, m), 1.68-1.80 (4H, m), 1.00-1.36 ppm (8H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.3, 24.8, 32.4, 33.3, 60.8, 74.0, 115.0, 119.0, 143.4, 150.2.

2-(4-{4-[(2-Hydroxycyclohexyl)amino]benzyl}anilino)-cyclohexanol (3w). ^{1}H NMR ($CDCl_3$): ppm 6.80 (4H, d, J = 5.85 Hz), 6.43 (4H, d, J = 4.36 Hz), 3.90-3.98 (2H, m), 3.59 (2H, s), 3.44 (4H, brs, NH, OH), 2.88-3.15 (2H, m), 0.84-1.87 ppm (16H, m); ^{13}C NMR: ppm ($CDCl_3$) 20.8, 24.2, 30.8, 31.3, 40.0, 60.3, 73.8, 114.2, 129.4, 146.0.

7-(2-Hydroxycyclohexyl)-5,6,7,8,9,10-hexahydro-2-H-

1,13,4,7,10-benzadioxatriaza-cyclopentadecine-3,11,(4H, 12H)-dione (3x). ^{1}H NMR ($CDCl_3$): ppm 8.03 (1H, s, NH), 6.96-7.01 (2H, m), 6.85-6.91 (2H, m), 4.51 (4H, s), 3.49 (4H, t, *J* = 5.37), 3.33-3.36 (1H, m), 3.18-3.20 (1H, m), 2.92-2.96 (4H, t, *J* = 5.35 Hz), 1.96-2.02 (2H, m), 1.69-1.80 (2H, m), 1.25-1.30 ppm (4H, m); ^{13}C NMR: ppm ($CDCl_3$) 24.0, 24.8, 32.1, 32.7, 38.0, 47.3, 66.8, 73.2, 120.0, 122.0, 165.0, 168.1, 168.6.

1-Phenyl-2-[(2-pyridylmethyl)amino]-1-ethanol (3y). ^{1}H NMR ($CDCl_3$): ppm 8.34 (1H, d, *J* = 4.9 Hz), 7.21-7.49 (1H, m), 7.02-7.21 (7H, m), 4.72 (1H, d, *J* = 3.4 Hz), 4.62 (2H, dd, *J* = 2.8, 2.8 Hz), 3.90 (1H, -NH), 3.82 (1H, -OH), 2.64-2.76 ppm (2H, m); ^{13}C NMR: ppm ($CDCl_3$) 54.1, 56.8, 72.1, 122.5, 125.9, 127.3, 128.2, 136.6, 137.1, 149.0, 159.4.

1-Phenoxy-2-[(2-pyridylmethyl)amino]-1-ethanol (3z). ^{1}H NMR ($CDCl_3$): ppm 8.20-8.43 (1H, m), 7.50-7.78 (1H, m), 7.03-7.16 (4H, m), 6.71-6.84 (3H, m), 5.60 (2H, brs, -NH, -OH), 3.78-4.05 ppm (5H, m); ^{13}C NMR: ppm ($CDCl_3$) 53.2, 59.0, 114.5, 115.6, 121.0, 129.3, 137.0, 148.9, 158.4.

1-Chloro-3-[(2-pyridylmethyl)amino]-2-prpanol (3a'). ^{1}H NMR ($CDCl_3$): ppm 9.07 (1H, d, *J* = 5.1 Hz), 7.7 (1H, d, *J* = 5.9 Hz), 7.27-7.32 (2H, m), 5.61 (2H, brs, -NH, -OH), 3.97-4.01 (2H, m), 3.54 (2H, s), 2.76-3.01ppm (3H, m); ^{13}C NMR: ppm ($CDCl_3$) 46.5, 54.2, 54.3, 122.7, 135.0, 148.6, 169.1.

RESULTS AND DISCUSSION

In order to delineate the standard operating conditions, cyclohexene oxide **1a** (5 mmol) was treated with 2-picolylamine **2a** (5 mmol) under solvent free conditions in the presence of SA (0.5 mmol) at 70 ºC in an oil bath. Complete conversions took place in 60 min leading to a quantitative yield of the resultant 2-(2-picolylamine) cyclohexanol **3a**. The catalyst was recovered by filtration after diluting the reaction mixture with diethyl ether and was reused repeatedly without any significant loss of catalytic activity.

To evaluate the generality, reactions of **1a** were carried out with various aromatic and aliphatic amines under the catalytic influence of SA and excellent results were obtained (Table 1). The reaction protocol is simple and does not require dry

Table 1. Reaction of **1** with Various Amines in the Presence of SA

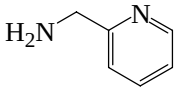
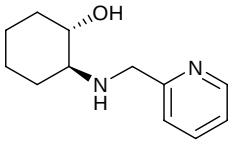
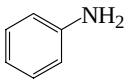
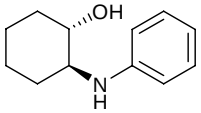
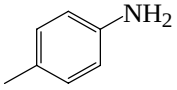
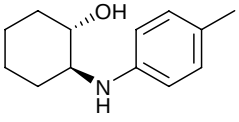
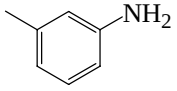
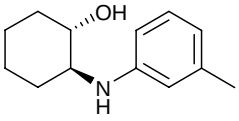
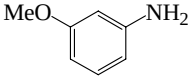
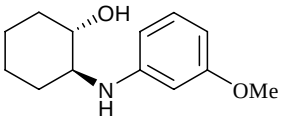
Entry	Substrate		Product		Time (h)	Yields (%)[a,b]
1		**2a**		**3a**	1	98
2		**2b**		**3b**	2	95
3		**2c**		**3c**	3	98
4		**2d**		**3d**	1	98
5		**2e**		**3e**	1	97

Table 1. Continued

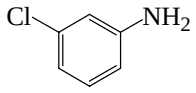
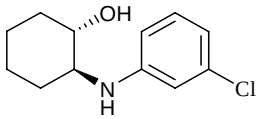
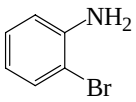
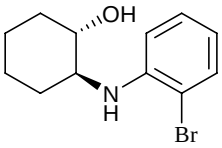
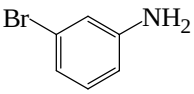
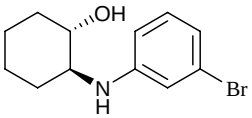
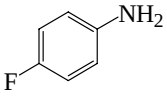
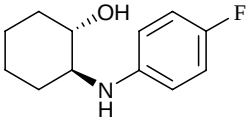
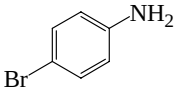
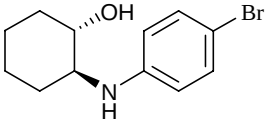
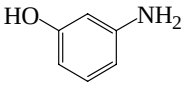
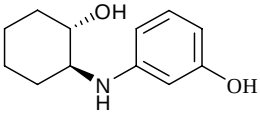
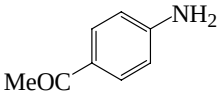
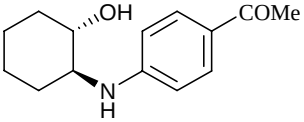
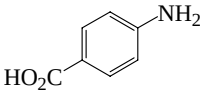
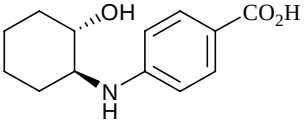
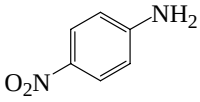
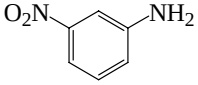
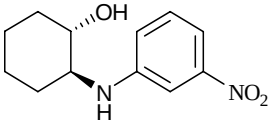
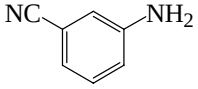
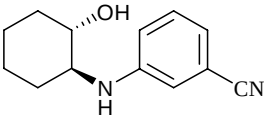
6		**2f**		**3f**	3	90
7		**2g**		**3g**	3	95
8		**2h**		**3h**	0.5	90
9		**2i**		**3i**	1	95
10		**2j**		**3j**	2	98
11		**2k**		**3k**	1	94
12		**2l**		**3l**	2	97
13		**2m**		**3m**	3.5	87
14		**2n**	No reaction		24	-
15		**2o**		**3n**	24	50
16		**2p**		**3o**	24	50

Table 1. Continued

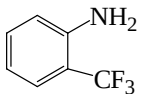
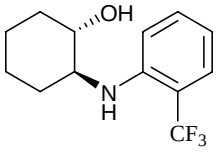
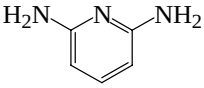
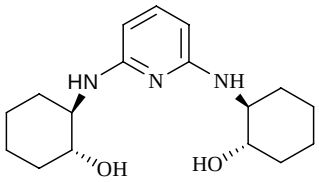
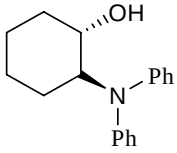
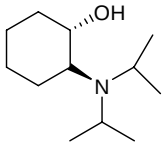
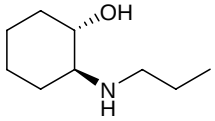
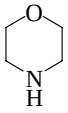
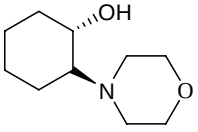
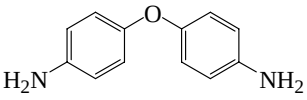
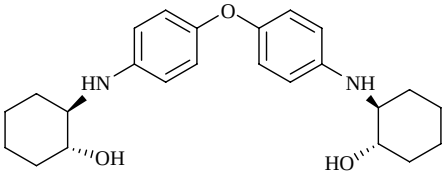
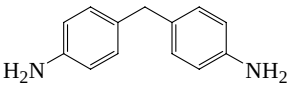
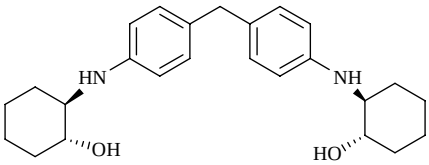
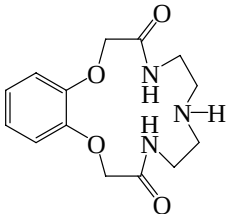
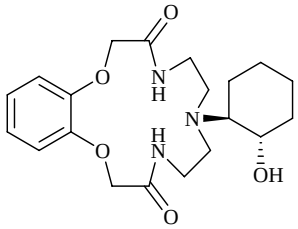
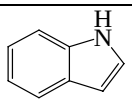
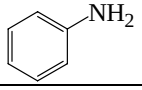
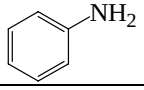
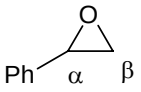
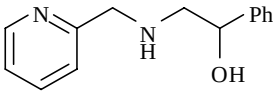
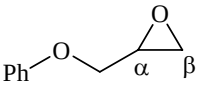
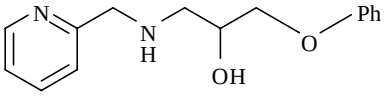
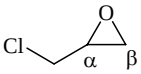
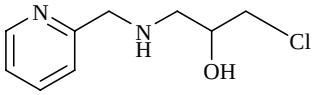
17		**2q**		**3p**	4	78
18		**2q**		**3q**	3	73
19	PhNHPh	**2r**		**3r**	24	50
20	$(CH_3)_2CHNHCH(CH_3)_2$	**2s**		**3s**	2	86
21	$CH_3CH_2CH_2NH_2$	**2t**		**3t**	3	94
22		**2u**		**3u**	1	95
23		**2v**		**3v**	2	90
24		**2w**		**3w**	2	93
25		**2x**		**3x**	3	82

Table 1. Continued

26		**2y**	No reaction		24	-
27				**3b**	4	90[c]

[a]The resultant racemic aminocyclohexanol was obtained. [b]Yields are the isolated compounds. [c]Reaction was recorded on 100 mmol scale.

Table 2. SA-Catalyzed ring Opening of 1,2-Epoxides **1b-d** with 2-Picolylamine **2a** under Solvent Free Conditions

Entry	1,2-Epoxide	Product	Time (h)	Yields (%)[a]
1	 **1b**	 **3y**	2	96[b]
2	 **1c**	 **3z**	3	95
3	 **1d**	 **3ab**	1	93

[a]Isolated yields. [b]α products were isolated in 4% yield.

glassware and reagents. This is very important for scaling-up the process. The final amino alcohol was isolated in >99% purity in 50-98% yield.

The results summarized in Table 1 reveal that excellent yields were obtained with aromatic and aliphatic amines and, in each occasion, the resultant racemic 2-aryl/ alkylaminocyclohexanol was obtained with exclusive *trans* diastereoselectivity as detected by ^{1}H NMR spectroscopic analysis. Primary and secondary amines react very rapidly.

Aniline and its derivatives with electron donating substitutes also react quite fast. However, anilines with electron withdrawing substitutes, as well as strically hindered anilines, react very slowly and aminolysis required prolonged reaction times. The reaction of diamines showed good results without any significant influence of their structures on the product yields. These products can be useful for preparation of macrocyclic compounds. The conversion of aniline into 2-aryl/alkylaminocyclohexanol on a 100 mmol scale (entry 27) proceeded just as well as the 1 mmol reaction.

The SA catalyzed conditions were then extended to a variety of 1,2-epoxides (Table 2). All the reactions were fast and completely β- or C_2- regioselective. Excellent chemoselectivity was achieved with epichlorohydrin (entry 3, Table 2) resulting in 93% yield of the aminoalcohol corresponding to nucleophilic attack at the terminal carbon of the epoxide moiety. No product arising from nucleophilic

displacement of the chlorine could be detected through MS analysis of the reaction mixture.

It has already been manifested that sulfamic acid was comprised not of the aminosulfonic acid form, but rather $^{+}H_3NSO_3^{-}$ zwitterionic units by both X-ray and neutron diffraction techniques [12]. Thus, sulfamic acid is immiscible with diethyl ether and it can be precipitated from the reaction mixture by dispersing it in a large amount of diethyl ether. After filtration, a neat product can be obtained by concentrating the filtrate.

The reusability and catalytic activity of H_2NSO_3H (SA) was studied in this system. The catalyst can be so easily separated by dispersing the reaction mixture in diethyl ether, that the recovery and reuse of SA could be very convenient. As shown in Table 3, the yields of 2-(2-picolylamine)cyclohexanol only decreases a little after the reuse of SA for three times.

Table 3. Reuse of SA

Number of use	Yield (%)	Recovery of SA
1	98	96
2	94	95
3	92	95

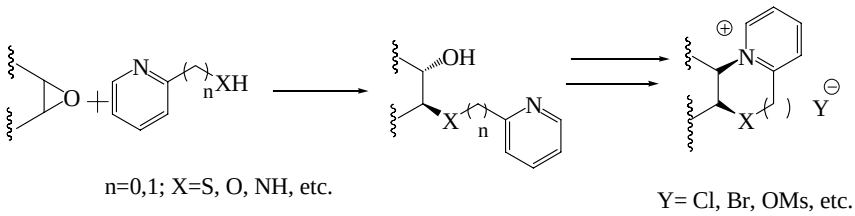
A comparison of the present method, using SA, with some of the previously known methods and some other acidic catalysts is collected in Table 4, which demonstrates that the present method is a useful method for this transformation.

According to Table 4, SA can catalyze the preparation of 2-(2-picolylamine) cyclohexanol in less than 1 h in 98% isolated yield. A comparison of the present method, with respect to the

Table 4. Ring Opening of Cyclohexene Oxide **1a** with 2-Picolylamine **2a** at 70 ºC: Effects of Catalysts

Entry	Catalyst	Solvent	Time (h)	Yields (%) [a]
1	$Zn(OTf)_2$ [9d]	None	3	<1
2	$Cu(OTf)_2$ [9d]	None	3	33
3	$In(OTf)_3$ [9d]	None	3	75
4	$Yb(OTf)_3$ [9d]	None	3	85
5	$Al(OTf)_3$ [9d]	None	3	99
6	$ZrCl_4$ [9d]	None	3	52[b]
7	$TiCl_4.(THF)_2$ [9d]	None	3	7[b]
8	$ZnCl_2$ [9d]	None	24	0
9	$Zn(OAc)_2.2H_2O$	None	24	0
10	$SnCl_4.5H_2O$	None	24	<1
11	$AlCl_3$	None	24	<1
12	$MeSO_3H$	None	3	0
13	*p*-TSA[c]	None	3	5
14	ASA[d] [21]	None	24	86
15	SA	MeCN	24	<1
16	SA	Diethyl ether	24	<1
17	SA	None	1	98

[a]Isolated yields. [b]Additional 18% conversion to *trans*-2-chlorocyclohexanol was obtained. [c]*p*-toluenesulfonic acid. [d]Aluminasulfonic acid.



Scheme 2

reaction time and product yield, with those of the literature reports dealing with the reaction of **1** with **2a** reveals that this newly developed method is superior to the reported procedures. Although the $Al(OTf)_3$ catalyzed reaction affords comparable yields and time, the susceptibility of $Al(OTf)_3$ to hydrolytic decomposition becomes determinant for handling and recycling of the catalyst and also $Al(OTf)_3$ is not commercially available. However, SA is a cheaper and commercially available catalyst that can be reused for several times. Other catalysts/reagents were in some cases truly effective but they completely failed with bihaptic nucleophiles such as 2-picolylamine **2a**.

Also many reported catalysts such as $CoCl_2$ [4f], $TaCl_3$ [4e], Zr-salt [7b] etc. were not effective for reaction with aliphatic amines. Possibly these catalysts are strong Lewis acids making the formation of complex metal salts with aliphatic amines cause the catalyst destruction and make these metal salts ineffective for use as catalysts for opening of epoxide rings by aliphatic amines. Due to the mild acidic nature of SA, it works effectively for epoxide ring opening reaction with aliphatic amines. The results summarized in Table 1 reveal that the present method is applicable for aromatic as well as aliphatic amines.

CONCLUSIONS

To conclude, we have shown that sulfamic acid is a highly active catalyst for the aminolysis of 1,2-epoxides in good yields. The title compounds are of chemical and medicinal interest. The advantages of this environmentally benign and safe protocol include a simple reaction set-up, dose not require specialized equipment, mild reaction conditions, high product yields, short reaction times, and the limitation of solvents.

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