Direct conversion of β, β'-dihydroxythioethers into thiols: Synthesis of new tridentate ligands

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Abstract: Various β, β'-dihydroxythioethers, derived from oxirane were readily converted to their corresponding new mono-substituted thioethers dithiols in good yields, by treatment with thiourea and hydrochloric acid in aqueous solution. The method is applicable to aliphatic and functional diols as well as primary and secondary alcohols.

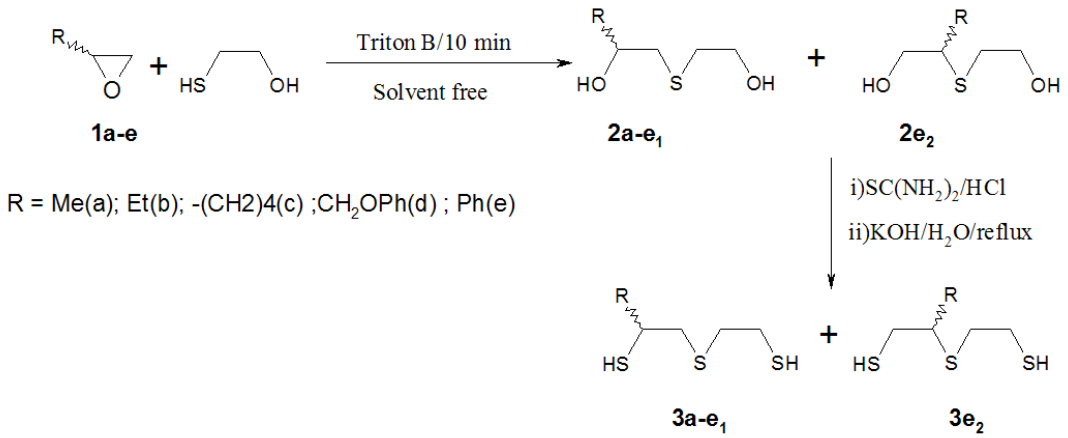
Keywords: hydroxythioethers, thiols, thiourea

INTRODUCTION

The development of new, efficient and environmentally benign synthetic protocols for the formation of C-S bonds is an important target in modern organic synthesis [1-4]. As a result, many recent reports focus on using organic halides and thiols to form C-S bonds [5-8]. However, the use of highly volatile and foul-smelling thiols leads to serious environmental and safety problems. Recently, it has been found that thiols can be replaced with odorless, non-toxic thiourea as a sulfur source for the formation of C-S bonds [9-11].

Therefore, we were interested in our work in the synthesis of sulfur containing compounds, precisely polydentate ligands [12-15] having three sulfur atoms. Interest in such compounds is due to their applications in various fields such as the synthesis of polymer [16-19], in the field of biochemistry [20-22], in the medical field [23,24] and they have been the subject of several other studies [25-28].

For instance, the incorporation of thiol groups into organic molecules allows their coordination to noble metal surfaces to form self-assembled



Scheme 1

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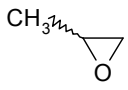
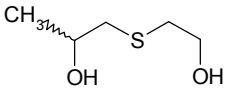
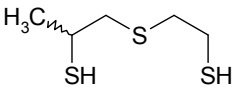
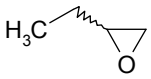
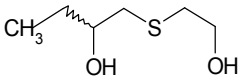
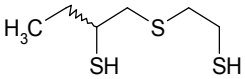
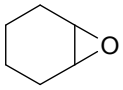
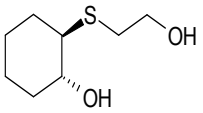
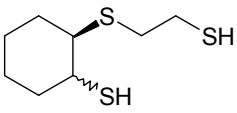
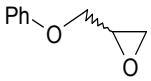
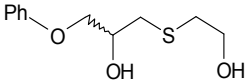
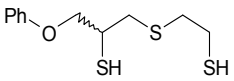
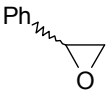
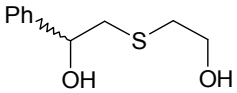
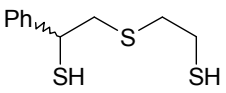
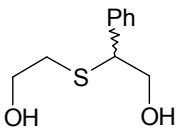
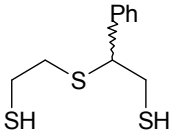
Table I: Unsymmetric substituted dithioether dithiols

Epoxyde	Thioetherdiols[a]	Yield(%)	thioethers dithiols[a]	BP(°C/mmHg)	Yield(%)
 **1a**	 **2a**	97	 **3a**	61/0,01	71
 **1b**	 **2b**	98	 **3b**	92/0,3	70
 **1c**	 **2c**	96	 **3c**	107/0,1	65
 **1d**	 **2d**	97	 **3d**	huileux	65
 **1e**	 **2e$_1$** (60%)	98[b]	 **3e$_1$** (55%)	78/0,2[c]	70[b]
	 **2e$_2$** (40%)		 **3e$_2$** (45%)		

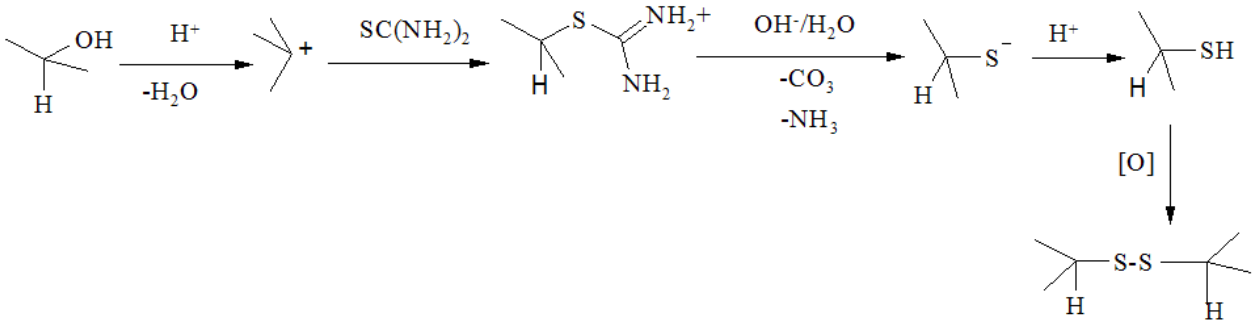
[a] The ratios were determined by ^{1}H NMR.
[b] Total yield of the two isomers
[c] Boiling point of the mixture of the two isomers.

monolayers (SAMs) [28-30] that have applications in molecular electronics [31] and in the synthesis of stable colloidal nanoparticles of noble metals, even in extreme conditions of pH and ionic strength due to strong interactions between gold and sulfur atoms [32-35].

In a previous Letter [36]; we reported the conversion of β,β´-dihydroxydithioethers into their homologous dithioetherdithiols. In the same context, we herein wish to report the synthesis of a new series of substituted thioetherdithiols **3a-e** obtained from the substituted thioetherdiols **2a-e** which are themselves prepared in one step as previously described [37] from alkyl or aryl oxirane (Scheme 1).

RESULTS AND DISCUSSION

According to literature [38,39], the condensation of alcohols in concentrated hydrochloric acid with thiourea followed by hydrolysis of thiouronium salt intermediate under basic conditions is considered to be a good thiolation method, which is widely used for preparation of primary and secondary thiols. It was found that a direct thiolation of the two hydroxyl groups was attempted. Therefore, new substituted



Scheme 2

thioether-dithiols **3a-e** were prepared in this way (Table I).

It should be noted that, in all cases, variable amounts of the corresponding disulfide and trisulfide compounds (dimers and trimers) were formed by air oxidation of the aqueous thiolates (Scheme 2). These secondary compounds were confirmed by HRMS.

The formation of compounds **3a-e** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and HRMS. In all cases, ^{1}H NMR spectra showed the absence of a singlet around δ 3.77 ppm due to the tow (OH) protons and presence of a multiplet between δ 1.70-1.80 ppm assigned to the protons of SH groups. The ^{13}C NMR spectra display characteristic signals of all carbons.

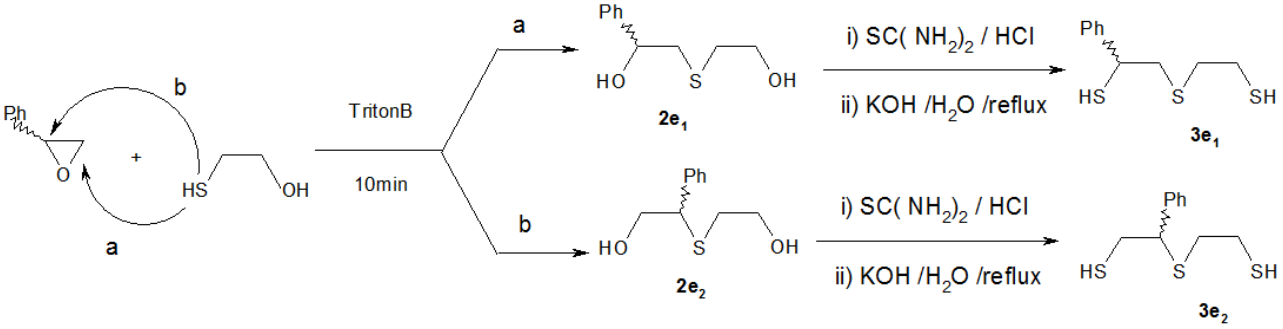
In the case of styrene oxide, we showed in a previous letter [37] that the ring opening of this epoxide with dimercaptoethane using benzyl-trimethylammonium hydroxide (Triton B) as catalyst led to a mixture of two regioisomers of β,β'-dihydroxythioethers **2e$_1$** and **e$_2$** (Scheme 3). The two isomers were converted into their homologous thioether dithiols **3e$_1$** and **3e$_2$** and the mixture of isomers was purified by distillation. The ratio of the tow isomers was determined by ^{1}H spectroscopy**.**

Under similar conditions, treatment of trans-*β*, *β*'-dihydroxy sulfide **2c** with thiourea gave a good yield of the corresponding expected trans-*β*, *β*'-dihydroxy sulfide**3c** (Scheme 4).

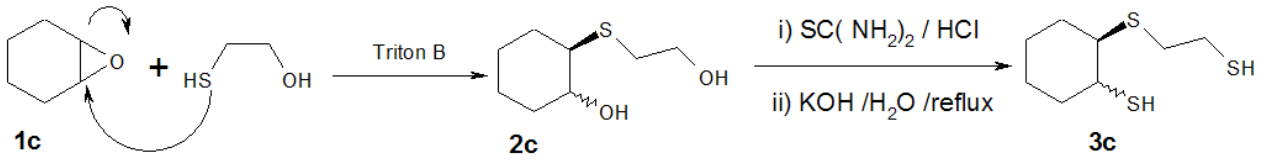
In summary, we have achieved the conversation of substituted thioetherdiols **2a-e** into their corresponding substituted thioether-dithiols **3a-e** in good yields and facile purification. To our knowledge, these com-pounds have not been reported previously and may be useful intermediates for the synthesis of various thiacrown ethers, chemically and pharmaceutically interesting compounds.

EXPERIMENTAL

The ^{1}H, ^{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.



Scheme 3



Scheme 4

Preparation of dithiols: To a stirred solution of thiourea 33 mmol (2.51 g) in 8 mL of concentrated hydrochloric acid was added the thioetherdiol **2** (15 mmol) at room temperature. The mixture was refluxed for 9 h. The resulting solution was then cooled in an ice bath and 5.65g (0.101mol) of KOH in 35 mL of water cautiously added. This mixture was refluxed for 3 h, then the resulting solution was allowed to cool, acidified with 10% aqueous hydrochloric acid to pH = 2-3 and extracted with diethyl ether (3x50 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The residue was purified by distillation except the product **3d** witch was isolated by column chromatography (silica Gel 60F254, heptane /ethyl acetate (80:20)).

3-Thiahexane-1, 5-dithiol (3a)

Yield: 71%, mp 61°C/0.01 mmHg. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.34 (d, 3H, *J*=9Hz, CH_3), 1.70- 1.81 (m, 2H, SH), 2.58 (system ABX, 3H, *J*=12Hz, *J*=6Hz, $CHCH_2S$), 2.73(t, 2H, *J*=6Hz, SCH_2), 2.78 (m, 2H, CH_2SH), 2.90 (m, 1H, CHSH), 3.06(m, 1H, CHSH). ^{13}C-NMR ($CDCl_3$, 75 MHz) : 23.9 (CH_3), 24.9 (CH_2SH), 31.6 (SCH_2), 34.5 ($CHCH_2S$), 43.5 (CHSH). HRMS: calculated for $C_5H_{12}S_3Na$ 190.9999 found 190.9978.

3-Thiaheptane-1, 5-dithiol (3b)

Yield: 70%, mp 92°C/0.3 mmHg. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.01 (t, 3H, CH_3), 1.50 (m, 2H, CH_3 CH_2), 1.74- 1.87 (m , 2H, CH_2SH), 2.69-2.90 (ma, 7H, SCH_2+ CH_2SH + CH_2S + CHSH). ^{13}C-NMR ($CDCl_3$, 75 MHz): 10.0 (CH_3), 25.3 (CH_2SH), 29.4 (CH_3-CH_2), 36.6 (SCH_2), 41.2 (SCH_2CH), 43.1 (CHSH). HRMS: calculated for $C_6H_{14}S_3Na$: 205.0155 found 205.0133.

2-(2-mercaptoethylthio)cyclohexanethiol (3c)

Yield: 65%, mp 107°C/0.1 mmHg. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.30-1.53 (ma, 4H, CH_2), 1.75 (m, 2H, SH), 2.16 (ma, 4H, SCH_2CH), 2.30 (t, 1H, CHSH), 2.52 (td, 1H, *J*= 9Hz, CHSH), 2.73-2.90 (m, 4H, CH_2SH + CH_2S). ^{13}C-NMR ($CDCl_3$, 75 MHz) : 24.0, 24.3, 26.8, 31.0 ($4CH_2$, cycle), 33.5 (SCH_2), 34.2 (CH_2SH), 46.7, 48.8 (2CHSH). HRMS: calculated for $C_8H_{16}S_3Na$: 231.0312, found 231.0280.

1-Phenyloxymethyl-3-thiapentane-1,5-dithiol (3d)

Yield: 65%, oil, ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.70 (m, 2H, SH), 2.50-3.20 (m, 6H, $CHCH_2S$ +SCH_2CH_2), 3.50 (m, 1H, CHSH), 4.20 (m, 2H, OCH_2), 6.90 -7.20 (m, 5H, H arom). ^{13}C-NMR ($CDCl_3$, 75 MHz): 26.5 (CH_2SH), 36.4 (SCH_2CH_2), 37.1($CHCH_2S$), 37.6 ($CHCH_2S$), 80.1 (OCH_2), 114.4, 120.3, 129.4, 158.1 (Carom). HRMS: calculated for $C_{11}H_{16}OS_3Na$: 283.0261, found 283.0220.

1-Phenyl-3-thiapentane-1, 5-dithiol 3e$_1$ + 2-Phenyl-3-thiapentane-1, 5-dithiol (3e)

Yield: 70%, mp 78°C/0.2 mmHg

1-Phenyl-3-thiapentane-1, 5-dithiol (3e$_1$)

^{1}H-NMR ($CDCl_3$, 300 MHz): 1.5(m, 2H, SH); 2.74 (t, 2H, SCH_2), 2.93 (m, 2H, CH_2CH_2SH), 2.90-3.15 (system ABX, 2H, $PhCH_2S$), 4.11 (m, 1H, PhCH), 7.20 (m, 5H, Harom). ^{13}C-NMR ($CDCl_3$, 75 MHz): 26.5 (CH_2CH_2SH), 36.4 (CH_2CH_2SH), 40.0 ($PhCHCH_2S$), 43.4 (PhCH), 127.2, 127.6, 128.8, 141.7 (Carom); HRMS: calculated for $C_{10}H_{14}S_3Na$: 253.0155, found 253.0130.

2-Phenyl-3-pentane-1, 5-dithiol (3e$_2$)

^{1}H-NMR ($CDCl_3$, 300 MHz): 1.5 (pic, 2H, SH), 2.74 (t, 2H, SCH_2), 2.93 (m, 2H, CH_2CH_2SH), 3.10 -3.35 (system ABX, 2H, $CHCH_2SH$), 4.13(1H, m, SCHPh), 7.2 (m, 5H, Harom). ^{13}C-NMR ($CDCl_3$, 75 MHz): 26.8 (CH_2CH_2SH), 33.5 (CH_2CH_2SH), 34.7 ($CHCH_2SH$), 48.7 (SCHPh), 127-139 (Carom). HRMS: calculated for $C_{10}H_{14}S_3Na$: 253.0155, found 253.0130 .

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