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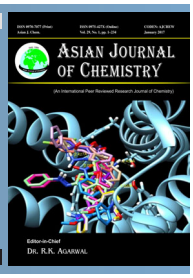

Regioselective Ring-Opening of Epoxides with Thiophenols in Presence of β-Cyclodextrin in Water

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This paper reports a simple, mild and convenient method to synthesize β-hydroxysulfides. These β-hydroxysulfides were achieved with excellent yields (> 80 %) and high regioselectivity by ring-opening reaction of oxiranes with thiophenols in presence of the β-cyclodextrin at 30 °C in water. β-Cyclodextrin as catalyst greatly accelerated the reactions and can be recovered.

Keywords: β-Hydroxysulfides, Oxiranes, β-Cyclodextrin, Thiophenol, Regioselectivity.

INTRODUCTION

Cyclodextrins (CDs) possess cyclic oligomers containing a polar cavity with primary hydroxyl groups lying on the outside and the secondary hydroxyl groups inside [1,2]. Cyclodextrins are widely used as food additives [3,4] for elimination of undesired tastes or stabilization of flavours. Cyclodextrins and their derivatives are also applied in drug delivery as auxiliary additives such as solubilizers and diluents in order to enhance the bioavailability of poor soluble drugs [5]. Cyclodextrins are also used to catalyze chemical reactions with high yield and selectivity [6-10] since cyclodextrins can bind substrates to form host-guest complexes. Complexation depends on the size, shape and hydrophobicity of the guest molecule.

β-Hydroxysulfides are useful intermediates in the synthesis of pharmaceuticals [11-13] and natural products [14,15] especially in the preparation of leukotrienes [16]. Most synthetic procedure for the preparation of β-hydroxysulfides is the nucleophilic ring opening of epoxides with thiols in the presence of various catalysts such as Lewis acids [17-19], heterogeneous catalysis [20], hetero-bimetallic system [21] or basic conditions [22-25]. However, most of these methods involve the use of expensive reagents, drastic reaction conditions, hazardous organic solvents and suffering from poor regioselectivity. In view of these limitations, inexpensive, environmentally benign and highly efficient catalysts are expected to develop for the ring-opening of epoxides directly with thiols. Our earlier study on ester hydrolysis successfully catalyzed by β-cyclodextrin derivatives [26] promoted us to attempt ring opening of aromatic epoxides with thiophenols in the presence of β-cyclodextrin in water.

EXPERIMENTAL

All the reactions were carried out without any special precautions in an atmosphere of air. Oxiranes and thiophenols were purchased from Sigma-Aldrich. β-cyclodextrin (β-CD, reagent grade) was recrystallized twice from H_2O and dried in vacuum for 12 h at 100 °C. Water used as the solvent in all reactions was double-distilled. The ^{1}HNMR, ^{13}CNMR and HMBC spectra were recorded on Bruker 500- or 400-MHz spectrometers. IR spectra were recorded on Shimadzu FT-IR 8700. High-resolution mass spectra (HRMS) were observed on Bruker LC-Q-TOF spectrometer.

Synthesis of hydroxysulfides: β-Cyclodextrin (0.50 mmol) was dissolved in water (15 mL) by warming to 50 °C until a clear solution was formed. After that oxirane (0.50 mmol) dissolved in acetone (2 mL) was added and the mixture was allowed to reach reaction temperature 30 °C. Thiophenol (0.50 mmol) was added and the mixture was stirred at reaction temperature until the reaction was complete (checked by TLC). The organic material was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The resulting crude product was further purified by silica-gel (200-300 mesh) column chromatography with petroleum ether:ethyl acetate (4:1) as eluent. The filtrate was evaporated to dryness under reduced pressure to get products. The resulting residue was dissolved in a small amount of hot water, then the aqueous solution was poured into ethyl acetate (25 mL) to give precipitate and filter to recover β-cyclodextrin (> 95 %). The recovered β-cyclodextrin was dried for 12 h at 95 °C before reuse. The compounds β-thio alcohols

2B, **3B**, **5A**, **7A** were reported previously. The new compounds **1B**, **6A**, **9A**, **10A**, **11A** were characterized by ^{1}H NMR, ^{13}C NMR, HMBC and HRMS spectra. The isomer was determined by HMBC spectra.

1-Phenoxy-3-(*p*-tolylthio)propan-2-ol (Table-1, 1B): Pale yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 4H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.26-3.96 (m, 3H), 3.23 (dd, *J* = 13.9, 5.3 Hz, 1H), 3.13 (dd, *J* = 13.9, 6.9 Hz, 1H), 2.76 (brs, 1H), 2.34 (s, 3H).^{13}C NMR (400 MHz, $CDCl_3$) δ 158.40, 137.02, 131.21, 130.76, 129.93, 129.50, 121.22, 114.56, 70.08, 68.57, 38.42, 21.03 ppm.

1-[(4-Methoxyphenyl)thio]-3-phenoxypropan-2-ol (Table-1, 2B): Pale yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.37 (m, 2H), 7.36-7.25 (m, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.94-6.78 (m, 4H), 4.14-3.98 (m, 3H), 3.81 (s, 3H), 3.16 (dd, *J* = 13.8, 5.0 Hz, 1H), 3.07 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.81 (brs, *J* = 2.9 Hz, 1H).^{13}C NMR (400 MHz, $CDCl_3$) δ 159.37, 158.42, 133.69, 129.49, 125.05, 121.20, 114.82, 114.56, 70.09, 68.49, 55.36, 39.72 ppm. HRMS (ESI) calculated for $C_{16}H_{18}O_3S$ $(M + Na)^+$ 313.0874, found $(M + Na)^+$ 313.0869.

1-[(4-Chlorophenyl)thio]-3-phenoxypropan-2-ol (Table-1, 3B): Pale yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.23 (m, 6H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.27-3.93 (m, 3H), 3.26 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.17 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.71 (d, *J* = 4.6 Hz, 1H).^{13}C NMR (400 MHz, $CDCl_3$) δ 158.26, 133.76, 132.73, 131.16, 129.56, 129.25, 121.37, 114.53, 69.94, 68.63, 37.83 ppm.

2-Phenyl-2-(*p*-tolylthio)ethan-1-ol (Table-1, 5A): Pale yellow solid, ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.19 (m, 7H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.27 (t, *J* = 6.9 Hz, 1H), 4.08-3.81 (m, 2H), 2.34 (s, 3H), 2.09 (br, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 142.17, 137.17, 131.11, 129.97, 128.54, 127.93, 125.87, 71.49, 44.88, 21.07 ppm. IR (KBr, ν_{max}, cm^{-1}): 3395.83 (OH), 3060.20, 3028.37 (sv(CH) of benzene), 2922.28 (asv(CH_2)), 2870.20 (sv(CH_2)), 1600.02, 1492.97, 1451.50 (benzene skeleton vibration), 1398.45, 1379.16 (sv(CH_3)), 1286.58, 1179.52, 1056.07, 1018.46, 977.95 (sv(C-O), sv(C-O-C)), 811.10 (*p*-substituted of benzene), 760.95 (sv(C-Cl)), 732.02, 698.26 (C-H out-of-plane bending vibrations of single substitued benzene), 614.56 (sv(C-S)).

2-[(4-Methoxyphenyl)thio]-1-phenylethan-1-ol (Table-1, 6A): Pale yellow solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.19 (m, 7H), 6.84-6.78 (m, 2H), 4.17 (t, *J* = 6.9 Hz, 1H), 3.99-3.85 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.92, 139.09, 136.09, 128.62, 128.11, 127.68, 123.36, 114.50, 64.68, 57.08, 55.32 ppm. HRMS (ESI) calculated for $C_{15}H_{16}O_2S$ $(M + Na)^+$ 283.0769, found $(M + Na)^+$ 283.0763. IR (KBr, ν_{max}, cm^{-1}): 3410.29 (OH), 3063.09, 3027.41, 3003.30, 2938.68 (asv(CH_2)), 2835.45 (sv(CH_2)), 1591.34, 1494.90, 1470.79 (benzene skeleton vibration), 1285.61, 1246.07, 1179.52.63, 1055.11, 1030.03 (sv(C-O), sv(C-O-C)), 828.46 (*p*-substituted of benzene), 762.88, 732.02, 698.26 (out-of-plane bending vibrations of single substitued benzene), 641.36 (sv(C-S)).

2-[(4-Chlorophenyl)thio]-1-phenylethan-1-ol (Table-1, 7A): Pale yellow solid,^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.07 (m, 9H), 4.30 (t, *J* = 6.9 Hz, 1H), 3.93 (qd, *J* = 11.5, 7.2 Hz, 2H), 2.09 (brs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.59, 133.97, 133.85, 132.14, 129.36, 129.09, 128.81, 128.07, 127.97, 65.20, 56.33 ppm. IR (KBr, ν_{max}, cm^{-1}): 3362.07 (OH), 3061.16, 3028.37 (sv(CH) of benzene), 2930.96 (asv(CH_2)), 2874.06 (sv(CH_2)), 1600.99, 1573.02, 1491.04, 1475.65, 1452.46 (benzene skeleton vibration), 1389.77, 1290.43, 1178.56, 1094.65, 1057.04, 1013.64 (sv(C-O), sv(C-O-C)), 821.71 (*p*-substitutedof benzene), 760.95 (sv(C-Cl)), 745.52, 698.26 (out-of-plane bending vibrations of single substitued benzene), 617.25 (sv(C-S).

1-(4-Chlorophenyl)-2-(*p*-tolylthio)ethan-1-ol (Table-1, 9A): Pale yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.25-7.20 (m, 4H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.23 (t, *J* = 6.8 Hz, 1H), 3.89 (d, *J* = 6.5 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.26, 137.76, 133.53, 133.44, 129.83, 129.44, 129.18, 128.78, 64.80, 55.91, 21.13 ppm. HRMS (ESI) calculated for $C_{15}H_{15}ClOS$ $(M + Na)^+$ 301.0430, found $(M + Na)^+$ 301.0424.

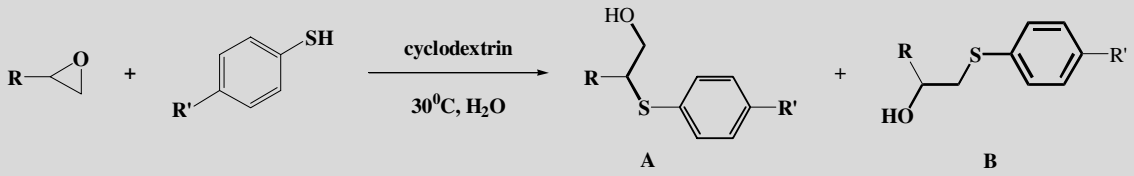
1-(4-Chlorophenyl)-2-[(4-methoxyphenyl)thio]ethan-1-ol (Table-1, 10A): Pale yellow oil,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.19 (m, 4H), 7.18-7.10 (m, 2H), 6.84-6.69 (m, 2H), 4.10 (t, *J* = 6.8 Hz, 1H), 3.85 (d, *J* = 6.9 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.08, 137.75, 136.30, 133.39, 129.48, 128.75, 122.75, 114.60, 64.41, 56.45, 55.36 ppm. HRMS (ESI) calculated for $C_{15}H_{15}ClO_2S$ $(M + Na)^+$ 317.0379, found $(M + Na)^+$ 317.0373.

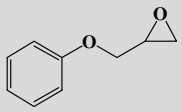
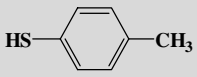
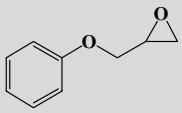
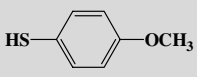
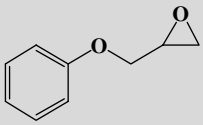
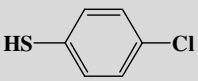
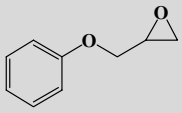
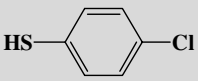
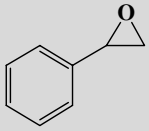
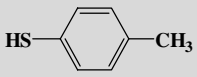
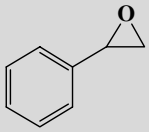
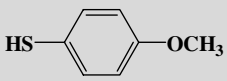
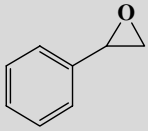
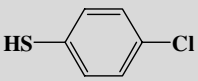
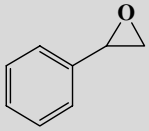
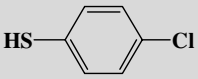
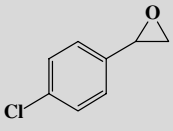
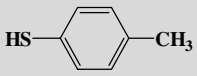
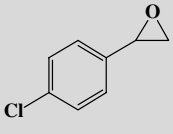
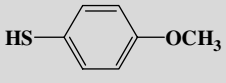
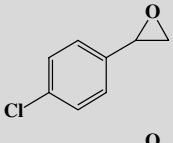
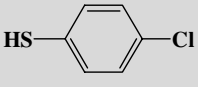
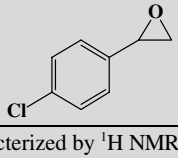
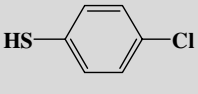
1-(4-Chlorophenyl)-2-[(4-chlorophenyl)thio]ethan-1-ol (Table-1, 11A): Pale yellow solid,^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.05 (m,8H), 4.26 (t, *J* = 6.8 Hz, 1H), 3.91 (dd, *J* = 6.6, 4.1 Hz, 2H), 2.08 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.30, 137.75, 133.58, 133.46, 129.86, 129.46, 129.15, 128.81, 64.80, 55.93 ppm. HRMS (ESI) calculated for $C_{15}H_{15}Cl_2OS$ $(M + Na)^+$ 320.9884, found $(M + Na)^+$ 320.9878. IR (KBr, ν_{max}, cm^{-1}): 3395.83 (OH), 3060.20, 3028.37 (sv(C-H) of benzene), 2922.28 (asv(CH_2), 2870.20 (asv(CH_2), 1600.02, 1492.97, 1451.50 (benzene skeleton vibration), 1387.84, 1091.76, 1056.07, 1047.39, 1009.78, 977.95 (sv(C-O), sv(C-O-C)), 822.68 (*p*-substituted of benzene), 790.81 (sv(C-Cl), 732.02, 698.26 (out-of-plane bending vibrations of single substitued benzene), 651.00 (sv(C-S)).

RESULTS AND DISCUSSION

Initially, the ring opening reaction of 1,2-epoxy-3-phenoxy propane was carried out with thiophenol in water in the presence of β-cyclodextrin at various temperature 20, 30, 40 and 50 °C. The experimental results show low yield when the temperature is lower than 20 °C. And the regioselectivity decreased as the temperature increased. The higher regioselectivity and yield were achieved at 30 °C. So the ring opening of various epoxides with different thiophenols was carried out at the optimum temperature 30 °C in water in the presence of β-cyclodextrin. The reaction time was determined through thin layer chromatography (TLC). The reactions were investigated with styrene oxide, 4-chlorostyrene oxide and1,2-epoxy-3-phenoxy propane as the substrates and series of thiophenols with electron-donating and electron-withdrawing groups as the nucleophiles.As listed in Table-1, β-thiol alcohols were obtained in high yield (> 80 %) and excellent selectivity (100

TABLE-1
RING-OPENING REACTION OF EPOXIDES WITH THIOLS IN THE PRESENCE OF β-CYCLODEXTRIN

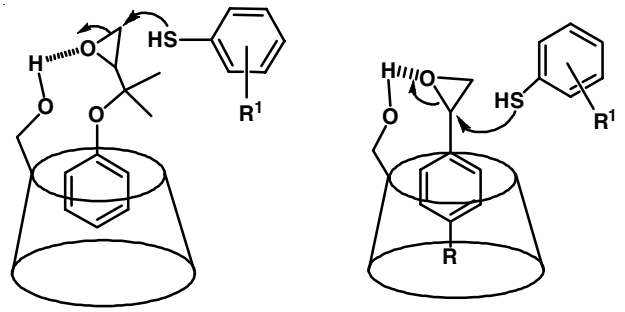


Entry	Epoxide	Thiophenol	Time (/h)	Yield (%)[a,b]	Ratio A:B [c]
1			3	88	0:100
2			3	91	0:100
3			5	81	0:100
4			5 [d]	41	0:100
5			6	83	74:26
6			6	85	80:20
7			6	80	80:20
8			6 [d]	38	82:18
9			6	80	72:28
10			6	83	81:19
11			8	80	81:19
12			8[d]	35	83:17

[a]All products were characterized by ^{1}H NMR and ^{13}C NMR; [b]Isolated yield; [c]The ratio of isomers were calculated by ^{1}HNMR; [d]No cyclodextrin

%). For unsymmetrical alkyl oxiranes 1,2-epoxy-3-phenoxy propane afforded products B (Table-1, entries 1, 2, 3 and 4) with preferential attack at the terminal carbon completely. For alkenyl oxiranes, a mixture of A and B was obtained (Table-1, entries 6-8, 10-12), of which isomer A is dominated (> 72 %). In order to show the important role of β-cyclodextrin, the control experiments were carried out. The results confirm that the yields are very low without β-cyclodextrin (Table-1, entries 5, 9, 13).

According to the literature [27], hydrophobic *tert*-butyl-benzyl group could insert into the cavity of β-cyclodextrin to form supramolecular complex. In the similar way, hydrophobic benzyl group in the epoxides can also insert into β-cyclodextrin partially. Then the hydroxyl group from β-cyclodextrin could bond the oxygen atom of epoxides *via* hydrogen bond, which could favour nucleophiles to attack epoxides. For alkyl oxirane 1,2-epoxy-3-phenoxy propane, terminal carbon is attacked more preferentially because of including complex of cyclodextrin and the group phenoxy of 1,2-epoxy-3-phenoxy propane. Steric effect may play important roles on the ring-opening reaction. For alkenyl oxiranes, benzylic carbon atom is attacked easily by electron rich nucleophiles. However, benzyl of epoxide is included in the cavity of cyclodextrin partially, which is big and not good for the nucleophiles to attack the benzylic carbon due to the steric-hindrance of the including complexes. So the mixture of isomers A and B was got and most of the products are isomer A since the thiophenols electronic effect affects this transformation dominantly. The mechanism of the ring-opening reaction catalyzed by β-cyclodextrin was proposed in **Scheme-I**.



R=H, Cl; R^1=CH_3, OCH_3, Cl

Scheme-I: Suggested mechanism for ring-opening of epoxide in the presence of β-cyclodextrin

The ring opening of 1,2-epoxy-3-phenoxy propane with *p*-methyl thiophenol was choosen to evaluate the recycling capability of β-cyclodextrin. As shown in Table-2, the recovered β-cyclodextrin showed almost equal efficiency in consecutive four cycles under identical reaction conditions, which indicated that the catalyst was stable and suitable to be reused for several times.

TABLE-2
REUSE OF β-CYCLODEXTRIN FOR THE RING-OPENING REACTION OF 1,2-EPOXY-3-PHENOXY PROPANE WITH *p*-METHYLTHIOPHENOL

Cycle	1	2	3	4
Isolated yield (%)[a]	88	87	86	87

Conclusion

The ring opening of epoxides containing benzene group with thiophenol derivatives was carried out in the presence of β-cyclodextrin with high yields and regioselectivity especially for alkyl oxirane. This method is very simple, economic, environmental and efficient, which would be a useful way to modern synthetic methodology in green chemistry.

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