J IRAN CHEM SOC (2013) 10:7–11
DOI 10.1007/s13738-012-0122-3

ORIGINAL PAPER

Catalyst-free regioselective ring opening of epoxides with aromatic amines in water and solvent-free conditions

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Received: 16 November 2011 / Accepted: 6 June 2012 / Published online: 3 July 2012

Abstract Without using any catalysts, a variety of epoxides undergo ring-opening by aromatic amines to afford the corresponding 1,2-amino alcohols in high to excellent yields with good regioselectivity in the presence of water as solvent and under solvent-free conditions.

Keywords Ring opening · Epoxides · Aromatic amines · Water · Regioselective · Solvent-free

Introduction

Increasingly, chemists are looking for cleaner, more environmentally benign procedures to devise new synthetic routes [1]. In order to this, chemists have placed a strong emphasis on the improvement of traditional ways for chemical reactions especially in organic synthesis. In recent years, design of green processes has become an eminent issue [2]. Currently, there are five main "green" systems: supercritical fluids (SCFs), using fluorinated solvents, ionic liquids (ILs) or water as solvent and solvent-free reactions [3]. In this report, we have used water as green medium or solvent-free systems for ring opening of epoxides. These two green approaches have gained special attention by synthetic organic chemists, because of their unique properties compared to the other three "green" systems. Reactions performed in water as solvent have attracted considerable attention due to a wide range of obvious advantages, such as cost, availability, safety, its environmental friendliness, and enhancement of selectivity with respect to the use of organic solvents [4–12]. Water also has practical advantages over organic solvents, since in contrast to many other solvents, water provides not only a medium for solution chemistry, but also often participates in elementary chemical events on a molecular scale and acts as a catalyst to accelerate reactions [1, 9–12].

On the other hand, solvent-free reactions have several advantages, such as reducing pollution and energy consumption, high efficiency, low cost, simplified procedures and handling, environmentally friendly with easy work up procedure [2, 13–16].

Epoxides are valuable intermediates in organic synthesis. The strain of the three-membered rings and the polarization of the C–O bonds in epoxides enhance their reactivity with a large number of nucleophiles. High reactivity of epoxides with various nucleophiles leads to highly regioselective and stereospecific ring opening products. Due to these properties of the epoxides and the ease of preparation, epoxides are used as useful intermediates in organic synthesis. Epoxides can undergo ring opening with amines, alcohols and thiols as nucleophilic compounds to form the C–C [17–20], C–N [21–26], C–O [27–30], or C–S [31, 32] bonds.

Since β-amino alcohols are a useful and important class of organic compounds, organic and medicinal chemists devoted considerable attention to use these compounds as versatile intermediates in the synthesis of variety of biologically active natural and synthetic products [33–40]. Nucleophilic ring-opening of epoxides by amines is an important reaction for synthesizing β-amino alcohols. In addition, almost all procedures reported so far for the preparation of β-amino alcohols by ring opening of

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epoxides are restricted to simple aromatic and aliphatic amines in the presence of various catalysts [33, 41–48]. But aromatic amines have received less attention, maybe due to their high affinity to Lewis acids or low nucleophilicity [22, 26]. Bonollo et al. [49] have reported aminolysis of epoxides with aliphatic and aromatic amines under mild basic and pH-controlled conditions. We have successfully used water as a reaction medium for the ring opening of epoxides with aliphatic amines [50]. Therefore, an efficient catalyst-free system for the ring opening of epoxides with aniline derivatives in water or under solvent-free conditions is developed.

Experimental

General

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. 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. ^{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 for the ring opening of epoxides with aromatic amines in water

To a stirred solution of an epoxide (2.5 mmol) and an amine (3 mmol), water (4 mL) was added, and the mixture was stirred at 60 °C for 18 h. The mixture was extracted by ethyl acetate (3 × 10 mL), and the crude product was purified by flash column chromatography to provide the corresponding product. For solvent-free conditions, the mixture of an epoxide (2 mmol) and an amine (2 mmol) was stirred at 60 °C for 18 h. All compounds were characterized on the basis of their spectroscopic data (NMR) and by comparison with those reported in the literature.

General procedure for large scale synthesis

In a 100-mL round bottom flask equipped with magnetic stir bar, aniline (10 g, 107 mmol), H_2O (50 ml) and 1,2-epoxybutane (7.7 g, 107 mmol) were added and the mixture stirred at 60 °C for 20 h. After completion, the mixture was separated and the organic phase was washed with water (100 mL), and evaporated in rotary evaporator to remove unreacted epoxide. The product was obtained in 95 % isolated yield with 84:16 ratios.

Selected spectroscopic data for the major isomer

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.22 (6H, d, $J = 6.1$ Hz), 3.11 (1H, dd, $J = 12.4$ and 3.8 Hz), 3.44–3.65 (3H, m), 3.95 (1H, m), 6.44 (1H, dd, $J = 8.7$ and 2.6 Hz), 6.69 (1H, d, $J = 2.2$ Hz), 7.17, (1H, d, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 22.5, 47.2, 69.3, 70.5, 72.8, 114.5, 116.9, 120.7, 131.1, 133.3, 148.1; MS (EI): $m/z = 279$, 277, 190, 188, 176, 174, 161, 99, 43 (100), 41 (Table 2, entry 7).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.20 (6H, d, $J = 6.1$ Hz), 3.11 (1H, dd, $J = 12.9$ and 7.1 Hz), 3.25 (1H, dd, $J = 12.4$ and 3.8 Hz), 3.42–3.63 (6H, m), 3.75 (3H, s), 3.95 (1H, m), 6.16–6.25 (3H, m), 7.02 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 22.5, 47.2, 55.2, 69.3, 70.8, 72.6, 99.6, 103.2, 106.6, 130.2, 150.1, 161.2; MS (EI): $m/z = 239$, 150, 136, 121, 93, 77, 45, 43 (100), 41, 39, 29, 27, 15 (Table 2, entry 9).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.68–3.89 (2H, m), 4.12 (1H, dd, $J = 14.1$ and 7.0 Hz), 4.60 (1H, br), 6.44 (1H, d, $J = 8.6$ Hz), 6.70 (1H, d, $J = 2.1$ Hz), 7.15–7.39 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 60.3, 67.3, 113.3, 116.9, 120.5, 127.1, 128.3, 129.4, 131.1, 133.0, 139.8, 147.4; MS (EI): $m/z = 283$, 281, 252, 250, 176, 174, 172, 147, 145, 103, 91, 77, 31(100) (Table 2, entry 11).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.95 (1H, br, –OH), 3.07–3.23 (2H, m), 3.43–3.51 (2H, m), 3.97–4.03 (3H, m), 4.20 (1H, br, –NH), 5.22–5.31 (2H, m), 5.88 (1H, m), 6.42 (1H, d, $J = 8.0$ Hz), 6.67 (1H, d, $J = 2.2$ Hz), 7.16 (1H, d, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 46.9, 68.9, 72.2, 72.7, 117.2, 114.8, 117.9, 120.2, 130.9, 133.0, 134.6, 148.2; MS (EI): $m/z = 277$, 275, 176, 174, 161, 84, 47, 39, 35 (100) (Table 2, entry 13).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.93 (3H, s), 3.10 (1H, dd, $J = 12.9$ and 7.4 Hz), 3.23 (1H, dd, $J = 12.9$, 4.0 Hz), 3.75 (1H, br, –NH), 4.05–4.22 (3H, m), 5.62 (1H, s), 6.15 (1H, s), 6.42 (1H, d, $J = 8.0$ Hz), 6.67 (1H, d, $J = 2.2$ Hz), 7.14 (1H, d, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 18.7, 46.8, 66.9, 68.7, 114.5, 116.8, 120.7, 126.9, 131.0, 133.3, 136.2, 147.9, 167.8; MS (EI): $m/z = 306$, 304, 303, 178, 176, 174, 69, 43, 41 (100), 39 (Table 2, entry 17).

Results and discussion

As part of our ongoing efforts to explore environmentally friendly synthesis [51–56], herein we describe a simple, catalyst-free, efficient, and regioselective method for the synthesis of β-hydroxyl amines in high to excellent yields in water or solvent-free conditions (Scheme 1).

In the first step, we have examined the reaction of 2,3-epoxypropyl isopropyl ether with aniline as a model

Scheme 1 Epoxide ring opening with aromatic amines

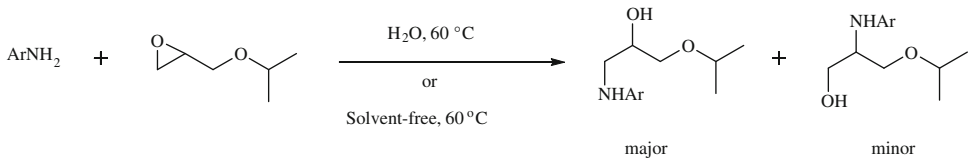
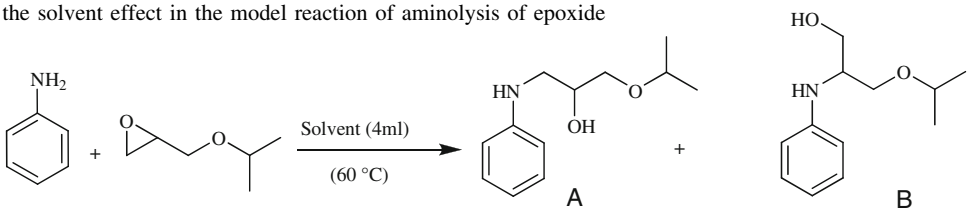


Table 1 Study of the solvent effect in the model reaction of aminolysis of epoxide



Entry	Solvent	Yield (%)	Ratio (A:B)[a]
1	MeOH	100	(81:19)
2	C_2H_5OH	100	(80:20)
3	Pentane	27	–
4	CH_3CN	100	(82:18)
5	$CHC1_3$	100	–
6	THF	23	–
7	CH_2CI_2	100	(80:20)
8	DMF	100	–
9	Toluene	100	–
10	$C_2H_4CI_2$	28	–
11	H_2O[b]	95	(83:17)
12[c]	S.F.	100	(73:27)

[a] Ratio was determined by NMR spectroscopy

[b] Double distilled water

[c] Solvent-free condition

reaction in water at room temperature (20 °C) to obtain the corresponding amino alcohol (Table 2, entry 5). The reaction was not complete at this temperature. By increasing the temperature, the epoxide was converted to the products completely. The optimum temperature was found to be 60 °C (Table 2, entry 5). It is clear that the temperature plays an important role in this reaction.

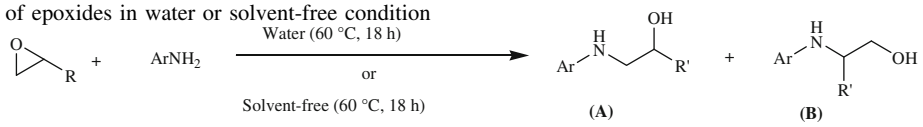
In the next step, we have performed the reaction in various common organic solvents. We have found that the reaction can also proceed in low-polar solvents such as toluene, $CHCl_3$, DMF, acetonitrile, and CH_2Cl_2. The yields were lower in 1,2-dichloroethane, THF, and pentane. Among these solvents, water was found to be the best solvent for this reaction. We also performed the model reaction in double distilled water to diagnose the effects of mineral ions in regular water. We observed that minerals in tap water had no effect on the reaction. Also, we have done the model reaction under solvent-free conditions and in the presence of two drops of water as catalyst. The result was the same as water was used as solvent.[1] The solvent optimization results are listed in Table 1.

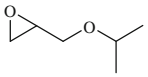
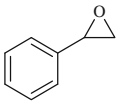
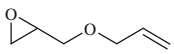
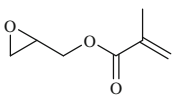
[1] It is difficult to distinguish in/on water in this reaction.

These results encouraged us to continue this procedure for exploiting the generality of this reaction by ring-opening of other epoxides with various activated and deactivated aromatic amines. Aniline, 4-chloroaniline, 3,4-dichloroaniline, and *p*-anisidine were reacted well with epoxides such as 2,3-epoxypropyl phenyl ether, 2,3-epoxypropyl methacrylate, 1,2-epoxybutane, 1,2-epoxypropane, allyl 2,3-epoxypropyl ether, epoxystyrene, and epoxycyclohexane to give the corresponding amino alcohols with good to excellent yields (Table 2). The reaction did not proceed with highly deactivated aromatic amines such as *p*-nitroaniline. Large scale synthesis of *β*-amino alcohol was also carried out by the reaction of aniline with 1,2-epoxybutane in water with 95 % yield (Table 2, entry 2).

In continuation of our attempt to approach green principles, we also investigated ring opening of epoxides with aromatic amines under solvent-free conditions. Since almost all of the epoxides that we used were liquid, it was possible to implement solvent-free condition. By mixing aromatic amines with all the epoxides (1 to 1 ratio) and stirring of the mixture at 60 °C for 18 h, the products were obtained as well as using water, except in the case of

Table 2 Aminolysis of epoxides in water or solvent-free condition



Entry	Epoxide	Aromatic amine	Water [yield % (A:B)[a,b]]	Solvent-free [yield % (A:B)]
1		Aniline	100 (75:25) [42]	–
2		Aniline	100 (86:14) [57]	
		Aniline	95 (84:16)[c] [57]	–
3		*p*-Chloroaniline	100 (96:4) [57]	–
4		*p*-Anisidine	100 (67:33) [57]	85 (68:32)
5		Aniline	100 (85:15) [57]	95 (80:20)
		Aniline	80 (89:11)[d]	–
		Aniline	92 (85:15)[e]	–
		Aniline	100 (79:21)[f]	–
		Aniline	96 (84:16)[g]	–
6		*p*-Chloroaniline	100 (94:6) [57]	98 (80:20)
7		3,4-Dichloroaniline	84	78 (80:20)
8		*p*-Anisidine	100 (96:4) [57]	100 (92:8)
9		*m*-Anisidine	–	94 (86:14)
10		Aniline	100 (19:81) [57]	90 (29:71)
11		3,4-Dichloroaniline	89 (22:78)	–
12		Aniline	100 (85:15) [57]	100 (72:28)
13		3,4-Dichloroaniline	63 (93:7)	43 (100:0)
14		*p*-Chloroaniline	100 (90:10) [57]	89 (82:18)
15		Aniline	100 (95:5) [57]	95 (81:19)
16		*p*-Chloroaniline	100 [57]	100 (100:0)
17		3,4-Dichloroaniline	80 (80:20)	72 (100:0)
18		Aniline	100 [42]	N.R.
19		*p*-Anisidine	100 [22]	–
20		*p*-Toluidine	100 [22]	–

[a] The ratio was determined by NMR spectroscopy

[b] References are given for known compound

[c] Large scale

[d] The reaction was carried out at 20 °C

[e] The reaction was carried out at 35 °C

[f] The reaction was carried out in the presence of two drops of H_2O

[g] The reaction was carried out with double distilled water

epoxycyclohexane (Table 2, entries 18–20). The results are listed in Table 2.

In conclusion, we have investigated an economical and practical procedure for the ring opening of a wide range of epoxides using aniline derivatives. Distinctive points of this work are using water as medium, catalyst-free, and also implementing solvent-free conditions, which are an important feature for the developing of green chemistry. Probably in these reactions water acts as a catalyst and implements the reaction with high efficiency and regioselectivity. The water accelerating effects have been attributed to the hydrogen bonding or hydrophobic effect in the aqueous phase. The key advantage of the reaction under solvent-free condition is to eliminate the solvent, purification and extraction from the aqueous solution. Although the mechanism of the reaction under solvent-free condition is not clear for us, but we propose S_N2-like mechanism for ring opening of the epoxides and hydrogen bonding of the amine with epoxide promotes the reaction. In the case of epoxystyrene S_N1-like mechanism is proposed.

Acknowledgments We are grateful to the research council of Sharif University of Technology for financial support. We also thank the Faculty of Chemistry of Tarbiat Moallem University for supporting this work.

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