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Efficient synthesis of β, β′-dihydroxy sulfides by ring opening of epoxides with mercaptoethanol catalyzed under solvent-free conditions

Moufida Romdhani-Younes [a] & Mohamed Moncef Chaabouni [a]
[a] Laboratoire de Chimie Organique Structurale, Département de Chimie, Faculté des Sciences de Tunis, Université Tunis El Manar, 2092, Tunis, Tunisia
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Efficient synthesis of β, β'-dihydroxy sulfides by ring opening of epoxides with mercaptoethanol catalyzed under solvent-free conditions

Moufida Romdhani-Younes* and Mohamed Moncef Chaabouni

Laboratoire de Chimie Organique Structurale, Département de Chimie, Faculté des Sciences de Tunis, Université Tunis El Manar, 2092 Tunis, Tunisia

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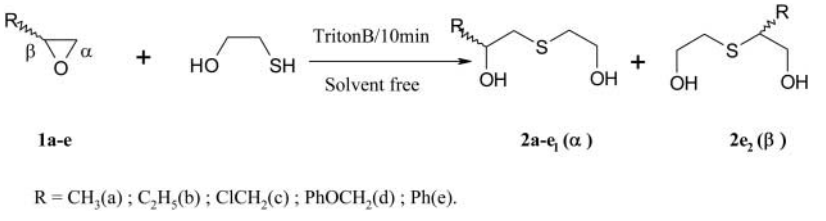
A simple and highly efficient synthesis of β, β'-dihydroxy sulfides has been achieved by ring opening of epoxides with mercaptoethanol using catalytic amount of benzyltrimethylammonium hydroxide (Triton B) under solvent-free conditions. Excellent regioselectivity was found for aliphatic unsymmetrical epoxides, with nucleophilic attack at the less-hindered carbon atom of the epoxide. However, this regioselectivity was not observed for styrene oxide and a mixture of two isomers was obtained. This process was also regio- and chemo-selective as illustrated using epichlorohydrin with two epoxide ring positions and mercaptoethanol with two functional groups (SH and OH).



Keywords: Mercaptoethanol; epoxides; Triton B; solvent-free; hydroxy sulfides; regioselectivity

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Introduction

Epoxides represent an important class of compounds in organic synthesis. For instance, their nucleophilic opening leads to a large number of 1,2-difunctionalized systems (*1–6*). Their reactions with different nucleophiles (*e.g.* amine, thiols, alcohol, and so on) have been the subject of extensive studies (*7–11*). Ring opening of epoxides by thiols constitutes a convenient, practical and widely employed method for the synthesis of β-hydroxysulfide moieties, which are useful as intermediates in organic chemistry (*12–15*) especially in the preparation of important naturally occurring products (*16–19*) and a variety of compounds with pharmacological and/or biological activities (*20–23*).

*Corresponding author. Email: moufida.romdhani@gmail.com

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While there are a few examples utilizing water or solvent-free conditions (*6,24,25*), most thiolysis of epoxides is realized in organic solvents using thiols under basic conditions (*26–28*) or Lewis acid catalysts (*29–32*), such as $InCl_3, ZnCl_2$ or $BF_3 \cdot OEt_2$. However, these methods usually suffer from limitations such as the use of toxic and expensive reagents, non-selective catalysts, long reaction times or elevated temperatures (*33–35*). Therefore, it is of significant interest to selectively synthesize β-hydroxysulfides and it still remains a highly desired goal in organic synthesis.

In our research, we have previously shown the specific role of Triton B as a catalyst in the synthesis of dihydroxy dithiacrown ethers (*36*) by ring opening of diglycidic ethers with dimercaptoethane using this catalyst. In continuation with our work on the application of Triton B for various organic transformations as an easily available catalyst, we report here a simple, efficient and practical procedure using this catalyst as an environmental-friendly and commercially available cheap catalyst for the synthesis of a new series of β, β'-dihydroxysulfides under solvent-free conditions.

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Results and discussion

We investigated the ring opening of various epoxides with mercaptoethanol and our successful results are reported in Table 1. As shown in Scheme 1, the ring opening of epoxides was initiated by thiolate ion produced by the reaction of mercaptoethanol with Triton B. The method provides high yields of versatile β, β'-dihydroxy sulfides.

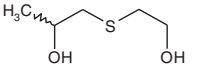
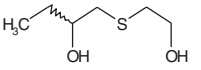
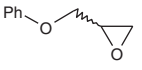
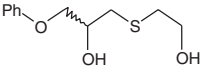
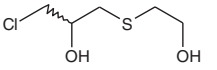
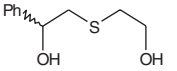
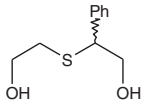
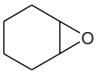
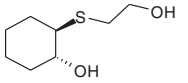
The ring-opening reactions were carried out in a simple manner by adding mercapthoethanol dropwise over a 10-min period to a stirred solution of epoxide and Triton B at room temperature without solvent. The best result was obtained using 2.5% of Triton B and a reactive mercapthoethanol:epoxide molar ratio of 1:1.

As shown in Table 1, excellent regioselectivity was observed for all aliphatic epoxides **1a**–**d**. Selective nucleophilic attack by the thiolate anion occurs at the less-substituted carbon atom. The ^1H NMR spectra of crude products **2a**–**d** showed particularly a triplet in the range of 3.75–3.85 ppm assigned to $-CH_2OH$ protons and multiplets centered at 3.90 ppm for $-CHROH$. No RCHS-proton signals around 2.75 ppm expected for the other isomer were observed, which implies that the absence of the attack on the (β)-carbon of the epoxide. For instance, the ^{1}H NMR spectrum of **2a** showed signals at $\delta = 1.25$ (d, 3H, $J = 6$ Hz, CH_3); 2.53–2.65 (m, 2H, $CHCH_2S$); 2.74 (t, 2H, $J = 6$ Hz, SCH_2CH_2); 3.75 (t, 2H, $J = 6$ Hz, CH_2OH); 3.89 (m, 1H, $CPhHOH$); 4.25 (broad s, 2H, OH), indicating the absence of the signal related to RCHS-proton of the other isomer. In addition, only five distinct signals were observed in the ^{13}C NMR spectrum of **2a**, in agreement with the proposed structure. This regiospecificity was not observed in the case of styrene oxide, as is usually observed in the literature (*37*), which led to a mixture of two regioisomers (60:40 α/β). In this case, the nucleophilic attack takes place predominantly on the less-substituted carbon (path α Scheme 1). The regioselectivity and the ratio of the two regioisomers were determined by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of the mixture of the two isomers $\mathbf{2e_1}$ and $\mathbf{2e_2}$ showed two multiplets at 3.93 and 4.70 ppm due to the $CHPh$ protons in the $\mathbf{2e_1}$ and $\mathbf{2e_2}$ isomers, respectively. The ^{13}C NMR spectra showed, in addition to the peaks related to the aromatic carbon, the existence of eight different peaks corresponding to the eight aliphatic carbons of the two isomers $\mathbf{2e_1}$ and $\mathbf{2e_2}$.

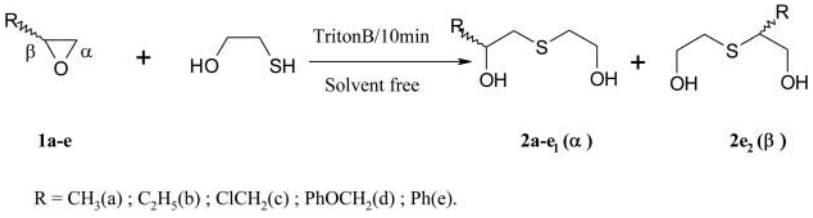
Under similar conditions, treatment of cyclohexeneoxide **1f** with mercaptoethanol gave a very good yield of the corresponding expected trans-β, β'-dihydroxy sulfide (Scheme 2).

The reaction of epichlorohydrin **1d** provides an excellent example of a chemo- and regioselective reaction. Reaction of mercaptoethanol with epichlorohydrin in the presence of Triton B gave the corresponding β, β'-dihydroxy sulfide by nucleophilic attack at the terminal carbon of

Table 1. Ring opening of epoxides by mercaptoethanol.

Epoxide	Thioetherdiols[a]	Boiling point (°C)/Torr	Yield (%)	Ratio α/β
 **1a**	 **2a**	102/0.4	97	100:0
 **1b**	 **2b**	110/0.4	98	100:0
 **1c**	 **2c**	130/0.1	97	100:0
 **1d**	 **2d**	Oil	92	100:0
	 60 % **2e$_1$**	159/0.1[b]		
 **1e**	 40 % **2e$_2$**		98[c]	60:40
 **1f**	 **2f**	136/0.4	96	–

Notes: [a]The ratios were determined by ^{1}H NMR.
[b]Boiling point of mixture of two isomers.
[c]Total yield of two isomers.



Scheme 1.

the epoxide moiety. No product from nucleophilic substitution of the chloride atom was observed (^{1}H and ^{13}C NMR).

The above process was also chemoselective as illustrated using mercaptoethanol with two potential reactive nucleophilic functional groups (thiol and alcohol). The reaction of mercaptoethanol with all of the epoxides in the presence of Triton B takes place chemoselectively with exclusive attack of the thiolate anion on less-hindered carbon atom of the epoxide. No significant amount of the product was observed from the attack of alcoholate anion. This may be due to the higher acidic and nucleophilic character of thiol when compared with alcohol.

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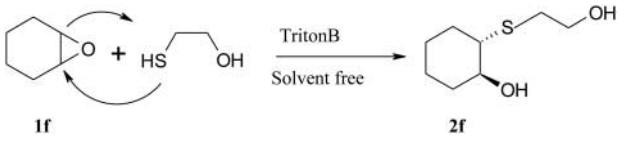
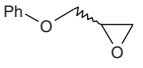


Scheme 2.

Table 2. Comparison of catalytic activity of Triton B with CsF-celite (*28*).

Epoxide	Catalyst (mol%)	*T*	Solvent	Time (min)	Yield (%)
 **1c**	CsF-celite(100%)	Reflux	CH_3CN	60	78
	Triton B (2.5%)	R.T.	Solvent-free	10	98
 **1e**	CsF-celite(100%)	Reflux	CH_3CN	60	84
	Triton B (2.5%)	R.T.	Solvent-free	10	97

The procedure described here appears to be highly efficient and competitive with other methods reported in the literature (*28*). The ring-opening reaction of phenoxymethyl oxide **1c** and styrene oxide **1e** with mercaptoethanol in the presence of the CsF-celiteas, a catalyst, is compared in Table 2.

In conclusion, we have reported the thiolysis of alkyl and aryl-1,2-epoxides with mercaptoethanol under solvent-free conditions catalyzed by Triton B (2.5%) at room temperature. This protocol is novel in terms of high regio- and chemoselectivity in comparison with other methods reported in the literature. The additional advantage is that these reactions were carried out at room temperature in short reaction times under solvent-free conditions with small amounts of catalyst in high yields. This, together with the use of an inexpensive easy to handle and stable catalysts makes this new methodology environmental-friendly and useful for the synthesis of chemically and pharmaceutically interesting β, β'-dihydroxy sulfides.

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Experimental

The products were characterized by ^{1}H and ^{13}C NMR spectroscopy and HRMS. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent on a Bruker AC 300 spectrometer. The chemical shifts were reported in δ-values relative to TMS (internal reference). For the ^{1}H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, m: multiplet. HRMS spectra were obtained using MAT 95 SBE instrument.

General procedure for the synthesis of β, β'-dihydroxy sulfides: mercaptoethanol (10 mmol) was added dropwise over a 10-min period to a stirred solution of epoxide **1a–f** (10 mmol) and Triton B (0.25 mmol) at room temperature. The consumption of the epoxide was monitored by thin layer chromatography. The mixture obtained was purified by distillation except the product **2d** which was isolated by column chromatography (Silica Gel 60 F254, acetone/ethyl acetate 1:1).

*3-Thiahexan-1,5-diol (**2a**).* ^{1}H NMR(300 MHz, $CDCl_3$): 1.25 (d, 3H, $J = 6$ Hz, C$\underline{H}_3$); 2.53–2.65 (m, 2H, $J = 6$ Hz, $J = 12$ Hz, CHCH_2S CHCH_2S); 2.74 (t, 2H, $J = 6$ Hz, SCH_2CH$_2$); 3.75 (t, 2H, $J = 6$ Hz, CH_2OH); 3.89 (m, 1H, C*H*OH); 4.25 (broad s, 2H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): 22.1 (C, *C*H$_3$); 34.5 (C, SCH$_2$CH$_2$); 40.2 (C, CH*C*H$_2$S); 61.2 (C, *C*H$_2$OH); 66.3 (C, C*H*OH). HRMS: calculated 159.0450 for ($C_5H_{12}O_2SNa$), found 159.0455 $(M + Na)^+$.

*3-Thiaheptan-1,5-diol (**2b**).* ^{1}H NMR (300 MHz, $CDCl_3$): 0.94 (t, 3H, $J = 6$ Hz, CH_3) ; 1.53 (m, 2H, CH_2CH$_3$); 2.50–2.59 (m, 2H, CHCH_2S); 2.73 (t, 2H, $J = 6$ Hz, SCH_2CH$_2$); 3.62 (m, 1H, C*H*OH); 3.73 (t, 2H, $J = 6$ Hz, CH_2OH); 3.96–4.19 (broad s, 2H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$):11.1 (C$_1$, *C*H$_3$); 28.8 (C$_2$, *C*H$_2$CH$_3$); 35.5 (C$_6$, S*C*H$_2$CH$_2$); 38.0 (C$_4$, *C*HCH$_2$S); 60.8 (C$_7$, *C*H$_2$OH); 70.7 (C$_3$, *C*HOH). HRMS: calculated 173.0612 for ($C_6H_{14}O_2SNa$), found 173.0619 $(M + Na)^+$.

*7-Phenoxy-3-thiahexan-1,5-diol (**2c**).* ^{1}H NMR (300 MHz, $CDCl_3$): 2.70 (t, 2H, $J = 6$ Hz, SCH_2); 2.80–2.86 (m, CHCH_2S); 3.7 (t, 2H, $J = 6$ Hz, CH_2OH); 3.83 (broad s, 2H, O*H*); 3.97 (m, 2H, CH_2OPh); 4.10 (m, 1H, C*H*OH); 6.86–7.24 (m, 5H, Ph). ^{13}C NMR(75 MHz, $CDCl_3$): 35.9 (C, *C*H$_2$OPh); 41.1 (C, CHCH$_2$S); 61.2 (C, *C*H$_2$OH); 68.6 (C, *C*HOH); 72.0 (C, *C*H$_2$OPh); 114.5; 120.7; 129.8; 158.0 (aromatic). HRMS: calculated 251.0712 for ($C_{11}H_{16}O_3SNa$), found 251.0727 $(M + Na)^+$.

*6-Chloro-3-thiahexan-1,5-diol (**2d**).* ^{1}H NMR (300 MHz, $CDCl_3$): 2.63 (t, 2H, SCH_2); 2.46–2.70 (m, 2H, CH_2CH); 3.4–3.70 (m, 2H, ClCH_2CH); 3.80 (m, 1H, C*H*OH); 3.90 (t, 2H, CH_2OH); 4.40 (broad s, 2H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): 34.5 (C, S*C*H$_2$); 42.5 (C, *C*H$_2$CH); 47.8 (C, ClCH_2CH); 61.2 (C, *C*H$_2$OH); 70.8 (C, *C*HOH). HRMS: calculated 193.0060 for ($C_5H_{11}O_2ClSNa$), found 193.0056 $(M + Na)^+$.

*1-Phenyl-3-thiapentan-1,5-diol (**2e$_1$**).* ^{1}H NMR (300 MHz, $CDCl_3$): 2.43–2.63 (m, 2H, SCH_2CH$_2$OH); 2.72–2.80 (m, 2H, CHCH_2S); 3.52–3.63 (m, 2H, CH$_2$CH_2OH); 4.10–4.25 (broad s, 2H, O*H*); 4.70 (m, 1H, PhC*H*OH); 7.25–7.29 (m, 5H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): 34.5 (C, S*C*H$_2$CH$_2$); 42.5 (C, CH*C*H$_2$S); 61.1 (C, *C*H$_2$OH); 72.9 (C, Ph*C*HOH); 127.2; 127.7; 129.0; 140.7 (aromatic).

*2-Phenyl-3-thiapentan-1, 5-diol (**2e$_2$**).* ^{1}H NMR (300 MHz, $CDCl_3$): 2.43–2.63 (m, 2H, SCH_2CH$_2$OH): 3.52–3.63 (m, 2H, CH$_2$CH_2OH); 3.76 (m, 2H, SCHCH_2OH); 3.93 (SC*H*Ph); 4.107–4.25 (broad s, 2H, OH); 7.10–7.29 (m, 5H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): 33.79 (C, S*C*H$_2$CH$_2$OH); 52.28 (C, S*C*HPh); 60.87 (C, SCH$_2$*C*H$_2$OH); 65.76 (C, SCH*C*H$_2$OH); 127.2; 128.7; 128.7; 139.0 (aromatic). HRMS: calculated 221.0606 for ($C_{10}H_{14}O_2SNa$), found 221.0600 $(M + Na)^+$.

*2-(2-Hydroxyethylthio)cyclohexanol (**2f**).* ^{1}H NMR (300 MHz, $CDCl_3$): 1.24–1.46 (m, 4H, (CH_2)$_2$); 1.73 (m, 2H, CH_2CHS); 2.07 (m, 2H, CH_2CHOH); 2.48 (ddd, 1H, $J = 12$ Hz, 9 Hz, 3 Hz, C*H*S); 2.80 (t, 2H, $J = 6$ Hz, SCH_2); 3.35 (ddd, 1H, $J = 11$ Hz, 9.8 Hz, 4.5 Hz, C*H*OH); 3.75 (t, 2H, CH_2OH); 3.95 (broad s, 2H, O*H*). ^{13}C NMR (75 MHz, $CDCl_3$): 24.3, 26. (*C*H$_2$)$_2$; 31.5 (*C*H$_2$CHS); 33.2 (*C*H$_2$CH$_2$OH); 33.7 (*C*H$_2$CHOH); 52.7 (*C*HS); 60.2 (*C*H$_2$OH); 72.2 (*C*HOH). HRMS: calculated 199.0763 for ($C_8H_{16}O_2SNa$), found 199.0769 $(M + Na)^+$.

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