



Borax-catalyzed thiolysis of 1,2-epoxides in aqueous medium

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ABSTRACT

A convenient, economical, and practical protocol for borax-catalyzed thiolysis of 1,2-epoxides in aqueous medium has been developed, which has greatly expanded the utility scope of borax in organic synthesis.

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Thiolysis of 1,2-epoxides represents an effective and convenient entry to β -hydroxy sulfides, an important class of intermediates for constructing both synthetic pharmaceuticals¹ and naturally occurring substances.² Tremendous research efforts have been devoted to this useful transformation. For instance, the reaction can be conducted in common organic solvents with the catalysis of $\text{Ti}(\text{OPr})_4$,^{3a} CeCl_3 ,^{3b} CoCl_2 ,^{3c} LiClO_4 ,^{3d} Sml_2 ,^{3b,3e} or AlR_3 .^{3f} Nowadays, reactions in aqueous medium have gained soaring popularity since water is inexpensive, non-toxic, safe, and environmentally benign as a solvent.⁴ Known promoters for epoxide thiolysis in water include Brønsted acid (TsOH^5), Lewis acid (InCl_3^6 and ZnCl_2^7), Brønsted base (NaOH^8 of stoichiometric amount), Lewis base (Bu_3P^9 , DABCO and Et_3N^{10}), and even microwave irradiation.¹¹ Some solvent-free examples for this reaction involved $\text{Ga}(\text{OTf})_3$ ¹² and K_2CO_3 ⁵ as catalysts. In spite of their respective features, the reported methods also suffer from the drawbacks in one way or another. For example, in most cases, thiolysis has to be carefully run at an appropriate pH value to ensure good regioselectivity and to minimize the side products resulted from hydrolysis^{6,7} and/or double thiolysis⁵ of the epoxides; Bu_3P (air labile), DABCO, Et_3N , or K_2CO_3 -catalyzed thiolysis usually takes long reaction time and ends up with unsatisfactory yields; some metal catalysts are too expensive to be useful for large-scale production. Consequently, efficient and practical thiolysis of 1,2-epoxides remains a daunting challenge to contemporary organic chemists.

Borax ($\text{Na}_2\text{B}_4\text{O}_7$), a naturally occurring material whose aqueous solution displays a pH value of 9.5, has emerged as a superb cata-

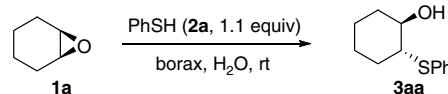
lyst or additive for many transformations such as Nef reaction, substitution, addition (including hetero-Michael reaction¹³), selective methylation of vicinal diols, and desilylation of trimethylsilyl alkynes.¹⁴

Having been fascinated by the unique characteristics of borax, we decided to explore thiolysis of 1,2-epoxides in water catalyzed by this inorganic salt. Herein, we wish to disclose our findings from the investigations along this line. The thiolysis of epoxide **1a** with PhSH (**2a**, 1.1 equiv) was initially performed in water in the presence of 5 mol % of borax (Table 1, entry 2). To our delight, the reaction proceeded smoothly at room temperature and after 2 h the desired trans-addition β -hydroxy sulfide **3aa** was afforded in good yield (85%). The chemical yield of **3aa** jumped to 93% when the dose of borax had been increased to 10 mol % (entry 3). For comparison, the same reaction reportedly⁹ provided **3aa** in only 15% yield without any catalysts (entry 1). Therefore, the quantity of borax was fixed at 10 mol % for the subsequent experiments.¹⁵

Table 1
Borax-catalyzed ring opening of **1a** with PhSH in water at room temperature

Entry	Borax (mol %)	Time (h)	Yield ^a (%)
1	None	12	15
2	5	2	85
3	10	2	93

^a Isolated yield.



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To examine the generality and scope of our borax-catalyzed thiolysis methodology, a series of epoxide¹⁶ and thiol substrates were scrutinized (Table 2). Both parent thiophenol (**2a**) and thiophenols with a substituent (e.g., 4-MeO, 4-Cl, and 2-NH₂) at the phenyl ring (**2b–d**) reacted with epoxide **1a** under the standard conditions to furnish the corresponding ring-opening products in excellent yields (92–95%, entries 1–4). Essentially no substituent effect was observed from this array of substrates when the reactions were run for 2 h. However, if the reaction time was shortened to 30 min, thiolysis of **1a** with **2a**, **2b**, and **2c** produced **3aa**, **3ab**, and **3ac** in 72%, 78%, and 63% yields, respectively. Obviously, the yields of the products increased with electron richness of the phenyl ring in the thiophenols. In addition, the chemoselectivity obtained with **2d** could be accounted for by the fact that the thiol functionality is much more nucleophilic compared to the amino group (entry 4). In contrast to thiophenols, alkyl mercaptans showed reduced or diminished reactivity toward **1a** in the presence of borax, due to relatively low acidity of the thiol protons. While reaction of benzyl mercaptan (**2e**) with **1a** for 12 h led to

3ae in only 43% yield (entry 5), product **3af** was not formed at all after 12 h in the case of *n*-butyl mercaptan (**2f**, entry 6). Nevertheless, the substrate (**1a**) was hydrolyzed to a certain extent, since -cyclohexane-1,2-diol was obtained in 8% yield.

Subsequently, reaction of PhSH (**2a**) with a series of epoxides (**1b–j**) other than 1,2-epoxycyclohexane (**1a**) was investigated (entries 7–15). The monosubstituted, 1,1- or 1,2-disubstituted, or trisubstituted epoxides, possessing either a single epoxy ring or a fused or spiro ring system, were attacked by **2a** only at the less substituted carbon (except **1f**, entry 11) to afford cleanly trans-addition β -hydroxy sulfides in 90–98% yields. In the case of **1f**, both possible regioisomers were formed, but favoring attack of PhSH at the benzylic position (with an α/β ratio of 4.2:1) as a result of electronic effect (entry 11). The preference is consistent with that observed with DABCO-catalyzed¹⁰ thiolysis, although Bu₃P⁹ as the catalyst gave the reverse selectivity. Although most reactions were completed within 2–3 h, some epoxides (**1b**,¹⁷ **1g**, **1h**, and **1j**) took slightly longer time (6–12 h) because of relatively greater steric hindrance (entries 7, 12, 13, and 15). Note that despite extended

Table 2
Borax-catalyzed ring opening of epoxides with thiols in water

Entry	Epoxide	Thiol	Product	Time (h)	Yield ^a (%)
1	(1a)	PhSH (2a)	3aa	2	93
2	1a	4-MeO-C ₆ H ₄ SH (2b)	3ab	2	95
3	1a	4-Cl-C ₆ H ₄ SH (2c)	3ac	2	92
4	1a	2-NH ₂ -C ₆ H ₄ SH (2d)	3ad	2	95
5	1a	BnSH (2e)	3ae	12	43
6	1a	ⁿ BuSH (2f)	3af	12	0
7	(1b)	2a	3ba	12	93
8	(1c)	2a	3ca	2	98
9	(1d)	2a	3da	3	92
10	(1e)	2a	3ea	3	98
11	(1f)	2a	3fa	3	98 ($\alpha/\beta = 4.2:1$) ^b
12	(1g)	2a	3ga	6	98
13	(1h)	2a	3ha	9	90
14	(1i)	2a	3ia	2	95
15	(1j)	2a	3ja	7	92

^a Isolated yield.

^b Ratios of the two regioisomers were determined by ¹H NMR.

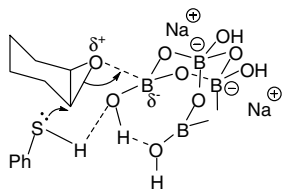


Figure 1.

reaction time (9 h), borax-catalyzed ring opening of epoxide **1h** in water gave rise to **3ha**¹⁸ in 90% yield. In contrast, replacement of borax with Lewis bases such as DABCO or Et₃N¹⁰ (PhSH (1.1 equiv), H₂O, rt, 12 h) resulted in very low yields (11–15%) of the product. While thiolysis of trisubstituted epoxide **1j** furnished **3ja** in excellent yield (92%) with borax as the catalyst, poor regioselectivity and low yields were obtained when TsOH,⁵ ZnCl₂,⁷ or InCl₃⁶-catalyzed reactions ($\alpha/\beta = 43:57$ – $55:45$). For chloro epoxide **1e**, the reaction stopped at the ring opening stage (**3ea**); the potential tandem chloride displacement failed to take place (entry 10). The opposite regioselectivity was obtained with the spiro epoxide **1i** (entry 14) if InCl₃⁶ or ZnCl₂^{7a} was employed instead of borax.

A tentative mechanism (Fig. 1) has been postulated in order to illustrate the present reaction rate enhancement in comparison with other base-catalyzed ring opening reactions. Borax might act as a bifunctional catalyst, which could bring the epoxide and the thiol into close proximity. The capability of boron species to coordinate to the epoxy oxygen atom, the weak basicity of the aqueous medium, and the hydrogen bonding might be among the most significant factors for this transformation.

In summary, a 'green', convenient, economical, and practical protocol for borax-catalyzed thiolysis of 1,2-epoxides in aqueous medium has been developed, which has expanded the utilities of borax in organic synthesis. The products were obtained in higher yields and with better regioselectivity when compared to the Brønsted acid or Lewis acid-catalyzed reactions. In addition, under the current conditions, the reaction proceeded faster than the Brønsted base or Lewis base-catalyzed counterparts. Other borax-catalyzed reactions are under investigation in our laboratory.

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- General procedure*: Thiol (1.1 equiv) was added to a solution of epoxide **1** (1.0 mmol) and borax (10 mol %) in water (2 mL). The reaction mixture was stirred at rt for the time reported in Table 2. Then the mixture was extracted with CH₂Cl₂ (3 × 5 mL). The combined extracts (dried with Na₂SO₄) were concentrated in vacuo and the resulting product was purified on silica gel. All products except **3ha** are known compounds, the characterization data of which are identical with those in literature reports.
- Compounds **1h**,^{16a} **1i**,^{16b} and **1j**^{16c} were obtained following the literature procedures while other substrates were commercially available: (a) Steinreiber, A.; Osprian, I.; Mayer, S. F.; Orru, R. V. A.; Faber, K. *Eur. J. Org. Chem.* **2000**, 3703; (b) Mosset, P.; Grée, R. *Synth. Commun.* **1985**, *15*, 749; (c) Fringuelli, F.; Germani, R.; Pizzo, F.; Saveli, G. *Tetrahedron Lett.* **1989**, *30*, 1427.
- This is presumably because the conformationally constrained bicyclo[3.1.0]hexane framework exerts steric hindrance against the addition.
- Compound **3ha**, a colorless liquid: ¹H NMR (CDCl₃, 300 MHz) δ 1.28 (s, 3H), 2.70 (s, 1H), 3.16 (d, $J = 13.5$ Hz, 1H), 3.23 (d, $J = 13.5$ Hz, 1H), 3.34 (d, $J = 8.7$ Hz, 1H), 3.46 (d, $J = 8.7$ Hz, 1H), 4.43 (s, 2H), 7.18–7.43 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ 23.7, 43.1, 72.5, 73.2, 75.4, 126.1, 127.6, 127.7, 128.4, 128.9, 129.4, 136.9, 137.8; MS (EI) m/z 288 (M⁺, 7), 167 (5), 149 (10), 124 (46), 91 (100). Anal. Calcd. for C₁₇H₂₀O₂S: C, 70.80; H, 6.99. Found: C, 70.72; H, 6.91.