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# Catalyst-Free Efficient Regioselective Ring Opening of Oxiranes with Thioacids in Water

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# CATALYST-FREE EFFICIENT REGIOSELECTIVE RING OPENING OF OXIRANES WITH THIOACIDS IN WATER

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# **GRAPHICAL ABSTRACT**



**Abstract** *Epoxide ring opening with thioacetic acid and thiobenzoic acid was investigated in the presence of water under catalyst-free conditions. This green and simple process gave an excellent yield. With simple decanting, the products were obtained in high purity and on a large scale. In this process, alkyl halide and ester cleavage were not observed.* 

Keywords Epoxide; ring opening; thioacids; water

# INTRODUCTION

The use of aqueous media in organic reactions offers significant environmental advantages and has attracted a great deal of interest because water is nontoxic and nonflammable, has a high heat capacity, and is relatively inexpensive. Since the use of water for acceleration of Diels–Alder reaction by Breslow,<sup>[1]</sup> considerable attention has been directed toward the development of organic reactions in water. Besides the Diels–Alder reaction, water was used in many useful organic reactions, even with water-sensitive materials.<sup>[2]</sup> Also, catalyst-free reactions are completely in compliance with the philosophy of green chemistry by reducing the hazardous materials and in some cases by reducing the number of steps needed for the extraction and purification of the products.

Epoxides play important roles in organic synthesis because their nucleophilic ring-opening reactions leads to 1,2-difunctional systems with regioselectivity. There are several reports in this area with different nucleophiles such as alcohols, thiols,

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amines, azides, and halides.<sup>[3]</sup> Although epoxide ring opening with thiols has been well documented to prepare  $\beta$ -hydroxy sulfids, valuable intermediates for constructing both synthetic pharmaceuticals and naturally occurring substances,<sup>[4]</sup> there are only a few reports on the synthesis of  $\beta$ -hydroxy thioesters in literature by this method in the presence of mineral or organic bases, alumina, and β-cyclodextrin.<sup>[5]</sup> β-Hydroxy thioesters can be easily converted to β-hydroxy thiols with hydrolysis.<sup>[6]</sup> Usually  $\beta$ -hydroxy thiols were synthesized with the epoxide ring opening by nucleophilic attack of H<sub>2</sub>S and Na<sub>2</sub>S.<sup>[7]</sup> The reported methods suffer from drawbacks such as  $H_2S$  odor, long reaction time, use of high pressure, and double thiolysis of epoxides. Also, reaction of thioacids with alkyl halides in the presence of epoxide in basic media is another limitation of the reported methods. Consequently, efficient and practical thiolysis of 1,2-epoxides remains a daunting challenge to contemporary organic chemistry. Recently, our research was focused on the catalyst-free synthesis of organic compounds in water<sup>[8]</sup> or solvent-free<sup>[9]</sup> conditions. In continuation of our interest, here we report the catalyst-free and regioselective ring opening of 1,2epoxides with thioacids in water.

#### **RESULTS AND DISCUSSION**

Sirinivas et al. have reported that the reaction of thioacids with epoxides does not proceed in the absence of  $\beta$ -CD in water.<sup>[5b]</sup> Against this claim, we have shown that the reaction was completed in water in the absence of catalyst with vigorous stirring.

The reaction conditions were optimized by investigation of the reaction of thioacetic acid and thiobenzoic acid with 2,3-epoxypropyl phenyl ether (Scheme 1). For this purpose, different solvents such as  $H_2O$ , tetra hydro furan (THF), ether, acetone, dimethyl formamide (DMF),  $CH_2Cl_2$ , acetonitrile, ethanol, and methanol were used, and we have found that the reaction was completed in water with higher yield.

After optimization of the reaction conditions, the efficiency of the process was checked with the reaction of thioacetic and thiobenzoic acids with different oxiranes. The results are summarized in Table 1. As is shown in Table 1, all 1,2-epoxides gave excellent yield with thioacids. Also, diepoxide (entries 11 and 12) were used as substrate in this reaction and gave excellent yields. The reaction of 2,3-epoxypropyl methacrylate with thioacetic acid gave both Michael adduct and  $\beta$ -hydroxy thioester. The reaction of epiclorohydrin and epibromohydrin with thiobenzoic acid gave only  $\beta$ -hydroxy thioester without carbon–halide bond cleavage. Reaction of styrene epoxide with thioacids gave S<sub>N</sub>2-like products in good yield.

The reaction of epichlorohydrin and epibromohydrin with thioacetic acid gave  $\beta$ -hydroxy thioester **1** as the only product at room temperature while at 30–35 °C, and both  $\beta$ -hydroxy thioester **1** and acyl transfer product **2** were obtained (Scheme 2). The ratio of **1** to **2** was obtained by comparing the area of -CH peaks in <sup>1</sup>H NMR spectra.



Scheme 1. Epoxide ring opening with thioacids in water at room temperature.

		X-SH= $CH_3COSH$ or PhCOSH		
Entry	Epoxide	Thioacid	Product	Yield (%) <sup>a</sup>
1 2	Ph <sup>O</sup>	CH₃COSH C <sub>6</sub> H₅COSH	OH Ph <sup>´</sup> OSX	88 85
3 4	~ <b>0</b> ~~ <b>0</b>	CH₃COSH C <sub>6</sub> H₅COSH	⊖OH SX	95 (83) <sup>b</sup> 100
5 6	, √0	CH₃COSH C <sub>6</sub> H₅COSH	OHSX	93 $(79)^b$ 100 $(85)^b$
7 8		CH₃COSH C <sub>6</sub> H₅COSH	OH SX	100 (69) <sup>b</sup> 96
9 10	Q	CH₃COSH C <sub>6</sub> H₅COSH	HO_SX	100 100
11 12	O≻⊕~O 4	CH₃COSH C <sub>6</sub> H₅COSH	OH OH XSSX	96 (80) <sup>b</sup> 100
13 14		CH₃COSH C <sub>6</sub> H₅COSH	OH O O O SX	73(27) <sup>c</sup>
15	Br	C <sub>6</sub> H <sub>5</sub> COSH	OH Br、SX	100
16	CI	C <sub>6</sub> H <sub>5</sub> COSH	OH ClSX	100
17 18	VIII 11	CH₃COSH C <sub>6</sub> H₅COSH	OH () 11 SX	66 60
19 20	Ph	CH₃COSH C <sub>6</sub> H₅COSH	HO_SX Ph	85 70
21 22	~~~0~~~0	CH₃COSH C₅H₅COSH	OH	89 100

Table 1. Epoxide ring opening with thioacids in water at room temperature

 $\xrightarrow{X-SH}_{H_2O, r.t.}$ 

R

R SX

<sup>a</sup>Isolated yields.

<sup>b</sup>Isolated yield for large-scale synthesis.

<sup>c</sup>The yield in parentheses refers to the Michael adduct.

 $\beta$ -Hydroxy thiol was also prepared in situ via epoxide ring opening with thioacetic acid and then hydrolysis of the product in 63% isolated yields (Scheme 3).

In conclusion, we have shown a catalyst-free method for the synthesis of  $\beta$ -hydroxyl thioesters with the reaction of epoxides and thioacids in water. This method is simple and green and gives high yields of products without use of any



Scheme 2. Epoxide ring opening with acyl transfer reaction.



Scheme 3. In situ epoxide ring opening and hydrolysis of thioester.

catalyst or organic solvents. It is notable that in large-scale synthesis, the product can be extracted by simple decanting and purified by distillation, which is completely in compliance with the green chemistry goal of doing the reactions in water.<sup>[10]</sup> The ester and alkyl halide cleavage was not observed in this method.

#### 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. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on 300-MHz spectrometers.

# **General Procedure**

In a round-bottomed flask equipped with a magnet, the epoxide (5 mmol), water (10 mL), and thioacid (5.5 mmol) were added. After vigorous stirring for 10 h, the oily product was extracted by ethyl acetate, washed with 2 M aqueous solution of NaHCO<sub>3</sub>, and evaporated to give a pure product in most of the cases. Further purifications have been done by column chromatography (silica gel; ethyl acetate/n-hexane; 2:8). The products were characterized by infrared and <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. It is notable that on large scale no solvent was required for extraction, and decanting of the oily product is sufficient.

### Spectroscopic Data for Selected Compounds

**Table 1, Entry 3.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 3.83 (1H, m), 3.43–3.59 (2H, m), 3.33 (1H, dd, J=9.4 and 6.5 Hz), 2.97–3.12 (2H, m), 2.80 (1H, br s, -OH), 2.31 (3H, s), 1.12 (6H, d, J=6.0 Hz). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 196.0, 72.2, 70.5, 69.6, 32.3, 30.4, 21.9. MS (EI): m/z = 191 (M-1), 159, 99, 89, 73, 57, 43 (100).

**Table 1, Entry 7.** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 5.81 (1H, dd, J = 10.5 and 6.2 Hz), 5.08–5.21 (2H, m), 3.93 (2H, d, J = 4.7 Hz), 3.81 (1H, m), 3.32–3.41 (2H, m), 3.13 (1H, br s, -OH), 2.91–3.05 (2H, m), 2.27 (3H, s). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 196.2, 134.8, 117.6, 73.1, 72.6, 69.8, 32.8, 30.8. MS (EI): m/z = 189 (M-1), 157, 149, 129, 103, 97, 73, 59, 55, 43 (100), 41.

**Table 1, Entry 11.** <sup>13</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 3.63 (2H, m), 3.04–2.77 (6H, m), 2.26 (6H, s), 1.42–1.33 (8H, m). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 196.4, 69.3, 35.8, 35.7, 30.4, 20.9. MS (EI): m/z = 295 (M + 1), 277 (100), 259, 235, 217, 187, 175, 141, 127, 43.

**Scheme 2, Compound 1(x = cl).** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 3.93 (1H, t, J = 5.5 Hz), 3.61 (1H, dd, J = 11.3 and 4.4 Hz), 3.54 (1H, dd, J = 11.3 and 5.9 Hz), 3.40 (1H, br s, -OH), 3.04–3.15 (2H, m), 2.34 (3H, s). <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm) 196.5, 70.8, 48.4, 33.3, 30.8. MS (EI): m/z = 167 (M – 1), 149, 135, 119, 103, 91, 79, 59, 43 (100).

# **Typical Procedure for Large Scale Synthesis**

Thioacetic acid (15.4 mL, 218 mmol) was added to a stirred solution of 2,3epoxy propyl isopropyl ether (25 mL, 198 mmol) in water (100 mL), and the reaction mixture was vigorously stirred at room temperature for 10 h. At completion, the organic layer was separated and washed with 2 M aqueous solution of NaHCO<sub>3</sub> (two times) to remove unreacted thioacetic acid. Then, the organic phase was evaporated under reduced pressure to remove excess of epoxide. The product was obtained in 83% isolated yield.

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