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RESEARCH LETTER

Boric acid/glycerol as an efficient catalyst for regioselective epoxide ring opening by aromatic amines in water

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Regioselective epoxides ring opening with aromatic amines using boric acid and glycerol in water as a green media have been investigated. Corresponding β-amino alcohols were obtained with excellent yields and considerable regioselectivity. High yields of the products and mild reaction conditions using green catalyst and water as a green solvent are some advantages of this procedure.

Keywords: epoxides; ring-opening; aromatic amines; water; boric acid; glycerol

Introduction

β-Amino alcohols are an important class of organic compounds that have found considerable use as a building block in the organic synthesis of various natural products and pharmaceuticals (*1, 2*). Many applications have been reported that show importance of these compounds as versatile intermediates in natural products, β-blockers, insecticidal agents (*3–5*), chiral auxiliaries for asymmetric synthesis (*6*), and also these compounds act as therapeutic agents for a wide variety of human diseases and disorders (*7–10*). For example, 2-aminoalcohols represent a broad range of β-adrenergic blockers widely used in the management of disorders related to the sympathetic nervous system (*11–18*). One of the most practical and straightforward synthetic procedures for the preparation of these important compounds involve the ring opening of epoxides with amines. Due to the high reactivity of epoxides that is related to both the strain of the three-member ring and also the polarization of the C-O bonds, these compounds are capable to use as starting materials to afford the corresponding β-functionalized alcohol products (*19, 20*). There are several reports in the literature for the ring opening of epoxides with alcohols, thiols, and amines, but aromatic amines have received less attention, perhaps due to their high affinity to Lewis acids or lower nucleophilicity (*21*).

To date, many procedures have been reported to promote epoxides ring opening. Several catalysts such as alumina (*22*), calcium trifluoromethanesulfonate (*2*), transition metal-based Lewis acids (*23*), lithium bistrifluoromethanesulfonimide (*20*), bismuth triflate (*24*), heteropoly acids (*25*), bismuth trichloride (*21*), Ti-S-(−)-BINOL complex (*26*), zinc(II) perchlorate hexahydrate (*27*), diisopropoxyaluminium trifluoroacetate (*28*), vanadium(III) chloride (*19*), indium tribromide (*29*), ZrCl$_4$ (*6*), samarium iodides (*30*), and copper(II) tetrafluoroborate (*31*) have been reported for the ring opening of epoxides with amines. Most of these methodologies have one or more drawbacks such as the cost of the catalyst, stoichiometry of the starting materials, sensitivity to moisture, and using hazardous organic solvents. Also, most of these procedures reported so far are restricted to simple aromatic and aliphatic amines and reports for the ring opening of epoxides with diactivated aromatic amines is rare. Giving a procedure to overcome these drawbacks will be interesting. In recent years, boric acid has gained special attention as a catalyst in organic synthesis because of many advantages such as excellent solubility in water, easy handling, inexpensiveness, commercially available, and environmentally friendly (*32, 33*). Therefore, boric acid has successfully been utilized in numerous reactions (*34, 35*).
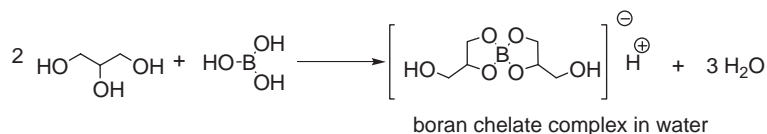
Results and discussion

In continuation of our research on finding green methods for organic transformations (*36–42*), herein we wish to report an efficient procedure for the ring opening of epoxide with aromatic amines to afford
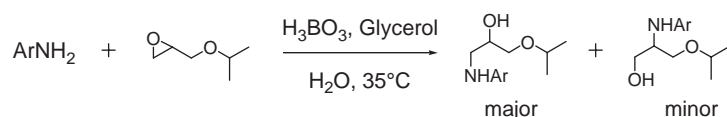
Scheme 1. Ring opening of epoxides with aromatic amines by boric acid and glycerol in water.

Scheme 2. Formation of boron chelate complex in water.

β-amino alcohols in water under mild conditions by using boric acid and glycerol (Scheme 1).

It is well known that boric acid and glycerol form a boron chelate complex in water. Because of boron chelate complex formation and releasing H^+, this complex is more acidic than boric acid (Scheme 2) (*43*).

We investigated the effects of boric acid complexation with glycerol in aqueous medium in term of pH values and the results are summarized in Table 1. As shown in Table 1 with increasing the concentration of boric acid in constant concentration of glycerol, the pH value was decreased. Also, when the concentration of boric acid is constant, with increasing the concentration of glycerol, the pH value was decreased. In continuation, we also used other polyols such as D-(–)-sorbitol and pentaerytrol and we have observed the same effect as glycerol (Table 1, entries 12 and 13).

We started our work on the ring opening of epoxides with aromatic amines in the present with a catalytic amount of boric acid and glycerol. Ring opening of 2,3-epoxypropyl isopropyl ether with aniline was selected as a model reaction. This reaction was carried out in the present of (30 mol%) boric acid with two drops of glycerol in water at room temperature (20°C) under the conditions shown in entry 4, Table 1. The reaction was not completed under this condition (entry 11, Table 3) and gives 73% yield. By varying the temperature of the reaction to 35°C, excellent yields were obtained and higher temperatures did not lead to an improvement in yield.

We have compared the efficiency of the reaction in water and various organic solvents. For this purpose, several polar and non-polar organic solvents were screened and we have found that the highest yields were obtained in water, methanol, and DMSO. The reaction gave poor to moderate yields in CH_2Cl_2, THF, CH_3CN, DMF, and absolute ethanol (Table 2).

With these improved conditions in hand, we sought to probe the generality of the reaction by opening of other epoxides with various aromatic

Table 1. pH values of solution of boric acid with polyols.

Entry	Boric acid (M)	Glycerol (M)	pH[a]
1	—	—	7.7 ⟸ H_2O
2	0.15	—	6.8
3	0.15	0.15	6.3
4	0.15	0.2	6.0 2⟸ drop (Glycerol)
5	0.15	0.4	5.8
6	0.15	1	5.0
7	—	0.4	7.7
8	0.2	0.4	5.6
9	0.4	0.4	5.1
10	0.6	0.4	4.6
11	1	0.4	4.0
		Polyhedrol (M)	
12	0.15	0.15[b]	5.5
13	0.15	0.15[c]	3.5

[a]pH was measured by pH-meter (827 pH lab, Metrohm, Swiss made).
[b]Pentaerytrol.
[c]D-(–)-sorbitol.

Table 2. Optimization of ring opening of epoxide catalyzed by boric acid (30 mol%) in different solvents in the presence of glycerol.

Solvent[a,b]	H_2O	CH_2Cl_2	THF	Pentane	CH_3CN	CH_3OH	DMF	DMSO	C_2H_5OH
Yield (%)	100	Trace	Trace	61	23	100	44	100	47

[a]Solvent was used as received.
[b]Reaction condition: aniline (3 mmol), epoxide (2.5 mmol), boric acid (30 mol%), glycerol (2 drops) and solvent (5 mL).

amines. Aniline, 4-chloroaniline, 2,4-dichloroaniline, 4-methoxyaniline, and 4-methylaniline were reacted well with epoxides such as glycidyl phenyl ether, glycidyl isopropyl ether, 1,2-epoxy-butane, 1,2-epoxypropane, allyl 2,3-epoxypropyl ether, and glycidyl methacrylate to give the corresponding amino alcohols with excellent yields (Table 3). Also, diep-oxide (Table 3, entries 23–25) gave excellent yields with aromatic amines. Reaction of 2,3-epoxypropyl methacrylate with amines gives the β-amino alcohols

Table 3. Aminolysis of epoxides in water in the presence of boric acid and glycerol[f].
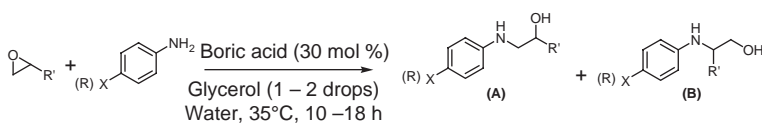
Entry	Epoxide	Aromatic amine	Yield%	Ratio (A:B)[a]	References[b]
1		R = H	95	89:11	(44)
2		R = Me	100	83:17	(44)
3		R = OMe	100	86:14	(44)
4		R = OH	100	81:19	
5		X = Cl	93	95:5	(44)
6		R = H	100	62:38	(44)
7		X = Cl	100	85:15	(44)
8		R = H	94	14:86	(44)
9		R = Me	100	17:83	(44)
10		X = Cl	100	15:85	(44)
11		R = H	93	87:13	(44)
			73[c]	87:13	
			100[d]	86:14	
			100[e]	85:15	
12		R = OMe	100	85:15	(44)
13		R = H	100	86:14	(44)
14		R = OMe	100	71:29	(44)
15		X = Cl	100	85:15	(44)
16		R = H	100	A > 99	(44)
17		R = Me	100	92:8	(44)
18		R = OMe	100	90:10	(44)
19		X = Cl	98	A > 99	(44)
20		R = H	93	80:20	(44)
21		R = Me	95	77:23	(44)
22		R = Me	100	66:34	(44)
23		R = H	100[f]	84:16	(44)
24		R = Me	100[f]	85:15	(44)
25		R = OMe	100[f]	88:12	(44)

[a]Ratio was determined by NMR spectroscopy.
[b]References for known compounds.
[c]Reaction was carried out at 20°C.
[d]Using pentaerythritol as polyol.
[e]Using D-(−)-sorbitol as polyol.
[f]Ring opening occurred for both of the epoxide rings.

as the only products and Michael addition adduct was not observed (entries 16–19). As shown in Table 3, all 1,2-epoxides except styrene epoxide give the S_N2 like adducts by nucleophilic attack of amine to the less substituted carbon. Also reaction of glycidyl isopropyl ether with aniline in the presence of polyols gives excellent yields (Table 3, entry 11).

In conclusion, we have developed an efficient and clean procedure for the ring opening of epoxides with aromatic amines using boric acid and glycerol in water with considerable regioselectivity and excellent yields. Low cost of catalyst, using water as solvent, neutral conditions, and high yields of products are the most advantageous of this procedure. Also we have shown the versatility of this transformation by applying this method to a wide variety of aromatic amines and epoxides. Although the reaction can be completed in lower pH, we carried out the reaction at pH = 6 as neutral medium.

Experimental

All reactions were carried out in an atmosphere of air. All chemicals and solvents except water (tap water) were purchased from Merck or Fluka and used as received. Crystalline boric acid was used for the reaction. All reactions were monitored by TLC on silica gel 60 F254 (0.25 mm), visualization being effected with UV and/or by developing in iodine. The pH was measured by pH-meter (827 pH lab, Metrohm, Swiss made). ^{1}H NMR and ^{13}C NMR were recorded on a Brucker 500 MHz spectrometer. Chemical shifts are reported in (ppm) relative to TMS or $CDCl_3$ as internal.

General procedure

To a stirred solution of epoxide (2.5 mmol) and amine (3 mmol) was added water (5 mL), boric acid (30 mol%), and glycerol (1–2 drops). The resulting mixture was stirred at 35°C for 15–18 h. The mixture was extracted by ethyl acetate (3 × 10 mL). After the solvent was evaporated, the crude product was purified by flash column chromatography to provide the pure product. All compounds were characterized on the basis of their spectroscopic data (^{1}H NMR and ^{13}C NMR) and by comparison with those reported in the literature.

Acknowledgements

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