JCBPS; Section A; November 2018 – January 2019, Vol. 9, No. 1; 065-072. E- ISSN: 2249 –1929

[DOI: 10.24214/jcbps.A.9.1.06572.]

Journal of Chemical, Biological and Physical Sciences

An International Peer Review E-3 Journal of Sciences

*Available online at*www.jcbsc.org

Section A: Chemical Sciences

CODEN (USA): JCBPAT Research Article

Triton B promoted highly regio- and chemoselective ring opening of epoxides with 2-aminobenzenethiol under solvent-free conditions

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Received: 11 November 2018; **Revised:** 22 November 2018; **Accepted:** 30 November 2018

Abstract: A simple and highly efficient synthesis of amino-β-hydroxysulfides has been carried out ring opening of epoxides with 2-aminobenzenethiol with catalytic amount of benzyl trimethylammonium hydroxide (Triton B) under solvent-free conditions. Excellent regioselectivity was achieved for aliphatic unsymmetrical epoxides, with nucleophilic attack at the less hindered carbon atom of the epoxide. In the case of styrene oxide the nucleophilic attack takes place exclusively on the more substituted carbon. This process was also regio- and chemo-selective as illustrated using epichlorohydrin with two epoxide ring positions and 2-aminobenzenethiol with two functional groups (SH and NH_2).

Keywords: 2-aminobenzenethiol, amino-β-hydroxysulfide, epoxides; Triton B; solvent-free; regioselecivity.

INTRODUCTION

Epoxides are considered as one of the most important intermediates in organic synthesis mainly due to the electrophilic nature of carbon which is susceptible to be attacked by several nucleophiles to undergo regioselective ring opening reactions contributing towards the synthesis of large number of 1,2-difunctionalized systems[1-3]. Their reactions with different nucleophiles (*e.g.* alcohol, amine, thiols...) have

been the subject of extensive studies[4-6]. Ring opening of epoxides with thiols provides a straight forward route for the preparation of *β*- hydroxy sulfides, which are useful as intermediates in organic chemistry[7,8]. *β*-hydroxy sulfides can be used for the synthesis of pharmaceuticals[9,10], natural products[11] , and in the synthesis of biologically important molecules including heterocycles[12.13].

Most thiolysis of epoxides is carried out in organic solvents using thiols under basic conditions[14,15] or Lewis acid catalysts[16] such as Al_2O_3[17], $ZnCl_2$[18], $BF3{\cdot}OEt_2$[19], $AlPW_{12}O_{40}$[20], $InCl_3$ [21.22] and $Zn(ClO_4)_2{\cdot}6H_2O$[23] . However, these methods are generally limited by the use of toxic and expensive reagents, long reaction times, non-selective catalysts or high temperatures. Consequently, it is of significant interest to selectively synthesize β-hydroxy sulfides, which still remains a highly desired goal in organic synthesis. 1, 2- Amino thiols are structural units of undoubted synthetic interest in organic chemistry[24] because they contain both an amine function and a thiol group. The cleavage of epoxides with amino thiols is interesting since the resultant amino hydroxysulfides are important for the synthesis of many biologically interesting molecules[25] and heterocycles such as benzothiazepines[26].

In our research, we have previously shown the specific role of Triton B as a catalyst in the synthesis of dihydroxy sulfides through ring opening of oxiranes with mercaptoéthanol [27]. In continuation of our work on the application of Triton B, we report here a simple, efficient and practical procedure using this catalyst as an environmentally friendly and commercially available cheap catalyst for the synthesis of a new series of amino-β-hydroxysulfide via ring opening of oxiranes with 2-aminobenzenethiol under solvent-free conditions.

MATERIAL AND METHODS

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker 400 MHz Advance III HD spectrometer at 400 and 100 MHz, respectively using TMS as the reference. HRMS spectra in C. I. mode were recorded on a MAT 95 SBE spectrometer. The silica gel used is of Silica Gel 60 F254 (Merck)

For the ^1H NMR, the multiplicities of signals are indicated by the following abbreviations: s: singlet, d: doublet, t: triplet, m: multiplet. General procedure for the synthesis of amino-β-hydroxysulfide: 2-aminobenzenethiol (10 mmol) was added dropwise over a 30-min period to a stirred solution of epoxide **1a**–**f** (10 mmol) and Triton B (0.25 mmol) at room temperature. The reaction mixture was allowed to stir for two hours. The products **3a, 3c and 3d** were purified by chromatography on silica gel column (Et_2O/petroleum ether = 60/40), while the products **3b, 3e** and **3f** were purified by recrystallization in hexane.

1-((2aminophenyl)thio)propan-2-ol : 2a: ^1H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 6.70 (m, 4H, H_{ar}), 3.75 (m, 1H, CH2-C<u>H</u>-OH), 2.98 – 2.62 (m, 2H, S-C<u>H2</u>), 1.23 (d, 3H, C<u>H3</u>-CH,*J* = 6.2 Hz,).^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.29 (<u>C</u>NH_2), 136.36, 130.18, 119.10, 115.38 (4C<u>ar</u>), 117.26 (<u>C</u>S), 65.88 (<u>C</u>HOH), 44.36 (<u>C</u>H_2S), 21.83 (<u>C</u>H3). HRMS: calculated 206.0616 for ($C_9H_{13}NNaOS$), found 206.0613 *(*M+Na*)*+.

2-((2-aminophenyl)thio)cyclohexanol : 2b: ^1H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 6.72 (m, 4H, H_{ar}), 4.47 (broad s, 2H, N<u>H</u>$_2$), 3.47 (broad s, 1H, O<u>H</u>), 3.31 (td, *J* = 10.0, 4.4 Hz, 1H, C<u>H</u>OH), 2.67 (ddd, *J* = 12.2, 9.8, 4.0 Hz, 1H, C<u>H</u>S), 2.17 – 2.04 (m, 2H, C<u>H</u>$_2$-CHOH), 1.70 (m, 2H, C<u>H</u>$_2$-CH-S), 1.50 – 1.20 (m, 4H, (C*H2*)$_2$).^{13}C NMR (101 MHz, $CDCl_3$) δ 149.16 (<u>C</u>NH_2), 138.17, 130.50, 119.01, 115.46 (4C<u>ar</u>), 115.60

(CS), 72.55 (CHOH), 56.91 (CHS),, 34.27, 32.92, 26.20, 24.38 $(CH_2)_2$.HRMS: calculated 246.0929 for ($C_{12}H_{17}NNaOS$), found 246.0926 *(*M + Na*)* +.

1-((aminophenyl)thio)-3-chloropropan-2-ol : 2c : ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 6.66 (m, 4H, H_{ar}), 3.86-3.84 (m, 1H, CHOH), 3.75 – 3.57 (m, 2H, CH_2Cl), 3.03 – 2.83 (m, 2H, CH_2S). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.30 (CNH_2), 136.44, 130.51, 119.34, 115.57 (4Car), 116.84 (CS), 69.83 (CHOH), 48.00 (CH_2Cl), 39.35 (CH_2S). HRMS: calculated 240.0226 for ($C_9H_{12}ClNNaOS$), found 240.0228 *(*M+Na)+.

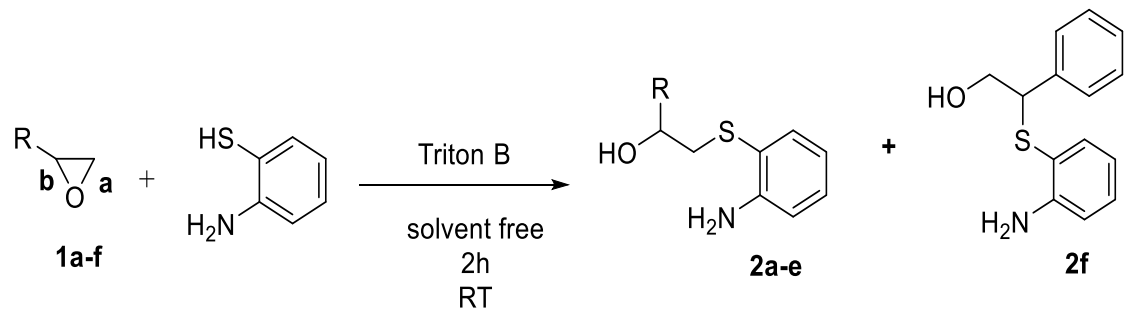
1-((2-aminophenyl)thio)hexan-2-ol : 2d: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 6.69 (m, 4H, H_{ar}), 3.89 (broad s, 3H, OH, NH_2)3.57 (m, 1H, CHOH),3.02 – 2.63 (m, 2H, CH_2S), 1.54 – 1.41 (m, 2H, CH_2CHOH), 1.36 – 1.28 (m, 2H, $CH_2CH_2CH_3$), 1.23 (t, 2H, CH_2CH_3, *J* = 7.0 Hz,), 0.89 (t, 3H, CH_3CH_2, *J* = 7.0 Hz,). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.27 (CNH_2), 136.28, 130.11, 119.07, 115.34 (4Car), 117.39 (CS), 69.78 (CHOH), 43.04 (CH_2S), 35.76 (CH_2CHOH), 27.91($CH_2CH_2CH_3$), 22.70 (CH_2CH_3), 14.01($CH3CH_2$). HRMS: calculated 248.1085 for ($C_{12}H_{19}NNaOS$), found 248.1088 *(*M+Na) +.

1-((2-aminophenyl)thio)-3-phenoxypropan-2-ol : 2e: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 6.65 (m, 9H, H_{ar}), 4.45 (broad s, 2H, NH_2,), 4.09 – 3.97 (m, 3H, CHOH+ CH_2O), 3.49 (broad s, 1H, OH), 3.18 – 2.88 (m, 2H, CH_2S). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.40 (CNH_2), 158.51, 136.34, 130.31, 129.55, 121.21, 119.17, 115.49, 114.64 ($8C_{ar}$), 117.24 (CS), 70.41 (CH_2O), 68.89 (CHOH), 38.90 (CH_2S). HRMS: calculated 298.0878 for ($C_{15}H_{17}NNaO_2S$), found 298.0876 *(*M+Na)+.

2-((2-aminophenyl)thio)-1-phenylethanol : 2f: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 6.63 (m, 9H, H_{ar}), 4.15 (t, 1H, CHS, *J* = 6.5 Hz,), 3.91 (d, 2H, CH_2OH, *J* = 6.5 Hz,), 3.70 (broad s, 3H, OH, NH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.04 (CNH_2), 139.41, 137.65, 130.71, 128.69, 128.47, 127.98, 118.96, 115.42 (8Car), 116.22 (CS), 65.04 (CH_2OH), 55.69 (CHS). HRMS: calculated 268.0772 for ($C_{14}H_{15}NNaOS$), found 268.0776 *(*M+Na)+.

RESULTS AND DISCUSSION

The opening reaction of various terminal epoxides with an alkyl, aryl, functional or cyclic group substituents with 2-aminobenzenethiol in the presence of benzyl triméthylammonium (Triton B) gives the corresponding amino-β-hydroxysulfides as shown in Scheme 1.



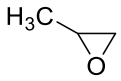
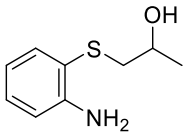
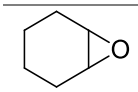
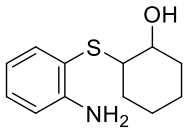
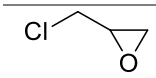
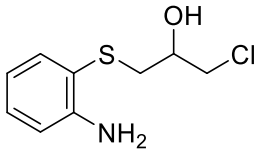
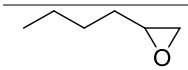
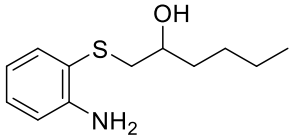
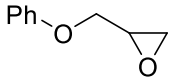
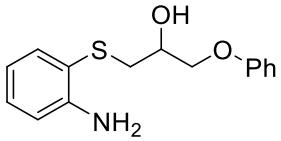
R = Me ; -$(CH_2)_4$- ; CH_2-Cl ; $(CH_2)_4$; PhO-CH_2 .

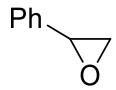
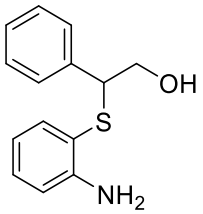
Scheme 1

The ring-opening reactions were carried out in a simple manner by adding 2-aminobenzenethiol dropwise over a 30-min period to a stirred solution of epoxide and Triton B (2.5%) at room temperature without solvent. This was under taken using a reactive 2-aminobenzenethiol: epoxide molar ratio of 1:1. The different results obtained are gathered in the Table1.

As shown in Table 1, the NMR spectrum of the reaction crude mixture showed signals for the possible regioisomer with excellent regiospecificity observed for all epoxides **1a**–**f**. Selective nucleophilic attack by the thiolate anion occurs at the less-substituted carbon atom, except forthe styrene oxide **1f** the nucleophilic attack takes place exclusively on the benzylic carbon. The method provides high yields of versatile amino-β-hydroxysulfide.

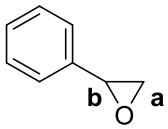
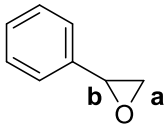
Table1: Ring opening of epoxides by 2-aminobenzenethiol

Epoxide	product	Yield %	Ratio a/b
 **1a**	 **2a**	**70**	100:0
 **1b**	 **2b**	**60**	100:0
 **1c**	 **2c**	**65**	100:0
 **1d**	 **2d**	**73**	100:0
 **1e**	 **2e**	**76**	100:0

 **1f**	 **2f**	**75**	0 :100

The procedure described here appears to be highly efficient and competitive with other methods reported in the literature[28]. The ring-opening reaction of styrene oxide **1f** with **2-**aminobenzenethiol in the presence of the KOH as catalyst is compared in **Table 2.**

Table 2: Comparison of regioselectivity of thiolysis of styrene oxide by 2-aminobenzenethiol

Epoxide	***catalyst (mol%)***	***solvent***	***T°C***	***Yield %***	***Time (h)***	***Regioselectivity (a/b) %***
 **[28]**	KOH (100%)	EtOH	reflux	38	1	mixture
 **1f**	Triton B (2.5%)	Solvent free	RT	75	2	0/100

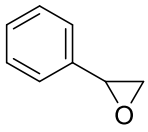
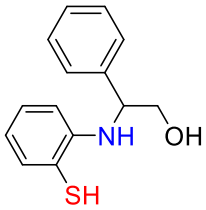
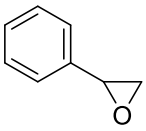
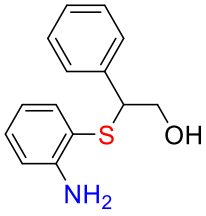
The regiospecificity of compound **2f** were determined by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum shows a signal at 4.15 ppm for the CHS proton and a signal at 3.91 ppm for CH_2OH protons. The ^{13}C NMR spectrum displays, in addition to peaks linked to the aromatic carbon, the existence of two signals corresponding to the two aliphatic carbon atoms *C*H_2OH and *C*HS at 65.04 and 55.69 ppm, respectively.

Under similar conditions, treatment of cyclohexene oxide **1b** with 2-aminobenzenethiol gave a good yield of the corresponding expected trans- amino-β-hydroxysulfide.

Reaction of 2-aminobenzenethiol with epichlorohydrin in the presence of Triton B gave the corresponding amino-β-hydroxysulfide through a nucleophilic attack at the terminal carbon of the epoxide moiety. No product from nucleophilic substitution of the chloride atom was observed (based on ^{1}H and ^{13}C NMR), which confirms the exclusive chemo and regioselectivity of the reaction.

The above process was also chemoselective as illustrated using 2-aminobenzenethiol with two potential reactive nucleophilic functional groups (thiol and amine). The reaction of 2-aminobenzenethiol with all of the aliphatic epoxides in the presence of Triton B takes place chemoselectively with exclusive attack of the thiolate anion on the less hindered carbon atom of the epoxide, but in case of styrene oxide the nucleophilic attack takes place exclusively on the more substituted carbon. No significant amount of the product was observed from the attack of amine anion. The ^{1}H NMR spectra of the crude products **2a-f** showed the presence of a broad signal which corresponds to the two protons of the amine (NH_2) at approximately 4 ppm, and the absence of the multiplet corresponding to the sulfur proton (SH) at 1.7 ppm and the appearance of a multiplet at 3.5 ppm attributed to the C*H*OH which further confirms the proposed thiolysis of epoxides. The chemeoselectivity observed can be explained by the use of Triton B (Table 3), in agreement with results previously reported using this catalyst [29].

Table 3: influence of catalyst in the chemoselectivity of 2-aminobenzenethiol reaction

epoxide	*catalyst*	*Time (h)*	*product*
 **[29]**	Free catalyst	3	
 **1f**	Triton B	2	 **2f**

CONCLUSION

We have reported the thiolysis of alkyl and aryl-oxiranes with 2-aminobenzenethiol under solvent-free conditions catalyzed by Triton B (2.5%) at room temperature. This protocol is novel in terms of high regio- and chemospecificity in comparison with other methods reported in the literature. The additional advantage is that these reactions were carried out at room temperature under solvent-free conditions with small amounts of catalyst and gave good yields.

ACKNOWLEDGEMENT

The authors would like to thank the Tunisian Ministry of Higher Education and Scientific Research for the financial support (LR99ES14) and Dr Sanhoury, Department of Chemistry, Faculty of Sciences of Tunis, for language correction.

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Online publication Date: 30.11.2017