Efficient, eco-Friendly and Regioselective Method for Thiolysis of 1,2-Epoxides with Diaryl Disulfides in the Presence of Zn/Bi(TFA)₃-TBPB or Zn/Bi(OTf)₃-TBPB

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Diaryl disulfides undergo regioselective ring-opening of 1,2-epoxides in the presence of zinc powder and 3-4 mol-% of bismuth(III) trifluoroacetate or 1 mol-% of bismuth(III) triflate in molten tetrabutylphosphonium bromide (TBPB) to afford the corresponding β -hydroxy thioethers in good to excellent yields.

Key words: Epoxide, Diaryl Disulfide, Thiolysis, Ionic Liquid, Bismuth(III) Compounds

Introduction

 β -Hydroxy thioethers are attractive compounds, either as useful intermediates in natural products or as building blocks for the synthesis of pharmaceuticals [1-6]. They also find application for synthesizing benzothiazepines [7], benzoxathiepines [8,9], α -thio-substituted ketones and esters [10] and β hydroxysulfoxides [11 - 13]. The most straightforward route for the preparation of β -hydroxy thioethers involves the ring opening of epoxides with an excess of a thiol in the presence of a base in a protic solvent [14]. Several approaches towards their synthesis using Lewis acids have been reported in the literature [15-20]. However, in spite of their potential utility some of them have limitations including long reaction times, drastic reaction conditions, unsatisfactory yields, poor regioselectivity and the use of stoichiometric amounts of the reagents. On the other hand, the use of toxic solvents and catalysts also limits the methods to small-scale synthesis. Due to the importance of these valuable compounds in synthetic organic chemistry, the development of efficient, convenient and eco-friendly methods for the synthesis of β -hydroxy thioethers could be of great benefit.

Results and Discussion

Organic solvents have posed a serious threat to the environment, since they are usually toxic and volatile.

Therefore, methods that reduce their use are focus of much interest. Consequently, ionic liquids attract increasing interest as alternative cleaner reaction media [21, 22]. Ionic liquids have interesting physical properties such as being non-flammable and having no measurable vapour pressure and high thermal stability.

Bismuth(III) compounds have recently attracted the interest of organic synthesis chemists [23, 24]. Among them, Bi(TFA)₃ and Bi(OTf)₃ have received much attention due to their high activity, low cost, watertolerance, easy handling and low toxicity [25-32]. There is no report on the thiolysis of epoxides employing these catalysts. However, to the best of our knowledge there is only one report that performed this transformation with disulfides in the presence of Zn/AlCl₃ in dry DMF and the corresponding products were obtained in long reaction times [33]. In addition, a stoichiometric amount of Lewis acid was required for completion of this reaction. In continuation of our recent studies on bismuth(III) salts [34-39] and immobilization of a catalyst in ionic liquid [40] we herein report the thiolysis of oxiranes with diaryl disulfides using zinc powder in the presence of catalytic amounts of Bi(TFA)₃ or Bi(OTf)₃ in tetrabutylphosphonium bromide as an ionic liquid (Scheme 1).

The ring-opening reactions of different epoxides with several diaryl disulfides were carried out and the results summarized in Table 1. The reactions proceeded efficiently in high yields and short reaction

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Table 1. Regioselective ring opening of oxiranes with diaryl disulfides in the presence of zinc powder and Bi(OTf)₃ or Bi(TFA)₃ immobilized on Bu₄PBr at 65 °C.

Entry	Oxirane	ArSSAr	Product ^a	Bi(OTf) ₃	Bi(TFA) ₃
		Ar =		Yield [%] /Time [min]	Yield [%] /Time [min]
1	Ph	Phenyl	2a	97/20	93/25
2	Ph	<i>p</i> -Tolyl	2b	95/20	90/25
3	Ph	2-Naphthyl	2c	92/20	88/20
4	○ ⁰	Phenyl	Che State St	85/40	82/45
5	\bigcirc°	<i>p</i> -Tolyl	сн, 2е	84/60	80/55
6	○ o	2-Naphthyl		82/50	78/55
7	$\sim _{\circ} \sim $	Phenyl	3g	85/60	83/55
8	$\sim \sim$	2-Naphthyl	3h	82/65	80/60
9		Phenyl	3i	90/30	86/30
10	$\sim \sim \sim \sim$	Phenyl	3ј	90/55	88/60
11	CI	Phenyl	3k	85/55	80/70
12	PhO	Phenyl	31	89/30	80/45
13	PhO	<i>p</i> -Tolyl	3m	93/30	85/30

^a The products are known compounds and were characterized by comparison of their spectral data (H NMR, ¹³C NMR and IR) with those reported in the literature[15-21]; ^b all yields refer to isolated products.

$$R^{1} \qquad \frac{Bi(OTf)_{3}/(n-Bu)_{4}PBr \text{ or } Bi(TFA)_{3}/(n-Bu)_{4}PBr}{Zn, ArSSAr} \qquad ArS \qquad OH + R^{1} \qquad SAr \\ R^{1} \qquad \qquad R^{1$$

Ar: Ph; p-Tolyl; 2-Naphthyl



Scheme 1.

times without the formation of any by-product. It should be mentioned that no reaction was observed in the absence of zinc powder or a catalytic amount of the bismuth (III) salts.

Styrene oxide as an aryl oxirane proceeded cleavage by different diaryl disulfides like diphenyl, di-ptolyl and di-2-naphthyl disulfides regioselectively with preferential attack at the more substituted carbon atom (Table 1, entries 1-3). The structures of the single products 2a-c were confirmed by ¹H NMR spectra of the crude products. 1,2-Epoxyoctane and epichlorohydrin, as alkyl oxiranes, reacted with the aryl disulfides regioselectively to afford the corresponding β hydroxy thioethers in high yields (Table 1, entries 9



Table 2. Competitive ring opening reactions of oxiranes with diaryl disulfides in the presence of zinc powder and Bi(OTf)₃ or Bi(TFA)₃ immobilized on Bu₄PBr at 65 °C.

a Isolated yields.

and 11). The isomer arising from the nucleophilic bimolecular attack on the less substituted carbon atom is regioselectively produced by these alkyl oxiranes. As can be seen in the case of unsymmetrical epoxides, the regiochemistry is strongly dependent on the nature of the substituent on the ring of epoxides. Cyclohexene oxide as a symmetrical cycloalkyl epoxide underwent cleavage with the aryl disulfides to produce the respective β -hydroxy thioethers in high yields and *trans*-stereochemistry. In all cases, the reactions proceeded rapidly at 65 °C with high regioselectivity and the reactions were completed within 60 min.

These catalysts are highly efficient and 1 mol-% of bismuth triflate and 3-4 mol-% of bismuth trifluoroacetate were sufficient to catalyze the ring opening reactions of oxiranes with aryl disulfides. This shows that the reactivity of Bi(OTf)₃ is higher than the reactivity of Bi(TFA)₃ in the ring opening reactions. In this method there is no need for exclusion of moisture from the reaction mixture.

However, dibenzyl disulfide and dicyclohexyl disulfide, as aliphatic disulfides, are quite resistant to the reaction conditions for ring opening of epoxides.

Competitive reactions were also studied to show further the selectivity and the results summarized in Table 2. High chemoselectivity was exhibited with epichlorohydrin and the corresponding β -hydroxy sulfide was obtained resulting from the nucleophilic sulfur attack at the terminal carbon atom of the epoxide in 80% yield. Another advantage of this method for this transformation is recyclability of these promoter systems. Since Zn/Bi(TFA)₃-TBPB or Zn/Bi(OTf)₃-TBPB were weakly soluble in Et₂O, they were separated by washing with Et₂O and dried at 80 °C under reduced pressure and reused in three runs without any loss of activity.

In conclusion, we have developed a new, efficient, convenient and chemoselective method for the ring opening of oxiranes with diaryl disulfides to produce the β -hydroxy thioethers. In addition, the high catalytic nature and non-toxicity of the catalysts, high selectivity, relatively mild reaction conditions, high reaction rates, easy work up and reusability of the catalytic media are worthy advantages of this method.

Experimental Section

General experimental procedure: To a molten mixture of tetrabutylphosphonium bromide (0.17 g, 0.5 mmol) and $Bi(O_3SCF_3)_3$ (0.007 g, 0.01 mmol) or $Bi(O_2CCF_3)_3$ (0.016 – 0.022 g, 0.03 – 0.04 mmol), epoxide (1 mmol), diaryl disulfide (1 mmol) and zinc powder (0.065 g, 1 mmol) were added and the reaction mixture stirred at 65 °C for the appropriate time (Table 1). The progress of the reaction was followed by TLC (n-heptane/ethyl acetate: 3/1). After completion of the

reaction, Et₂O (20 ml) was added and the mixture filtered. The evaporation of the ether gave the corresponding crude products, which were purified by chromatography on a silica gel plate to afford the pure β -hydroxy thioethers in 78–97% yields.

Spectroscopic data for products **2a**, **3j**, **3m**: Compound **2a**: Oil. – IR (NaCl): v = 3340 (OH), 1590, 1495, 1245, 1045, 740, 700 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): $\delta = 2.15$ (br s, 1H, OH), 3.95 (d, J = 6.9 Hz, 2H), 4.35 (t, J = 6.9 Hz, 1H), 7.25 – 7.45 (m, 10H). – ¹³C NMR (50 MHz, CDCl₃): $\delta = 139.4$, 134.2, 133.0, 129.4, 128.5, 128.2, 128.0, 124.1, 66.0, 56.5. Compound **3j**: Oil. – IR (NaCl): v = 3424, 3010, 2920, 2830, 1600, 1490, 1430, 1365, 1110, 735, 695 cm⁻¹. – ¹H NMR (200 MHz, CDCl₃): $\delta = 0.95$ (t, J = 5.7 Hz, 3H), 1.30–1.50 (m, 2H), 1.55 –

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1.70 (m, 2H), 2.8 (br s, 1H, OH), 3.05 - 3.25 (m, 2H), 3.30 - 3.50 (m, 4H), 3.85 - 4.00 (m, 1H), 7.20 - 7.45 (m, 5H). $-^{13}$ C NMR (50 MHz, CDCl₃): $\delta = 136.1$, 130.0, 129.4, 126.8, 73.3, 71.8, 69.4, 37.8, 32.4, 19.7, 14.4. Compound **3m**: Oil. - IR (NaCl): v = 3408, 3050, 2950, 1600, 1500, 1450, 1380, 1290, 1240, 1170, 1070, 1030, 800, 750, 690 cm⁻¹. $-^{1}$ H NMR (200 MHz, CDCl₃): $\delta = 2.80$ (s, 3H), 3.48 (br s, 1H, OH), 3.55 - 3.78 (m, 2H), 4.45 - 4.62 (m, 3H), 7.38 - 7.88 (m, 9H). $-^{13}$ C NMR (50 MHz, CDCl₃): $\delta = 158.9$, 137.3, 131.9, 131.1, 130.4, 130.0, 121.7, 115.1, 70.6, 69.1, 46.5, 38.7.

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