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Synthesis of novel 1,5 bis-propargyloxy-sulfides via β, β'-dihydroxythioethers derived from epoxides

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Abstract: Various β, β'-dihydroxythioethers, derived from oxirane were readily converted to their corresponding 1,5 bis-propargyloxy-sulfides, by treatment with propagyl bromide and Sodium hydride in anhydrous THF. These new compounds were obtained in good yields. This method is applicable to aliphatic, cyclic and aryl diols. The use of NaH allows the transformation of primary and secondary alcohols.

Keywords: Epoxides, dihydroxythioethers, propargyl bromide, bis-propargyloxy-sulfides.

INTRODUCTION

Investigation of combined acetylene chemistry[1,2] and sulfur chemistry[3-6] provides a wide range of opportunities for development and applications of new intermediates for fine organic synthesis[7], compounds with anticorrosive activity[8] and biologically active compounds[9-12]. Mono- and dialkynyl sulfides are successfully used as precursors for producing synthetic analogues of various natural compounds[13], optically active natural compounds[14] and for synthesis of various types of chiral sulfur derivatives[15].

Propargyl ethers are also important starting materials for a wide range of organic reactions[16]. They are very useful for large synthetic applications. Synthetic methods of organic chemistry demonstrate alkyne groups to be most reactive ones which increase the importance of the compound[17]. Low cost, high yield of the compound has attracted the attention of scientists to synthesize the compound as monomer for many

polymeric compounds[18, 19]. They are used as an intermediate for the synthesis of triazole by the click chemistry[20,21]. Propargyl ether compounds are also used in synthesis of large number of functionalized dendrons[22, 23]. The bis-propargyloxy ether derivatives constitute an interesting substrate for the yne-yne metathesis reactions[24, 25]. These compounds have shown pharmacological and biological activities[26-28]. They also serve as key intermediates for the synthesis of many natural products including important antibiotics[29, 30] and related polyaromatic compounds[31].

In the course of our work on the synthesis of sulfur containing compounds, we have prepared a number of products owing either a thioether or an oxathioether moiety as an additional donor function and in the context of the study of reactivity of thioethers diols, we have previously reported the conversion of β,β´-dihydroxythioethers into their homologous thioetherdithiols[32]. We herein report the synthesis of a new series of substituted bis-propargyloxy-sulfides through the propargylation of thioetherthiol with propargyl bromide in basic conditions.

MATERIAL AND METHODS

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.

Synthesis of the bis-propargyloxysulfides : In a round bottom flask, equipped with a dropping funnel, and cooled at 0 °C, 6.61 mmol of β,β'-dihydroxy sulfides **1,** dissolved in 15 mL of anhydrous THF, are introduced. Then 0.48 g (20 mmol, 3 equiv) of NaH is added. The reaction mixture was stirred for 15 min at 0 °C. Then 1.53 g (20 mmol, 3 equiv)) of propargyl bromide was added dropwise except for **2d** where 40 mmol (6 equiv) were used. The mixture was stirred for 12 h at room temperature. At the end of the reaction, 3 mL of ethanol were added to the mixture to ensure the consumption of the NaH excess. The mixture was then diluted with 20 mL of water and extracted with dichloromethane 3 x 20 mL. The organic phase was dried over $MgSO_4$. After removing the solvents, the resulting crude was purified by silica gel column chromatography using petroleum ether/ether 90/10 as eluent. The pure compounds **3** were isolated as yellowish oils

5-Méthyl-4,10-dioxa-7-thiatrideca-1,12-diyne 3a: ^{1}H NMR (300 MHz, Chloroform-*d*): δ 4.33 – 4.11 (m, 4H,CC*H*$_2$, CC*H*$_2$), 3.88 -3.76 (m, 1H, C*H*O) ; 3.72 (t, 2H *J* = 6.6 Hz, SCH$_2$C*H*$_2$O) ; 2.88 -2.70 (m, 2H, SC*H*$_2$CH$_2$) ; 2.67 - 2.55 (m, 2H, CHC*H*$_2$S) ; 2.47 (dt, 2H *J* = 14.5, 7.1 Hz, CC*H*, CC*H*) ; 1.26 (d, 3H, *J* = 6 Hz, C*H*3).^{13}C NMR (75 MHz, Chloroform-*d*): δ 80.04(*C*CH); 79.53 (*C*CH) ; 74.75(*C*HO) ; 74.49(C*C*H) ; 74.25(C*C*H) ; 69.54(SCH$_2$*C*H$_2$) ; 58.07 (CH$_2$O*C*H$_2$) ; 55.96(CHO*C*H$_2$) ; 38.30(CH*C*H$_2$S) ; 32.12 (S*C*H$_2$CH$_2$) ; 19.00(*C*H$_3$) ; HRMS: calculated 235.0769 for ($C_{11}H_{16}NaO_2S$), found 235.0763 *(*M + Na*)* +.

5-Ethyl-4,10-dioxa-7-thiatrideca-1,12-diyne 3b : ^{1}H NMR (300 MHz, Chloroform-*d*): δ 4.33 – 4.02 (m, 4H, CC*H*$_2$, CC*H*$_2$), 3.77 – 3.52 (m, 2H, SCH$_2$C*H*$_2$O), 3.50 – 3.45 (m, 1H, C*H*O), 2.76 – 2.62 (m, 2H, SC*H*$_2$CH$_2$), 2.52 – 2.41 (m, 2H, CHC*H*$_2$S), 2.37 (t, J = 3.0 Hz, 2H, CC*H*, CC*H*), 1.59 – 1.31 (m, 2H, C*H*$_2$CH$_3$), 0.93 (t, J = 5.8 Hz, 3H, C*H*$_3$CH$_2$).^{13}C NMR (75 MHz, Chloroform-*d*): δ 78.92 (*C*CH); 78.91 (*C*CH) ; 75.78(*C*HO) ; 75.76 (C*C*H) ; 75.25(C*C*H); 69.75(SCH$_2$*C*H$_2$) ; 57.77 (CH$_2$O*C*H$_2$) ; 56.96

(CHO*C*H_2) ; 36.30 (CH*C*H_2S) ; 33.32 (S*C*H_2CH_2) ; 28.73 (*C*H_2CH_3); 9.80(*C*H_3 CH_2); HRMS: calculated 249.0925 for ($C_{12}H_{18}NaO_2S$), found 249.0928 *(*M + Na*)* +.

5-Phenoxy-4,10-dioxa-7-thiatrideca-1,12-diyne 3c: ^{1}H NMR (300 MHz, Chloroform-*d*): δ 7.32 – 6.95 (m, 5H, H_{Ar}), 4.35 – 4.28 (m, 2H, C*H*$_2$OPh), 4.11 – 4.00 (m, 4H, CC*H*$_2$, CC*H*$_2$), 3.82 – 3.74 (m, 2H, SCH$_2$C*H*$_2$O), 3.57-3.53 (m,1H, C*H*O), 2.77 – 2.63 (m, 2H, SC*H*$_2$CH$_2$O), 2.53 – 2.40 (m, 2H, CHC*H*$_2$S), 2.37 (t, *J* = 3.0 Hz, 2H, CC*H*, CC*H*).^{13}C NMR (75 MHz, Chloroform-*d*): δ 158.77, 129.46, 120.61, 115.18 (C_{ar}), 78.95(*C*CH) , 78.92 (*C*CH) , 75.76 (*C*HO) , 75.53 (C*C*H) , 75.28 (C*C*H) , 69.76 (SCH$_2$*C*H$_2$), 68.74 (*C*H$_2$OPh), 57.76 (CH$_2$O*C*H$_2$), 56.99 (CHO*C*H$_2$) , 34.95 (CH*C*H$_2$S) , 33.39(S*C*H$_2$CH$_2$). HRMS: calculated 327.1031 for ($C_{17}H_{20}NaO_2S$), found 327.1035 *(*M + Na*)* +.

1.5-Phenyl-4,10-dioxa-7-thiatrideca-1,12-diyne 3d$_1$:^{1}H NMR (300 MHz, Chloroform-*d*): δ 7.45 – 7.31 (m, 5H, H_{ar}), 4.85 (m, 1H, C*H*O), 4.33-4.07 (m, 2H, CC*H*$_2$), 4.04 – 3.78 (m, 2H, CC*H*$_2$), 3.77 – 3.50 (m, 2H, SCH$_2$C*H*$_2$O), 3.05 – 2.75 (m, 2H, CHC*H*$_2$S), 2.72 – 2.45 (m, 2H, SC*H*$_2$CH$_2$O), 2.37 (t, *J* = 3.0 Hz, 2H, CC*H*, CC*H*).^{13}C NMR (75 MHz, Chloroform-*d*): δ 141.69, 128.45, 128.11, 127.21 (C_{ar}), 79.46 (*C*HO), 78.95 (*C*CH), 78.92 (*C*CH), 75.76 (C*C*H), 75.28 (C*C*H), 69.76 (SCH$_2$*C*H$_2$), 57.76 (CH$_2$O*C*H$_2$), 55.50 (CHO*C*H$_2$), 38.36 (CH*C*H$_2$S), 33.39 (S*C*H$_2$CH$_2$).

2.6-Phenyl-4,10-dioxa-7-thiatrideca-1,12-diyne 3d$_2$: ^{1}H NMR (300 MHz, Chloroform-*d*): δ 7.36 (s, 5H, H_{ar}), 4.34 – 4.13 (m, 2H, CC*H*$_2$), 4.08 (m,2H, C*H*$_2$CHPh), 4.02 (t, *J* = 6.7 Hz, 1H, CH$_2$C*H*Ph), 3.92 – 3.89 (m, 2H, CC*H*$_2$), 3.88 – 3.82 (m, 2H, SCH$_2$*C*H$_2$), 2.76-270 (m, 2H, SC*H*$_2$CH$_2$), 2.37 (t, *J* = 3.0 Hz, 2H, CC*H*, CC*H*). ^{13}C NMR (75 MHz, Chloroform-*d*): δ 139.30, 128.72, 127.90, 127.76 (C_{ar}), 79.06 (*C*CH), 78.95 (*C*CH), 75.42 (*C*H$_2$CHPh), 75.38 (C*C*H), 75.28 (C*C*H), 70.08 (SCH$_2$*C*H$_2$), 57.94 (C*C*H$_2$), 57.76 (C*C*H$_2$), 49.46 (*C*HPh), 32.56 (S*C*H$_2$). HRMS: calculated 297.0925 for ($C_{16}H_{18}NaO_2S$), found 297.0921 *(*M + Na*)* +.

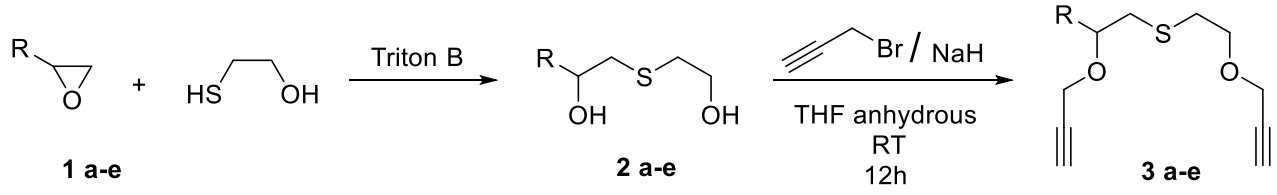
(2-(Propargyloxy)cyclohexyl)(2-(propargyloxy)ethyl)sulfane 3f: ^{1}H NMR (300 MHz, chloroform-*d*): δ 4.34 - 4.07 (m, 2H, CC*H*$_2$), 4.05 – 3.84 (m, 2H, CC*H*$_2$), 3.80 – 3.58 (m, 2H, SCH$_2$C*H*$_2$), 3.55 – 3.48 (m, 1H, C*H*O), 2.76 – 2.67 (m, 2H, SC*H*$_2$), 2.49 (m, 1H, C*H*S), 2.37 (t, *J* = 3.0 Hz, 2H, CC*H*, CC*H*), 1.95 – 1.14 (m, 8H, C*H*$_{2cyclohexyl}$). ^{13}C NMR (75 MHz, Chloroform-*d*): δ 80.63 (*C*HO), 78.95 (*C*CH), 78.92 (*C*CH), 75.76 (C*C*H), 75.28 (C*C*H), 70.08 (SCH$_2$*C*H$_2$), 57.76 (C*C*H$_2$), 56.82 (C*C*H$_2$), 49.86 (*C*HS), 32.77 (S*C*H$_2$), 32.63, 26.87, 24.70, 24.60 (4C *C*H$_{2cyclohexyl}$). HRMS: calculated 275.1082 for ($C_{14}H_{20}NaO_2S$), found 275.1086 *(*M + Na*)* +.

RESULTS AND DISCUSSION

To access to the bis-propargyloxy-sulfide**s 3** we used thioetherdiols **2** as intermediates. These compounds were prepared from the reaction of mercaptoethanol with epoxides in basic conditions using the method described previously[33] **(Scheme 1).**

According to the literature Williamson reaction is the best-known and most widely used method for the preparation of propargyl ethers[34]. The procedure involves treatment of a propargyl halide with alkoxide prepared from an alcohol under basic conditions. Initially a systematic study was carried out for evaluation of the propargylation reaction of compounds **2** with propargyl bromide under various conditions. When thioether diols **2** were treated with potassium carbonate as a base, no propargylation reaction was observed. Next, when **2** was treated with sodium hydroxide, a mixture of products was found, poor yields were obtained and the reaction was not complete. Consequently, the use of sodium hydride gave a complete

propargylation of the two hydroxyl groups. Therefore, the new substituted 1,5 bis-propargyloxy-sulfide **3** have been prepared in this way (Scheme 1).



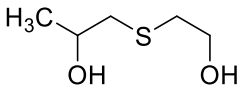
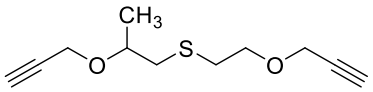
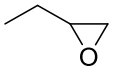
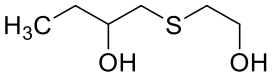
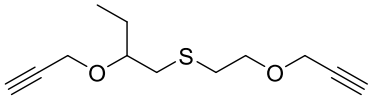
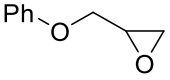
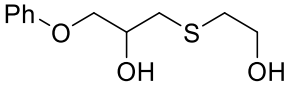
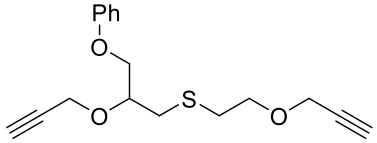
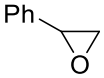
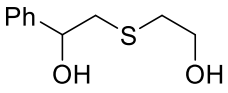
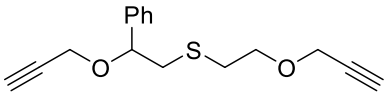
R= Me; Et; CH_2OPh; Ph; $-(CH_2)_4-$

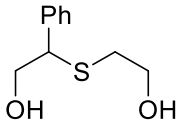
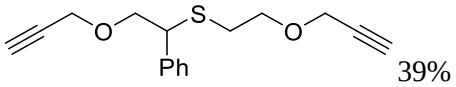
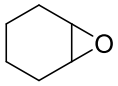
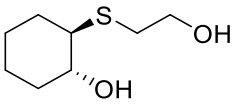
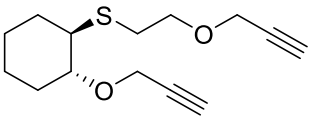
Scheme 1

As shown in **Tables 1**, the bis propargyloxy-sulfides were obtained in good yields. The use of a sodium hydride (NaH) in anhydrous THF, at room temperature affords exclusively, within 12h, the bis propargyloxysulfides **3.**

The NaH acts as a strong base that is capable to deprotonate both primary and secondary alcohols, affording therefore the bis propargylation products **3** according to a substitution reaction S_N2.

Tables 1: synthesis of bis-propargyloxy-sulfides **3a-e**

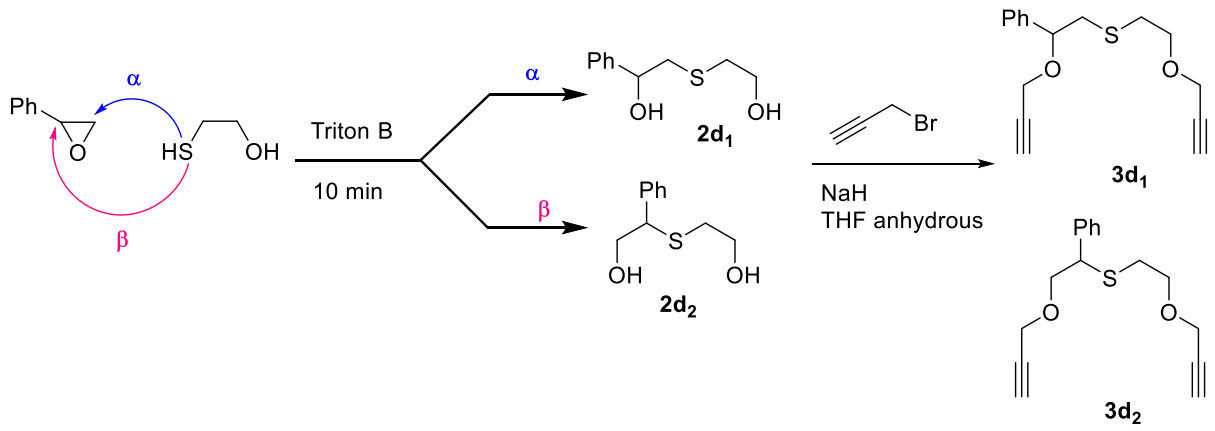
Epoxide	Thioetherdiols [a]	Bis Propargyloxy-thioether [a]	yields % [b]
 **1a**	 **2a**	 **3a**	75
 **1b**	 **2b**	 **3b**	70
 **1c**	 **2c**	 **3c**	80
 **1d**	 60% **$2d_1$**	 61% **$3d_1$**	79 [b]

	 40% **2d₂**	 39% **3d₂**	
 **1e**	 **2e**	 **3e**	85

[a]The ratios of isomers were determined by [1]H NMR.
[b]Total yield of two isomers

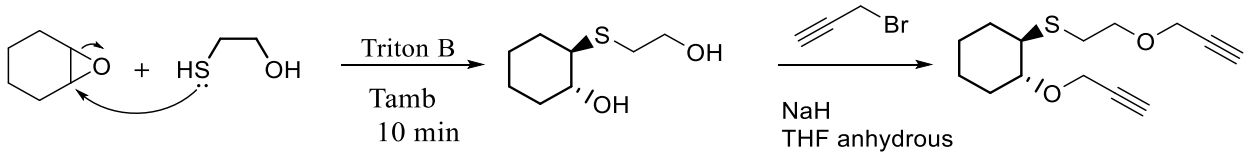
The formation of compounds **3a-e** was confirmed with ^{1}H and ^{13}C NMR spectroscopy and HRMS. In all cases, ^{1}H NMR spectra show the absence of a singlet around δ 3.77 ppm due to the tow (OH) protons in the starting diols and presence of a multiplet between 4.33 – 4.11 ppm for the 2 CH_2 protons of propargyl and a multiplet between 2.51 – 2.46 ppm for the 2 CH protons of propargyl. The ^{13}C NMR spectra show the absence of signal of CHOH and CH_2OH at 66 and 61 ppm respectively and the presence of new six signals, which correspond to the two propargyl groups.

In the case of styrene oxide, we showed in a previous letter[33] that the ring opening of this epoxide with mercaptoethanol using benzyltrimethylammonium hydroxide (Triton B) as catalyst led to a mixture of two regioisomers of β,β'-dihydroxysulfide **2d₁** and **2d₂ (Scheme 2).** The two isomers were converted into their homologous bis-propargyls **3d₁** and **3d₂**. The mixture of isomers was purified using column chromatography. The ratio of the two isomers was determined by ^{1}H NMR spectroscopy.



Scheme 2

Under similar conditions, treatment of trans-*β*, *β*'-dihydroxy sulfide **2e** with propargyl bromide gave of the corresponding expected trans-bispropargyloxy sulfide **3e** in good yield (Scheme 3).



Scheme 3

CONCLUSION

A good yielding conversation of substituted thioetherdiols **2a-e** into their corresponding substituted bis propargyloxy sulfides **3a-e** was carried out. To our knowledge, these products have not been reported previously and may be useful intermediates for the synthesis of various chemically and pharmaceutically interesting compounds.

ACKNOWLEDGEMENT

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