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ORIGINAL ARTICLE

Na/THF- Mediated cleavage of organic disulfides/diselenides. An efficient and one-pot regioselective method to the synthesis of β-hydroxy sulfides/selenides

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Abstract A new, facile, and efficient methodology for synthesizing β-hydroxy sulfides/selenides has been reported. In this study, 1,2-epoxide ring opening was used as the synthetic protocol, and this reaction was examined using metallic sodium with no additional catalyst. This lead to the synthesis of the desired ring-opened products. Relatively short reaction times, mild reaction conditions, a simple work-up, moderate to good yields of products, and remarkable regioselectivity of the nucleophilic attack were other important features of this study.

1. Introduction

1,2-Epoxies represent one of the most widely used functional groups in organic synthesis because of their susceptibility to reactions with numerous nucleophiles. This nucleophilic and regioselective cleavage yields valuable bifunctional compounds in a rather simple procedure (Lanke and Bhanage, 2013; Cossy et al., 2002; Tomioka et al., 2014). The ring opening of epoxides through nucleophilic attack has been studied extensively, and there are several references to the opening of epoxides with substances such as alcohols, thiols, amines and ethers (Trikittiwong et al., 2013; Shah et al., 2014; Aramesh et al., 2013; Ertürk et al., 2012; Thomas et al., 2014; Panchadhayee and Misra, 2009; Bandgar et al., 2007).

Since rigorous methodologies for asymmetric epoxidations are now available (Azizi and Saidi, 2006; Yang et al., 2008; Johnson and Sharpless, 2000; Katsuki, 2000) epoxide ring opening, if performed with rigid stereo- and regiocontrol, can be applied beneficially for constructing two adjacent

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stereochemically distinct sp^3 chiral carbon centers in a one-step process.

Furthermore, β-hydroxy sulfides/selenides have emerged as two important classes of organic compounds and have found useful in medicinal chemistry (Tokareva et al., 2009; Jesse et al., 2008) and organic synthesis (Costa et al., 2004; Sala et al., 2002; Movassagh et al., 2003; Chimni et al., 2013; Tiecco et al., 2004). The best reported protocol for synthesizing these compounds is the ring opening of epoxides with nucleophilic sulfur and selenium species. However, the reported methods have some limitations such as the use of strong and nonselective catalysts, toxic and expensive reagents, low yield, long reaction times, and undesirable side reactions. Thus, the search for newer methodologies for epoxide ring opening is still an active area of research in organic chemistry (Sridhar et al., 2005; Khodaei et al., 2005; Azizi et al., 2009; Guo et al., 2009; Amantini et al., 2003; Fringuelli et al., 2003; Yadav et al., 2002; Polshettiwar and Kaushik, 2004; Sun et al., 2009; Movassagh and Soleiman-Beigi, 2007; Chen and Chen, 2007; Gao et al., 2008; Mojtahedi et al., 2012).

We were encouraged to search for a novel, mild, and efficient methodology for the ring opening of various epoxides in which some of the aforementioned limitations could be avoided. This study will report a novel catalyst-free procedure for synthesizing β-hydroxy sulfides/selenides including Na-mediated breaking of S—S and Se—Se bonds and nucleophilic epoxide ring opening with aryl thiolate or selenolate ions as nucleophiles.

2. Materials and methods

2.1. Chemicals and instruments

All solvents were purified by standard methods. Chemicals were purchased from commercial suppliers, Merck and Sigma-Aldrich, and used without further purification. Yields refer to isolated products. All the products are known compounds (Oil compounds) and were characterized by comparison of NMR and IR spectral data with those reported in the literature. The IR spectra were obtained on a FT-IR Hartman–Bomen spectrophotometer using KBr disks. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in CDCl3 solution. The progress of the reaction was monitored using TLC with silica gel SILG/UV 254 plates.

2.2. Procedure for synthesizing β-hydroxy sulfides/selenides through epoxide ring opening

A mixture of diphenyl disulfide derivatives (1 mmol) and sodium metal (2 mmol) in dry THF (4 mL) was stirred for 30 min at room temperature and monitored using TLC (EtOAc:*n*-Hexane, 1:10). After complete transformation to thiolate/selenolate anions, 1,2-epoxide derivative (1.2 mmol) was added to the reaction mixture, and the mixture was stirred at 25 °C until the reaction completed (TLC analysis, EtOAc:*n*-Hexane, 1:4). The THF solvent was evaporated in vacuo, and the reaction mixture was acidified by 20% (*v*/*v*) HCl solution and stirred at 25 °C for 15 min. The mixture was then extracted using dichloromethane (3 × 30 mL), and the combined organic layer was collected, dried over Na_2SO_4, and evaporated in vacuo. The remaining oil in order to obtain the pure β-hydroxy sulfides/selenides was then purified by preparative TLC (Silica gel; EtOAc:*n*-Hexane, 1:4).

2.3. Spectroscopic data for selected β-hydroxy sulfides/selenides prepared using the above mentioned procedure

2.3.1. 1-(4-Bromophenylthio)butan-2-ol (Table 2, entry 6)

Yield 95%; ^1H NMR (400 MHz, DMSO-d_6) δ in ppm: 0.98 (*t*, 3H, J = 7.6 Hz, CH_3), 1.59 (*m*, 2H, CH_2), 2.49 (br s, 1H, OH), 2.86 (dd, 1H, J = 13.8, 8.4 Hz, CH_2), 3.13 (dd, 1H, J = 13.6, 3.6 Hz, CH_2), 3.62 (*m*, 1H, CH), 7.4 (dd, 4H, J = 8.8 Hz, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ in ppm: 9.98, 29.05, 41.47, 70.73, 120.40, 131.36, 132.10, 134.84.

2.3.2. 1-(4-Bromophenylthio)propan-2-ol (Table 2, entry 10)

Yield 94%; ^1H NMR (400 MHz, DMSO-d_6) δ in ppm: 1.27 (*d*, 3H, J = 6.4 Hz, CH_3), 2.67 (br s, 1H, OH), 2.87 (dd, 1H, J = 13.6, 8.4 Hz, CH_2), 3.07 (dd, 1H, J = 13.6, 3.6 Hz, CH_2), 3.86 (*m*, 1H, CH), 7.29 (dd, 4H, J = 8.4 Hz, Ar–H) ^{13}C NMR (100 MHz, DMSO-d_6) δ in ppm: 22.09, 43.4, 65.72, 120.41, 131.35,132.10, 134.76.

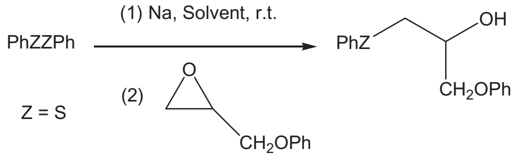
2.3.3. 1-Phenoxy-3(phenylselenenyl)propan-2-ol (Table 2, entry 14)

Yield 97%; ^1H NMR (400 MHz, DMSO-d_6) δ in ppm: 3.01 (br s,1H, OH), 3.20 (dd,1H, J = 12.8, 6.8 Hz, CH_2), 3.28 (dd, 1H, J = 12.8, 6 Hz, CH_2), 4.08 (*m*, 2H, CH_2), 4.20 (m, 1H, CH_2), 6.94 (*d*, 2H, J = 8 Hz, Ar–H), 7.04 (*t*, 1H, J = 7.2 Hz, Ar–H), 7.32 (m, 5H, Ar–H), 7.61 (dd, 2H, J = 3.6, 7.2 Hz, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ in ppm: 31.88, 69.23, 70.58, 77.30, 114.66, 121.30, 127.38, 129.37, 129.61, 132.89, 158.45.

3. Results and discussion

Initially, we explored the optimized reaction conditions for the Na-mediated cleavage of diphenyl disulfide followed by the addition of phenoxymethyl epoxide at room temperature as our model reaction (Scheme 1).

The results are summarized in Table 1. As indicated in Table 1, the cleavage process was performed with 2 mmol of Na in proportion to 1 mmol of diphenyl disulfide or diselenide and 1.2 mmol of phenoxymethyl epoxide (Table 1, entry 9). Using lower amounts of Na resulted in a dramatic decrease in the yield of ring-opened product (Table 1, entry 10). Moreover, the addition of more Na to the reaction interestingly lead to lower yields relative to the case of using 2 mmol of Na (Table 1, entries 7 and 8). Furthermore, the model reaction did not proceed at all in other solvents, such as CH_2Cl_2, DMF, Et_2O, $CHCl_3$, and *n*-hexane. Small amounts of reactivity were observed only in CH_3CN (Table 1, entries 1–6). Based on these



Scheme 1 Reaction conditions optimization.

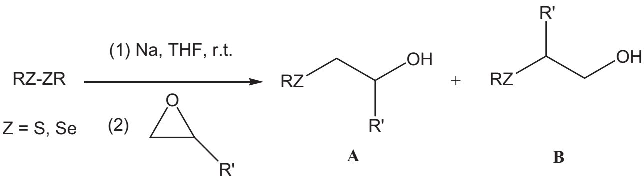
Table 1 Optimization of the solvent and sodium molar ratio in the diphenyl disulfide cleavage reaction/and β-hydroxysulfide synthesis by thiols of 1,2-epoxide at room temperature.

Entry	Solvent	Na[a] (eq)	Time (h)	Yield[b] (%)
1	DMF	2	10	N.R.
2	CH_2Cl_2	2	10	N.R.
3	$CHCl_3$	2	10	N.R.
4	Et_2O	2	10	N.R.
5	*n*-Hexane	2	10	N.R.
6	CH_3CN	1	10	38
7	THF	2	3.5	76
8	THF	1.5	3.5	79
9	THF	1	3.5	86
10	THF	0.5	3.5	35

[a] Na equivalent relative to disulfide.
[b] Isolated yield.

results, THF was chosen as the optimal reaction medium. These results show that both the type of solvent and the amount of sodium can affect the process of converting disulfide to the corresponding thiolate anion, as in the first step of the reaction. As expected, metallic sodium is able to react with disulfide in THF because the sodium ions formed because of the conversion of disulfide to thiolate anion can be better stabilized by coordination to THF molecules.

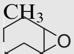
To evaluate the scope and generality of this reaction for the ring opening of epoxides, the procedure with optimized reaction conditions was conducted on various disulfides and diselenides as well as numerous epoxide derivatives (Scheme 2, Table 2).



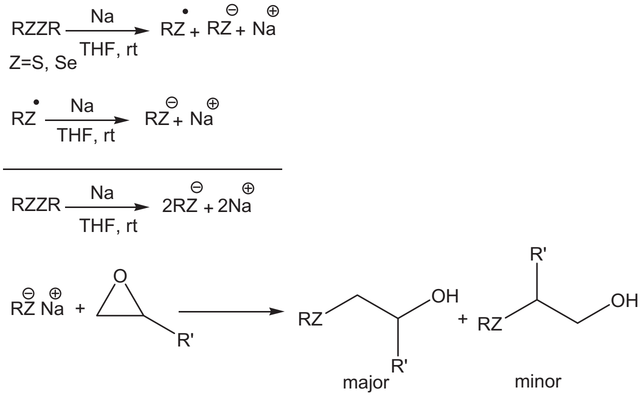
Scheme 2 β-hydroxysulfides/selenides derivatives synthesis through ring opening of epoxides.

All reactions were completed in a simple manner under air atmosphere with relatively short reaction times at ambient temperature (3.5–7 h) and with moderate to good yields of the products. The work-up stage of the processes was performed using preparative TLC. When common aliphatic epoxides were used with disulfides, the reactions proceeded with remarkable regioselectivity, and the β-hydroxy sulfides were obtained solely as regioisomers (A). No sign of regioisomer (B) was detected by PTLC and NMR analysis (Table 2, entries 1–15). This observation might be due to the fact that the nucleophilic attack by disulfides on aliphatic epoxides is performed in a pure SN_2 manner exclusively on the less sterically hindered carbon atom of the ring. This means that the only governing factors in these cases would be steric. The same pattern was observed for the case of a diphenyl diselenide nucleophile in the ring opening process (Table 2, entries 13–16). The results were achieved using diphenyl disulfide/diselenide as the

Table 2 Na mediated synthesis of β-hydroxysulfides/selenides through ring opening of epoxides.

Entry	*R*	*Z*	*R′*/epoxy	Time (h)	Yield[a] (%)
1	C_6H_5	S	CH_2OPh	3:30	96[b]
2	$C_6H_5CH_2$	S	CH_2OPh	5	70[c]
3	$4\text{-}CH_3C_6H_5$	S	CH_2OPh	4:30	81[d]
4	$4\text{-}BrC_6H_5$	S	CH_2OPh	3:45	89[e]
5	C_6H_5	S	C_2H_5	4	76[b]
6	$4\text{-}BrC_6H_5$	S	C_2H_5	5	95[e]
7	C_6H_5	S	CH_3	4.50	86[b]
8	$C_6H_5CH_2$	S	CH_3	6	73[c]
9	$4\text{-}CH_3C_6H_5$	S	CH_3	6	71[c]
10	$4\text{-}BrC_6H_5$	S	CH_3	4.50	94[e]
11	C_6H_5	S		4	83[b]
12	$4\text{-}CH_3C_6H_5$	S		4.5	74[g]
13	C_6H_5	Se		3.5	80[f]
14	C_6H_5	Se	CH_2OPh	4	97[f]
15	C_6H_5	Se	C_2H_5	4.5	75
16	C_6H_5	Se	CH_3	4	81
17	C_6H_5	S	C_6H_5	5	33(A), 57(B)[b]
18	$4\text{-}BrC_6H_5$	S	C_6H_5	5.5	33(A), 52(B)[e]
19	C_6H_5	Se	C_6H_5	6	38(A), 51(B)[h]

[a] Isolated yield.
[b] Maiti and Bhattacharyya (1994).
[c] Bandgar et al. (2007).
[d] Guo et al. (2009).
[e] Azizi et al. (2009).
[f] Sridhar et al. (2005).
[g] Khodaei et al. (2005).
[h] Tiecco et al. (2004).



Scheme 3 A proposed mechanism for cleavages of organic disulfide/diselenide by Na/THF.

nucleophile for the ring opening of phenoxymethyl epoxide (Table 2, entries 1 and 14).

In the case of reactions involving epoxides with aryl oxacyclopropane ring, no strong regioselectivity was observed. This could be due to the fact that in these cases, the substituents can distort the electron distribution on the three-membered ring, which leads to the formation of some partial positive charge on the ring carbon atom bearing these substituents. No notable regioselectivity or yield was observed in these cases due to this partial charge formation on the more sterically hindered carbon atom of the epoxide ring, which somewhat facilitates the nucleophilic attack on the ring atom with more substituents (Table 2, entries 17–19). The competition between two carbon atoms of the ring to be the center for the nucleophilic attack by the thiolate or selenolate anions can be the reason for poor regioselectivity observed in these cases. However, this process still indicates a noticeable inclination for synthesizing the desired β-hydroxy sulfides and selenides with significant regioselectivity and high yields.

Although the exact reaction mechanism is not understood completely, thiolate/selenate appears to be generated first in the Red/Ox reaction between S—S/Se—Se bond and Na in THF. The generated thiolate/selenate is then reacted successfully with 1,2-epoxides to produce β-hydroxy sulfides/selenides (Scheme 3).

4. Conclusion

In summary, a new efficient methodology for synthesizing β-hydroxy sulfides/selenides through the ring opening of epoxides has been reported. In this protocol, metallic sodium was used for the in situ conversion of disulfides/diselenides to their corresponding thiolate (selenolate) anions, which subsequently open the epoxide rings by nucleophilic attack. The major advantages of the reported methodology are: no use of any extra acidic catalyst for activating the epoxide ring, mild reaction conditions, simple work-up, moderate to good yield of products, and remarkable regioselectivity in most cases.

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