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Highly Chemoselective Addition of Amines to Epoxides in Water

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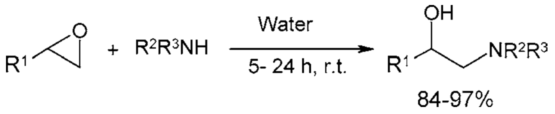
ABSTRACT



Aminolysis of a variety of epoxides by aliphatic and aromatic amines in water, in the absence of any catalyst with high yields, is reported. β-Amino alcohols were formed under mild conditions with high selectivity and in excellent yields.

β-Amino alcohols are important organic compounds of considerable use in medicinal chemistry, amino acids, and chiral auxiliaries.[1] One of the most practical and widely used routes for the synthesis of these compounds is the direct aminolysis of epoxides at elevated temperature with an excess of amine.[2] Recently, several methods using promoters or catalysts in different organic solvents[3] have been reported. These include supercritical carbon dioxide (scCO$_2$),[4a] microwave irradiation,[4b] hexafluoro-2-propanol,[4c] ionic liquid,[4d] Bi(OTf)$_3$ in water,[4e] and solvent-free conditions.[4f,g]

However, there are some limitations with these methodologies such as elevated temperatures, use of stoichiometric or moisture-sensitive catalyst, and hazardous organic solvents. By contrast, there is no report of the aminolysis of epoxides in water without using any catalyst.[4e]

The preparation of β-amino alcohols in water is desirable, since using water instead of an organic solvents has become more important due to environmental considerations in recent years.[5]

Herein, we wish to report the ring-opening of epoxides with a variety of amines in water at room temperature.[6] Treatment of epoxide **1** with 1.2 equiv of amine **2** resulted in formation of the β-amino alcohol **3**. The reactions were

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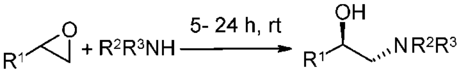
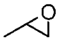
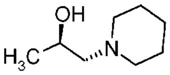
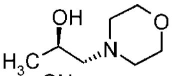
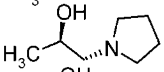
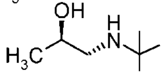
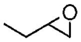
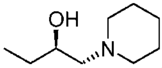
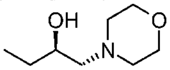
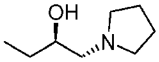
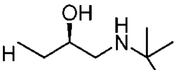
Table 1. Reactions of Aliphatic Epoxides with Aliphatic Amines in Water



1 2 3 (84-97%)

entry	epoxide	product	yield (%)
1			96
2			93
3			94
4			89
5			97
6			90
7			88
8			90
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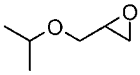
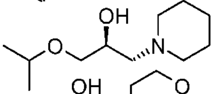
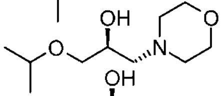
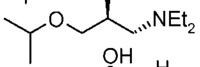
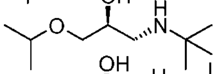
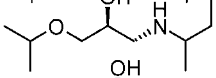
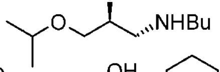
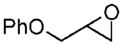
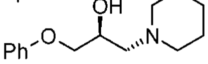
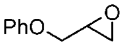
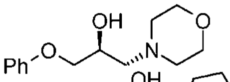
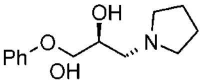
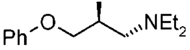
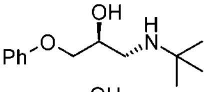
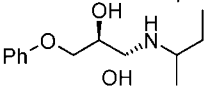
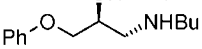
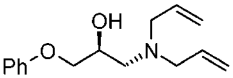
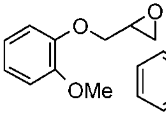
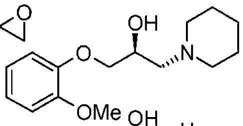
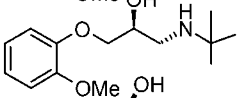
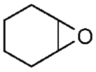
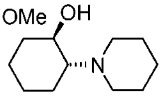
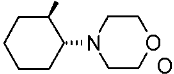
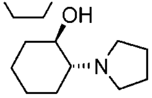
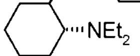
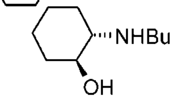
10			96
11			94
12			88
13			88
14			90
15			92
16			97
17			97
18			96
19			96
20			96
21			96
22			96
23			93
24			95
25			90
26			93
27			90
28			92
29			86
30			84

carried out with a very simple procedure in water at room temperature without adding any organic solvent or catalyst. In some cases, the β-amino alcohols precipitated from the solution and were separated by a simple filteration. Otherwise, they were extracted from the aqueous solution by diethyl ether.

To show the generality and scope of this new protocol, structurally diverse amines were treated with various epoxides. In general, the reaction rate of aminlolysis in water depends on the structure of the epoxide and on the nucleophilicity of the amines. The results are summarized in (Tables 1 and 2). The data in Table 1 clearly show that the reaction of aliphatic amines with different epoxides in water gives the corresponding β-amino alcohols in high yield and in a regioselective manner. The advantage of this procedure over the reported methods is the formation of the β-amino alcohols from attack at the terminal carbon of the epoxides (with the exception of styrene oxide) as the only product.[3,4] The procedure of these reactions is very simple, and the yields are generally high.[8] To the best of our knowledge, these results represent the highest regioselectivity reported to date for nucleophilic ring opening of epoxide with amines.

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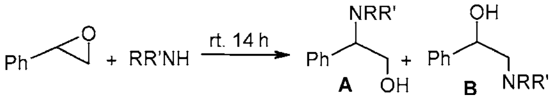
(6) (a) Azizi, N.; Saidi, M. R. *Organometallics* **2004**, *23*, 1457−1458. (b) Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383−387. (c) Azizi, N.; Saidi, M. R. *Eur. J. Org. Chem.* **2003**, 4630−4633. (d) Azizi, N.; Saidi, M. R. *J. Organomet. Chem.* **2003**, *688*, 283−285. (e) Azizi, N.; Rajabi, F.; Saidi, M. R. *Tetrahedron Lett.* **2004**, *45*, 9233−9236.

Table 2. Reaction of Styrene Oxide with Amines in Water

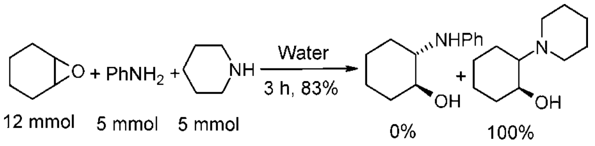


entry	amine	yield (%)	ratio A:B	entry	amine	yield (T)	ratio[a] A:B
1	aniline	97	96:4	11	pyrrolidine	93	35:65
2	*p*-isopropylaniline	94	90:10	12	Et$_2$NH	92	24:76
3	PhCH$_2$NH$_2$	88	70:30	13	Et$_2$NH[b]	0.0	
4	*n*-BuNH$_2$	94	25:75	14	Et$_2$NH[c]	0.0	
5	*tert*-BuNH$_2$	92	8:92	15	Et$_2$NH[d]	0.0	
6	diallylamine	90	30:70	16	Et$_2$NH[e]	0.0	
7	*sec*-BuNH$_2$	86	21:79	17	Et$_2$NH[f]	50	45:55
8	cyclohexylamine	92	20:80	18	Et$_2$NH[g]	0.0	
9	piperidine	96	35:65	19	Et$_2$NH[h]	0.0	
10	morpholine	96	10:90				

[a] Regioselectivity was determined by NMR spectra. [b] CH$_2$Cl$_2$. [c] CH$_3$CN. [d] Hexane. [e] Toluene. [f] Ethanol. [g] Diethyl ether. [h] Solvent-free.

Additions of aromatic amines such as aniline and 4-nitroaniline to alkyl epoxides are sluggish and give very low yields with the exception of styrene oxide. Therefore, the low reactivity of aromatic amines such as aniline shows the chemoselectivity in the addition of aliphatic amines to epoxides with this method. To show the chemoselectivity, cyclohexene oxide was treated with the mixture of aniline and piperidine. Analysis of the mixture after 10 h shows that only piperidine reacted with cyclohexene oxide (Scheme 1).

Scheme 1. Chemoselective Addition of Aliphatic Amines in the Presence of Aromatic Amines



Aniline and *p*-isopropylaniline react with styrene oxide and give high yields of the corresponding β-amino alcohols.

On the other hand, treatment of styrene oxide with different aromatic, aliphatic, and hindered amines gives a mixture of two regioisomers, **A** and **B**, in high yields (Table 2). Aminolysis of styrene oxide with aromatic amines afforded **A** as the major regioisomer, by nucleophilic attack at the benzylic carbon. In the case of aliphatic amines, preferential attack occurs at the terminal carbon, and the major product is regioisomer **B** (Table 2). For the sake of comparison, opening reactions of styrene oxide with diethylamine were carried out in the classic way in different organic solvents and under solvent-free conditions at room temperature. In common organic solvents (CH$_2$Cl$_2$, CH$_3$CN, toluene, and hexane) under solvent-free conditions and without using a catalyst, the reaction does not take place after 2 days. However, in the case of protic solvents such as ethanol, the reaction gives up to 50% of the product after 1 day.

The role of the water as reaction medium is still not clear. Hydrophobic and hydrogen bonding interactions and polarity are the main factors that influence the reactivity and selectivity of the process. We propose an S$_N$2 mechanism for these processes by comparison of the reaction conditions with those reported in the literature.[7] We are currently investigating the mechanism of the reaction of styrene oxide in aqueous medium.

In summary, we have demonstrated an economical and practical method for the synthesis of a wide range of β-amino alcohols under mild conditions in water. In light of its operational simplicity, simple purification procedure, high yields, complete regioselectivity (except styrene oxide), ability to proceed without a catalyst, and environmentally friendly conditions, this protocol is superior to the existing methods.

Acknowledgment. We are grateful to the Research Council of Sharif University of Technology for financial support.

Supporting Information Available: General experimental procedure for opening the epoxide ring in water and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051220Q

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(7) Amantini, D.; Fringuelli, F.; Piermatti, O.; Torttoioli, S.; Vaccaro, L. *Arkivoc* **2002**, 293−311.

(8) **General Procedure for the Synthesis of β-Amino Alcohols.** An epoxide (5 mmol) and water (2 mL) were placed in a test tube equipped with a magnetic stirrer. Then, an amine (6 mmol) was added in one portion, and the test tube was kept at room temperature under vigorous magnetic stirring for 5−24 h. The reaction was monitored with TLC. Then, water (2 mL) was added, and the organic materials were extracted with diethyl ether (2 × 10 mL). The organic layer was separated and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to give the β-amino alcohols in the almost pure form. The crude product was analyzed by GC and ^{1}H and ^{13}C NMR. In some cases, further purification was carried out by short-column chromatography on silica gel (ethyl acetate/petroleum ether).