

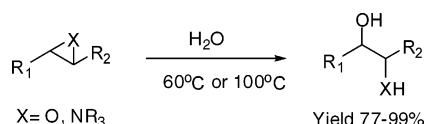
Hot Water-Promoted Ring-Opening of Epoxides and Aziridines by Water and Other Nucleophiles

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Received November 10, 2007

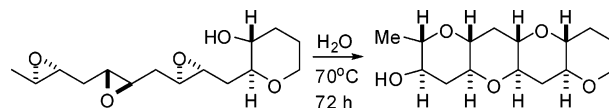


Effective hydrolysis of epoxides and aziridines was conducted by heating them in water at 60 or 100 °C. Other types of nucleophile such as amines, sodium azide, and thiophenol could also efficiently open epoxides and aziridines in hot water. It was proposed that hot water acted as a modest acid catalyst, reactant, and solvent in the hydrolysis reactions.

Introduction

Although water is cheap, safe, and clean compared with organic solvents, water is not a regular choice for the medium of organic reactions because of the insolubility of reactants and incompatibility of reaction intermediates. In certain situations, the special physical and chemical properties of water, such as high dielectric constant, high heat capacity, hydrophobic interactions between reactants, hydrogen bond formation between water and reactant, and acid or base characters may be utilized to promote organic reactions. In the early 1980s, Breslow's group reported that Diels–Alder reaction was remarkably accelerated in water owing to the hydrophobic effect.¹ This important finding dramatically changed chemists' attitudes toward the use of water as solvent for organic reactions. After that, a number of organic reactions were found to proceed very well in water.² A very recent work from Jamison's research group revealed that the cascade epoxide-opening yielding ladder polyether could be promoted by water. This finding presented a highly efficient synthesis of natural trans-fused polycyclic ethers as well as provided new evidence for the biosynthesis of this kind of natural products (Scheme 1).³ In this paper, we report that the ring-opening reactions of epoxides and aziridines can be promoted by hot water. A general acid-catalyzed mechanism was proposed based on the observed selectivity of the reactions in hot water.

SCHEME 1. Epoxide-Opening Cascades Promoted by Water



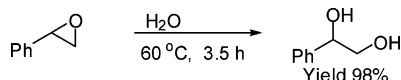
Results and Discussion

Hydrolysis of epoxides is a pivotal protocol for making synthetically useful vicinal diols. Compared with the use of protic acid,⁴ the hydrolysis of epoxides now can be conducted under milder condition by using solid or solid-supported Lewis acids,⁵ one-electron-transfer reagents,⁶ and other newly discovered reagents.⁷ In the course of our research to finding catalysts for enantioselective ring-opening of epoxides, we accidentally found that styrene oxide could be hydrolyzed in hot water (60 °C) within 3.5 h and the corresponding vicinal diol was obtained in 98% yield (Scheme 2). A literature search showed that in 1993, Kotsuki's group reported a catalyst-free hydrolysis

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SCHEME 2. Hydrolysis of Styrene Oxide in Hot Water

TABLE 1. Hydrolysis of Styrene Oxide and Cyclohexene Oxide in Water or a 1:1 Mixture of Water and Other Solvents^a

epoxide $\xrightarrow{\text{H}_2\text{O}:\text{organic solvent} = 1:1}$ vicinal diol			
entry	epoxides	other solvents	yield (%) ^b
1	styrene oxide	pure water	98
2	styrene oxide	MeOH	70
3	styrene oxide	EtOH	60
4	styrene oxide	<i>i</i> -PrOH	40
5	styrene oxide	<i>t</i> -BuOH	50
6	styrene oxide	ethylene glycol	96
7	styrene oxide	CH ₃ CN	9
8	styrene oxide	THF	1
9	styrene oxide	acetone	20
10	styrene oxide	DMF	6
11	styrene oxide	DMSO	38
12	styrene oxide	PEG400	40
13	styrene oxide	1,4-dioxane	95
14 ^c	cyclohexene oxide	pure water	89
15 ^c	cyclohexene oxide	1,4-dioxane	47
16 ^c	cyclohexene oxide	ethylene glycol	85

Reaction conditions: 2 mmol of epoxides in water or a 1:1 mixture of water and organic solvent was heated at 60 °C for 3.5 h. ^b GC yield. ^c The reaction was carried out at 80 °C for 12 h, isolated yield.

of epoxides in the mixed solvent of acetone and water at 60 °C under 10 kbar, but the substrate scope was limited and the yield was unsatisfied.⁸

Solvent screening was carried out by employing an equal volume of water and water miscible organic solvent (Table 1). For the hydrolysis of styrene oxide, water gave the highest yield while the introduction of CH₃CN, THF, DMF, acetone, or DMSO gave little conversion of styrene oxide. The addition of different alcohols gave moderate conversion. It seemed that a 1:1 mixture of water and 1,4-dioxane or ethylene glycol was also a good solvent system in which a similar yield was obtained compared with that of water. However, when a relatively inert substrate cyclohexene oxide was hydrolyzed, an 89% yield of 1,2-dihydroxycyclohexane was obtained in water compared with an 47% and 85% yield in the mixture of water and 1,4-dioxane or ethylene glycol, respectively. Thereby, water is the choice of solvent.

We also found that the amount of water had a significant influence on reaction rate. As shown in Figure 1a, for the hydrolysis of styrene oxide, the product yield climbed higher following the increase of water amount and the curve went to a plateau after the ratio of water to substrate was raised to 6 mL of water per millimole of substrate. This critical amount of water requirement was also observed in recently reported *N*-tert-butyloxycarbonylation of amines in which water was also used as solvent.⁹ Temperature effect was also examined with cyclohexene oxide being a test substrate; superior yield was obtained at higher temperature and the reaction rate reached a maximum in boiling water (Figure 1b).

A variety of epoxides could be hydrolyzed by heating them in water (Table 2). All aromatic epoxides (entries 1 to 6) showed high reactivity and nearly quantitative yields of diols were

obtained. Acyclic aliphatic terminal epoxides (entries 7 to 9) could be hydrolyzed efficiently at 100 °C. A large-scale reaction was carried out by applying 6 mmol of 6,7-epoxycitronellol in 12 mL of water, and the epoxide could be transformed to the corresponding triol in 97% yield. The acetyl-protected 6,7-epoxycitronellol (entry 11) could also be hydrolyzed without removal of the acetyl group. α -Hydroxyl epoxides (entries 12 to 14) also reacted smoothly with excellent yields. Cyclopentene oxide and cyclohexene oxide were hydrolyzed with excellent stereoselectivity since only trans vicinal diols were detected (entries 15 and 16). For trisubstituted 1,2-epoxylimonene (entry 17), 36 h of reaction in boiling water gave the hydrolyzed product in 90% yield. Cyclic α,β epoxy ketone (entry 18) was hydrolyzed to trans-diol in 77% yield (compared to 47% in Kotsuki's method).⁸

Further studies showed that this method is suitable for the hydrolysis of aziridines as well.¹⁰ As shown in Table 3, various aziridines, including aromatic, aliphatic, and cyclic aliphatic aziridines, could be hydrolyzed successfully and the yields were excellent. For *N*-tosyl-2-phenylaziridine (entry 1), exclusive product was obtained from water attacking at the benzylic position. The alkyl terminal aziridine (entry 2) was preferentially attacked at the less substituted position. In the case of cycloalkyl aziridines (entries 3, 4, and 5), the stereochemistry of the products was determined to be trans by comparing with the reported data. Nonactivated aziridines such as *N*-benzylcyclohexanoaziridine were also tested, but the reactions were very slow.

Recently the ring-opening reactions of epoxides or aziridines with various types of nucleophiles have been extensively studied.¹¹ Several methods with different catalysts employed water as solvent and it was believed that water was essential for the success of the reactions.¹² In 2005, Saidi's group reported an effective aminolysis of epoxides in water around room temperature without additional catalyst.¹³ To extend the generality of our simple method, three representative substrates were treated with different nucleophiles in hot water without additional catalyst (Table 4). In Saidi's report, the additions of aromatic amines to alkyl epoxides were sluggish at room temperature. We found that at 60 °C, both benzylamine and aniline could equally and effectively add to styrene oxide and cyclohexene oxide.¹⁴ Moreover, the addition of amines to *N*-tosylcyclohexanoaziridine proceeded very well and gave quantitative yield of products.¹⁵ Instead of using expensive TMSN₃, cheap and water-soluble NaN₃ could be added to both

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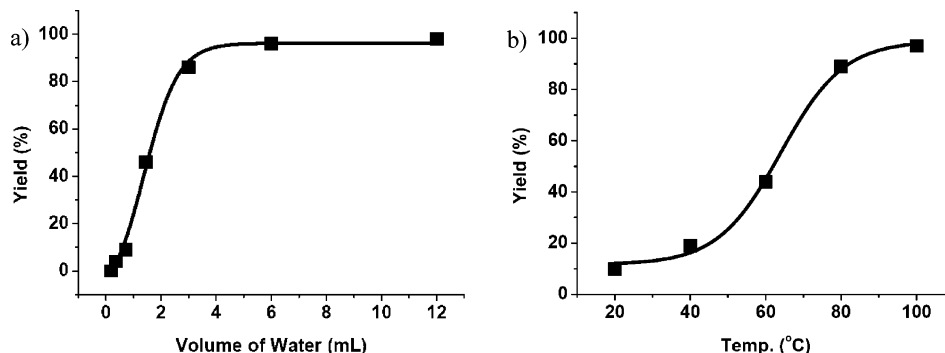


FIGURE 1. (a) A 2 mmol sample of styrene oxide was hydrolyzed in the indicated volume of water at 60 °C for 3.5 h and the yields were analyzed by GC. (b) A 2 mmol sample of cyclohexene oxide was hydrolyzed in 12 mL of water at the indicated temperature for 12 h and the yields were analyzed by GC.

epoxides and aziridines, giving azidolysis products at neutral condition.¹⁶ It has been reported that thiophenol could be efficiently added to epoxides in water around room temperature.¹⁷ We found that the ring-opening of aziridine by thiophenol could proceed in neutral hot water without catalyst and gave 73% of sulfur attacking product accompanied by the diol byproduct.^{15a–c,18}

Efforts were also made to understand the role of hot water in the above reactions. One possibility is that the hydrogen-bonding formation between epoxide oxygen and water may activate epoxides based on the reports, showing that the hydrogen bond between alcohol (or phenol) and epoxide can accelerate their ring-opening reactions.^{14b,19} In several reported catalytic ring-opening reactions of epoxides or aziridines operating in ambient water, including the newly published cascade epoxide-opening in water at 70 °C, the hydrogen bond between water and epoxide or aziridine was also used to explain the rate enhancement.^{3,12b,13} But in the present studies, the rates of hydrolysis reaction reached the maximum in boiling water, while actually the hydrogen bond donating ability of water drops quickly from 25 to 100 °C because the hydrogen-bonding formation is exothermic.²⁰ An alternative and more likely explanation of the rate acceleration in hot water may be that the self-ionization of water enhances as temperature rises, the

–log K_w (K_w is the self-ionization constant of water) value of water at 100 °C is 12,²¹ where both H^+ and OH^- are 10 times more abundant than that in ambient water (–log $K_w = 14$ at 25 °C), therefore water itself can act as a modest acid or base catalyst.²² It was reported that some traditionally acid- or base-catalyzed reactions, such as hydrolysis of esters and ethers²³ and dehydration of alcohols,²⁴ could take place in neutral high-temperature water (> 200 °C, –log $K_w = 11$ at 200 °C) without additional acid or base. As the ring-opening reactions of epoxides or aziridines are conventional acid or base catalyzed, it seems reasonable to assume that it can also be facilitated where the self-ionization of water is progressively enhanced along with the increase of temperature. Acid catalysis dominates the reported organic reactions in high-temperature water.^{23a,c} The observed cis/trans ratio of diol products of entries 4 and 5 in Table 2 was found to be similar with the product distribution in the protic acid-catalyzed hydrolysis (cis-diols are predominant in the hydrolyzed products).²⁵ If hot water acts as a modest acid, we predicted that an intramolecular hydroxyl group should open epoxide in hot water, with higher reaction rate since these reactions are also traditionally acid catalyzed.

To test our hypothesis, two simple epoxides with a hydroxyl group at the terminal site were prepared. Both *trans*-4,5-epoxyhexanols **1** and *cis*-4,5-epoxyhexanols **3** were cyclized in water at 60 °C in 0.5 h with almost quantitative yield. The 5-exo-opening of epoxide was preferred and the observed ratio of oxalane to oxane product produced from *trans* and *cis* substrates was exactly the same compared with the reported product distribution from the $BF_3 \cdot Et_2O$ -catalyzed cyclization of the same substrates (Scheme 3).²⁶ The ratio of oxalane to oxane product was not changed in the reactions conducted in water at 0 °C

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TABLE 2. Hydrolysis of Epoxides in Hot Water^a

Entry	Epoxide	Product	Temp (°C)	Time (h)	Yield (%) ^b
1			60	3.5	98
2 ^c			60	1	98
3			60	1	97
4 ^d			60	3	98
5 ^e			60	1	97
6 ^f			60	2	99
7			100	9	96
8			100	12	97
9			100	4	99
10 ^g			60	1	97
11			60	1.5	96
12			100	9	99
13			60	4	98
14			60	4	98
15			100	18	96
16			100	12	98
17 ^h			100	36	90
18			100	10	77

^a The reaction was conducted with 2 mmol of epoxide in 12 mL of water at the indicated temperature. ^b Isolated yield; the ratio of the isomers was determined by integrations of the signals in the ¹H NMR spectrum. ^c Threo/erythro: 60/40. ^d Trans/cis: 25/75. ^e Trans/cis: 25/75. ^f Threo/erythro: 75/25. ^g 6 mmol of epoxide in 12 mL of water. ^h 1 mmol of a 1:1 mixture of *trans*-(R)-(+)-limonene oxide and *cis*-(R)-(+)-limonene oxide in 12 mL of water.

but more than 15 h was required for completion of the same reactions. Another reported Lewis acid-catalyzed cyclization of diepoxide was also tested in hot water.²⁷ A diastereomeric mixture of 1,5-diepoxides **5**²⁸ was completely consumed in water at 60 °C in 0.5 h (Scheme 4). Acylation of the resulting crude mixture gave 44% of seven-member-ring product **6a** and 24%

TABLE 3. Hydrolysis of Aziridines in Hot Water^a

Entry	Aziridine	Product	Time (h)	Yield (%) ^b
1			7	99
2			48	62
3			7	99
4			5	99
5			4	99

^a The reaction was conducted with 2 mmol of aziridine in 12 mL of water at 100 °C. ^b Isolated yield; the ratio of the isomers was determined by integrations of the signals in the ¹H NMR

TABLE 4. Ring-Opening Reactions of Epoxides and Aziridines in Hot Water^a

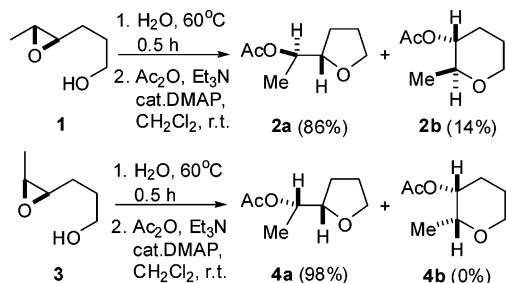
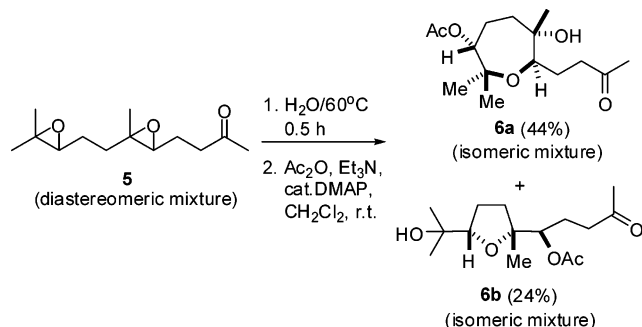
Entry	Substrate	Nucleophile	Product	Time (h)	Yield (%) ^b
1				3	92
2				3	93
3				3	93
4				3	97
5				5	98
6				5	99
7				72	73
8				5	99

^a The reaction was conducted with 1 mmol of substrate and 2 mmol of nucleophile in 6 mL of water at 60 °C. ^b Isolated yield.

of five-member-ring product **6b**, which was parallel with the result from BF₃-etherate-promoted cyclization. The same reaction could also complete in water at 100 °C within 10 min or more than 24 h at 0 °C with the same product distribution. This

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SCHEME 3. Hydroxy-Epoxy Cyclization in Water at 60 °C**SCHEME 4. Oxacyclization of 1,5-Diepoxyde**

evidence implies that the ring-opening reactions in hot water was acid catalyzed.

The dielectric constant of ambient water is 80 and this number quickly reduces to 55 at 100 °C, which implies that water is more like a polar organic solvent at high temperature. Therefore, some substrates that were originally water insoluble dissolve and react at elevated temperatures.²⁹

In conclusion, efficient hydrolysis of epoxides and aziridines has been achieved by just heating them in water. Other nucleophiles such as amines, sodium azide, and thiophenol could also effectively open epoxides and aziridines in hot water. Hydroxyl epoxides could also undergo cyclization to give cyclic ether in hot water. Simple workup (without the wash step) or direct evaporation of water led to pure ring-opening products and the yields are generally over 90% for a variety of substrates. Moreover, the present method avoided the use and subsequent disposal of additional catalyst, which will satisfy both laboratory and industrial operations. Furthermore, the present finding revealed another type of organic reaction that may benefit from the enhanced self-ionization of water. The utilization of

manageable hot water (60–100 °C) rather than high-temperature water (>200 °C) makes the present reactions safe and practical.

Experiment Section

A Typical Procedure of Hydrolysis of Epoxide in Hot Water (Table 2, entry 1). The suspension of styrene oxide (1 mmol, 120 mg) in distilled water (6 mL) in a 10 mL flask with a condenser was stirred at 60 °C and monitored by TLC. After completion, the mixture was extracted with EtOAc, washed with brine, dried over MgSO₄, and then concentrated to give the crude product. Purification by silica gel flash column chromatography provided diol product (135 mg, 98%).

1-Phenyl-1, 2-ethanediol: ¹H NMR (400 MHz, CDCl₃) δ 7.31–7.37 (m, 5H), 4.83 (dd, *J* = 3.2, 8.0 Hz, 1H), 3.76 (dd, *J* = 3.0, 11.4 Hz, 1H), 3.66 (dd, *J* = 8.2, 11.1 Hz, 1H), 2.69 (br s, 1H), 2.27 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 140.34, 128.36, 127.77, 126.00, 74.63, 67.88.

A Typical Procedure of Hydrolysis of 2-Phenyl-1-tosylaziridine in Hot Water (Table 3, entry 1). The suspension of 2-phenyl-1-tosylaziridine (2 mmol, 546 mg) in distilled water (12 mL) in a 25 mL flask with a condenser was stirred at 100 °C and monitored by TLC. After completion, the mixture was extracted with EtOAc, washed with brine, dried over MgSO₄, and then concentrated to give the crude product. Purification by silica gel flash column chromatography provided product (576 mg, 99%).

2-(*N*-Tosylamino)-1-phenyl-1-ethanol: ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.23–7.25 (m, 7H), 5.68 (s, 1H), 4.76 (dd, *J* = 2.4, 8.4 Hz, 1H), 3.48 (br s, 1H), 3.14–3.17 (m, 1H), 2.94–3.00 (m, 1H), 2.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.40, 140.76, 136.48, 129.65, 128.39, 127.89, 126.94, 125.78, 72.58, 50.18, 21.39.

A Typical Procedure of the Ring-Opening Reactions of Epoxides or Aziridines by Other Nucleophiles (Table 4, entry 4). To a stirred suspension of cyclohexene oxide (1 mmol, 98 mg) in distilled water (6 mL) was added the sodium azide (2 mmol, 130 mg) in a 10 mL flask with a condenser; the resulting mixture was stirred at 60 °C and was monitored by TLC. After completion, the mixture was extracted with EtOAc, washed with brine, dried over MgSO₄, and then concentrated to give the crude product. Purification by silica gel flash column chromatography provided product (137 mg, 97%).

2-Azidocyclohexanol: ¹H NMR (400 MHz, CDCl₃) δ 3.42–3.35 (m, 1H), 3.22–3.15 (m, 1H), 2.52 (s, 1H), 2.07–2.00 (m, 2H), 1.78–1.72 (m, 2H), 1.36–1.19 (m, 4H).

Acknowledgment. This work was financially supported by The National Natural Science Foundation of China (Nos. 20402007 and 20421202), NanKai University, the 111 Project (B06005), and the Project 863 of the Ministry of Science and Technology of China (No. 2006AA020502). We thank Prof. Chi Zhang for helpful discussions. We thank Mr. Xiangcai Ge for involvement in some early works.

Supporting Information Available: General experimental procedures and ¹H NMR and ¹³C NMR spectra of compounds in Tables 2–4 and Schemes 3 and 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO702401T

(28) Compound 5 is an inseparable 3.7:1 mixture of two diastereomers. It was prepared from geranylacetone by Shi enantioselective double epoxidation. Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(29) Styrene oxide was not soluble in water at room temperature but it dissolved at 60 °C. (a) Akerlof, G. C.; Oshry, H. I. *J. Am. Chem. Soc.* **1950**, *72*, 2844. (b) Miller, D. J.; Hawthorne, S. B. *J. Chem. Eng. Data* **2000**, *45*, 78.