Microwave-assisted ring opening of epoxides with thiols on montmorillonite K-10 solid support

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Abstract

Solvent-free ring opening of 1,2-epoxides with aromatic thiols under microwave irradiation in the presence of montmorillonite K-10 clay affords high yields of β-hydroxy sulfides. Nucleophilic attack of the thiols occurs regioselectively at the less hindered side of the epoxides.

Keywords: Solvent-free reaction, thiols, epoxides, clays, microwave irradiation

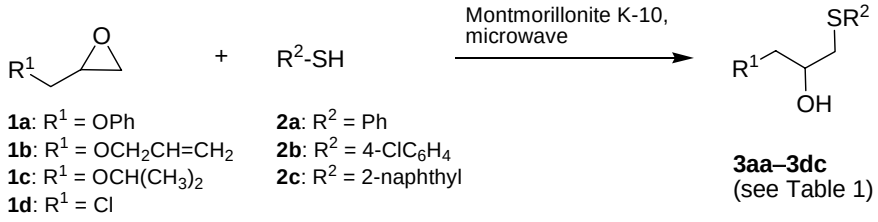
Introduction

Ring opening of epoxides with thiols is an important method of organic transformation and has found much use in pharmaceutical[1] and natural product chemistry,[2] particularly for the synthesis of leukotrienes.[3] The classical approach for the synthesis of β-hydroxy sulfides involves nucleophilic ring opening of epoxides with thiols in the presence of species such as $InCl_3$,[4] $ZnCl_2$,[5] $B(C_6F_5)_3$,[6] ceric ammonium nitrate,[7] hexafluoroisopropyl alcohol,[8] lithium bistrifluoromethanesulfonimide,[9] $CoCl_2$,[10] alumina,[11] polyethylene glycol,[12] gallium complexes,[13] $NiCl_2{\cdot}6H_2O$,[14] CsF on celite,[15] lanthanide complexes,[16] and lithium perchlorate.[17] In many of these cases, the ring opening of epoxides is carried out in a halogenated solvent normally requiring long time treatment under refluxing temperatures or environmentally unfriendly conditions.

Stringent environmental protection laws in recent years prompted an increasing emphasis on the use and design of eco-friendly reagents, solid state procedures, and solvent-free reactions.[18] Application of microwave techniques is currently under extensive examination,[19] and dry procedures have recently attracted much attention because they can be carried out in open vessels, and the use of expensive and hazardous organic solvents can be avoided.[20] We extended our previous experience on solid supported microwave-promoted ring opening of epoxides with amines.[21] Here, we report a simple fast procedure for efficient thiolysis of epoxides on an inexpensive and convenient heterogeneous catalyst surface under solvent-free conditions.

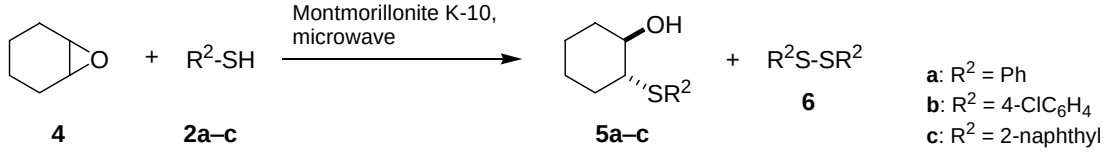
Results and Discussion

Initially, 2-(phenoxymethyl)oxirane **1a** was treated with an equimolar amount of thiophenol **2a** in the presence of montmorillonite K-10 clay under microwave irradiation and without any solvent. The experiments were complete within 75 seconds as monitored by TLC showing the disappearance of the starting epoxide **1a**. The ^{1}H NMR spectrum of the crude reaction mixture revealed the formation of the β-hydroxy sulfide **3aa** indicating that the nucleophilic attack of the thiol occurred at the less hindered side of the epoxide (Scheme 1). Moreover, in the crude mixture the opposite regioisomer was detected in a very small amount (~5%) proving the high regioselectivity of the reaction. Bulb to bulb distillation of the crude mixture gave 92% of the desired product **3aa** (Table 1, entry 1). Control experiments confirmed the combined promoting effect of the solid support and microwave irradiation. When a mixture of thiophenol **2a** and **1a** was irradiated in a microwave oven without the solid support for more than 5 minutes, no product was detected. An alternative reaction without microwave irradiation led to formation of only 20% of **3aa** after several hours. Epoxide **1a** reacted in a similar manner with *p*-chlorothiophenol **2b** and 2-thionaphthol **2c** producing of **3ab** and **3ac** in 85% and 77% yield, respectively (entries 2, 3). The generality of the method was illustrated by subjecting epoxides **1b**–**d** to the reaction with thiols **2a**–**c** on the same solid support (entries 4–12). Consequently, products **3ba**–**3dc** were obtained in 78–87% yields in less than 2 minutes microwave irradiation.



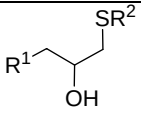
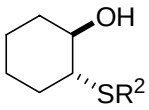
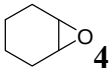
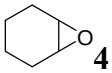
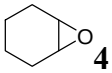
Scheme 1. Microwave promoted thiolysis of epoxides **1** on monmorillonite support.

Under the same reaction conditions sterically more hindered epoxides gave lower yields of products **5**. Thus, the reaction of 1,2-epoxycyclohexane **4** with an excess of thiols **2a**–**c** gave 51–60% of **5a**–**c** with *trans* stereochemistry, and disufides **6** (Scheme 2,[4a,16] entries 13–15).



Scheme 2. Thiolysis of 1,2-epoxycyclohexane **4**.

Table 1. β-Hydroxysulfides **3** and **5**

Entry	Epoxides **1**, R^1; **4**	Thiol **2**, R^2	Time [sec]	 **3**	 **5**	Yield [%]
1	OPh	Ph	75	3aa		92
2	OPh	4-ClC_6H_4	75	3ab		85
3	OPh	2-naphthyl	90	3ac		77
4	O-allyl	Ph	90	3ba		83
5	O-allyl	4-ClC_6H_4	90	3bb		81
6	O-allyl	2-naphthyl	105	3bc		78
7	O-*i*-propyl	Ph	90	3ca		87
8	O-*i*-propyl	4-ClC_6H_4	90	3cb		87
9	O-*i*-propyl	2-naphthyl	105	3cc		83
10	Cl	Ph	60	3da		85
11	Cl	4-ClC_6H_4	60	3db		81
12	Cl	2-naphthyl	75	3dc		79
13	 **4**	Ph	60	5a		60
14	 **4**	4-ClC_6H_4	60	5b		55
15	 **4**	2-naphthyl	75	5c		51

Conclusions

In summary, the microwave-promoted ring opening of epoxides with thiols was carried out in less than 2 minutes under solvent-free conditions in the presence of montmorillonite K-10 clay. The environmental safety of the process, high yields of the products, good regioselectivity of the ring opening, and rapid completion of the reactions are among the advantages of this method, which makes it an attractive addition to the existing literature.

Experimental Section

General Procedures. A conventional microwave oven (900 W) was used for the irradiation of the reaction mixtures. All reported yields are isolated yields. Melting points were determined with a Buchi melting point apparatus and are corrected. TLC experiments were carried out on silica gel plates with UV indicator from Aldrich; visualization was by UV fluorescence or by staining with iodine vapor. IR spectra were recorded on a Bruker Vector 22 FT-IR

spectrophotometer using KBr disks or as neat samples. ^{1}H NMR spectra were recorded on FT-NMR Bruker Ultra Shield^{TM} (500 MHz) or Bruker AC (80 MHz) instruments with $CDCl_3$ as solvent and TMS as internal reference. GC-MS spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O-Rapid instrument. All chemicals were available from Aldrich and used as purchased.

β-Hydroxysulfides 3 and 5. General procedure

A mixture of epoxide (**1** or **4**; 5.0 mmol), aromatic thiol **2** (5.0 mmol) and montmorillonite K-10 clay (1.0 g) was placed in a beaker (50 mL), and the mixture was irradiated at high power in a conventional microwave oven for an appropriate length of time (Table 1). The course of the reaction was monitored by TLC until complete disappearance of the starting material was observed. The mixtures were cooled to room temperature, dissolved in dichloromethane (10 mL), and filtered through a celite column. The solvent was removed at reduced pressure and the respective product **3** or **5** was purified by column chromatography over silica gel or by bulb to bulb distillation. The ^{1}H NMR, IR, and GC-MS spectra of the products were obtained and compared with those reported in the literature.

1-Phenoxy-3-(phenylsulfanyl)propan-2-ol (3aa).[4a] Colorless oil, bp 220–222 °C (4 mm Hg). R_f = 0.66 (EtOAc/hexane 2:8).

1-(4-Chlorophenylsulfanyl)-3-phenoxypropan-2-ol (3ab).[15] Colorless oil, bp 227–229 °C (4 mm Hg). R_f = 0.55 (EtOAc/hexane 2:8).

1-(Naphthalen-2-ylsulfanyl)-3-phenoxypropan-2-ol (3ac). White solid, mp 69–70 °C. R_f = 0.17 (EtOAc/hexane 2:8). ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.70–2.88 (m, 2H), 3.20–3.35 (m, 2H), 3.90–4.01 (m, 2H), 6.75–7.90 (m, 12H). ^{13}C NMR (80 MHz, $CDCl_3$): δ 44.4, 50.0, 68.5, 114.4, 121.5, 125.7, 126.9, 126.5, 127.2, 129.5, 129.0, 135.7, 139.3. MS: *m*/*z* (%) 310 (41) [M^+], 173 (50), 159 (100), 115 (100), 77 (35). IR (KBr): $\tilde{\nu}$ 3426, 1583, 1071, 738 cm^{-1}. Anal. calcd for $C_{19}H_{18}O_2S$: C, 73.52; H, 5.84. Found: C, 73.1; H, 5.5.

1-Allyloxy-3-(phenylsulfanyl)propan-2-ol (3ba).[22] Colorless oil, bp 180–182 °C (4 mm Hg). R_f = 0.61 (EtOAc/hexane 2:8).

1-Allyloxy-3-(4-chlorophenylsulfanyl)propan-2-ol (3bb).[15] Colorless oil, bp 212–214 °C (4 mm Hg). R_f = 0.48 (EtOAc/hexane 2:8).

1-Allyloxy-3-(naphthalen-2-ylsulfanyl)propan-2-ol (3bc). White solid, mp 78–79 °C. R_f = 0.35 (EtOAc/hexane 2:8).^{1}H NMR (500 MHz, $CDCl_3$): δ 2.74 (br s, 1H), 3.21 (dd, *J* = 7, 14 Hz, 1H), 3.28 (dd, *J* = 5.5, 14 Hz, 1H), 3.57 (dd, *J* = 7, 11 Hz, 2H), 3.64 (dd, *J* = 5.5, 11 Hz, 2H), 4.04 (m, 2H), 5.24 (d, *J* = 10 Hz, 1H), 5.30 (dd, *J* = 1, 15 Hz, 1H), 5.90–5.96 (m, 1H), 7.54–8.03 (m, 7H). MS: *m*/*z* (%) 274 (53) [M^+], 159 (100), 128 (42), 115 (65), 41 (62). IR (KBr): $\tilde{\nu}$ 3431, 1578, 1080, 739 cm^{-1}. Anal. calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61. Found: C, 70.2; H, 6.4.

1-Isopropoxy-3-(phenylsulfanyl)propan-2-ol (3ca). White solid, mp 44 °C. R_f = 0.59 (EtOAc/hexane 2:8). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.13 (d, *J* = 6.5 Hz, 6H), 2.55–2.70 (m, 1H), 2.93–3.20 (m, 2H), 3.50–3.95 (m, 4H), 7.10–7.45 (m, 5H). ^{13}C NMR (80 MHz, $CDCl_3$): δ 22.0, 38.1, 69.5, 71.3, 73.0, 127.5, 128.0, 129.3, 137.5. MS: *m*/*z* (%) 226 (16) [M^+], 123 (26), 109

(100), 77 (24), 43 (17). IR (KBr): $\tilde{\nu}$ 3431, 1588, 1086, 738 cm^{-1}. Anal. calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.9; H, 8.3.

1-(4-Chlorophenylsulfanyl)-3-isopropoxypropan-2-ol (3cb). Colorless oil, bp 170–171 °C (4 mm Hg). R_f = 0.37 (EtOAc/hexane 2:8). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.5 Hz, 6H), 3.02–3.20 (m, 2H), 3.45–3.65 (m, 4H), 3.86–3.92 (m, 1H), 7.26–7.45 (m, 4H). MS: *m*/*z* (%) 260 (42) [M$^+$], 157 (97), 143 (100), 99 (63), 73 (57), 43 (76). IR (neat): $\tilde{\nu}$ 3443, 1575, 1093, 747 cm^{-1}. Anal. calcd for $C_{12}H_{17}ClO_2S$: C, 55.27; H, 6.57. Found: C, 55.2; H, 6.7.

1-Isopropoxy-3-(naphthalen-2-ylsulfanyl)-propan-2-ol (3cc). White solid, mp 116 °C. R_f = 0.17 (EtOAc/hexane 2:8). ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.5 Hz, 6H), 3.02–3.20 (m, 2H), 3.45–3.65 (m, 4H), 3.86–3.92 (m, 1H), 7.36–7.85 (m, 7H). ^{13}C NMR (80 MHz, $CDCl_3$): δ 21.7, 37.3, 69.0, 71.5, 73.4, 114.0, 121.9, 125.7, 126.3, 126.5, 127.7, 129.0, 129.6, 135.7, 139.9. MS: *m*/*z* (%) 276 (13) [M$^+$], 160 (49), 115 (53), 73 (73), 43 (100). IR (KBr): $\tilde{\nu}$ 3457, 1583, 1040, 738 cm^{-1}. Anal. calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.4; H, 7.4.

1-Chloro-3-(phenylsulfanyl)propan-2-ol (3da).[17] White solid, mp 42 °C. R_f = 0.62 (EtOAc/hexane 2:8).

1-Chloro-3-(4-chlorophenylsulfanyl)propan-2-ol (3db). Colorless oil, bp 198–201 °C (4 mmHg). R_f = 0.40 (EtOAc/hexane 2:8). ^{1}H NMR (500 MHZ, $CDCl_3$): δ 2.80-2.90 (br s, 1H), 3.10 (dd, *J* = 7, 14.5 Hz, 1H), 3.19 (dd, *J* = 5.5, 14 Hz, 1H), 3.9–3.74 (m, 2H), 3.94–3.98 (m, 1H), 7.26–7.45 (m, 4H). ^{13}C NMR (80 MHz, $CDCl_3$): δ 38.1, 48.2, 69.6, 129.0, 130.5, 132.2, 135.4. MS: *m*/*z* (%) 237 (27) [M$^+$], 194 (31), 157 (100), 143 (45), 108 (52), 75 (37), 45 (57). IR (neat): $\tilde{\nu}$ 3421, 1572, 1093, 742 cm^{-1}. Anal. calcd for $C_9H_{10}Cl_2OS$: C, 45.58; H, 4.25. Found: C, 45.7; H, 4.1.

1-Chloro-3-(naphthalen-2-ylsulfanyl)propan-2-ol (3dc). White solid, mp 142 °C. R_f = 0.21 (EtOAc/hexane 2:8). ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.75–2.90 (br s, 1H), 3.10–3.33 (m, 2H), 3.56–3.66 (m, 2H), 3.92–4.10 (m, 1H), 7.25–7.80 (m, 7H). ^{13}C NMR (80 MHz, $CDCl_3$): δ 37.8, 47.8, 69.5, 114.4, 121.5, 125.7, 126.9, 126.5, 127.2, 129.5, 129.0, 135.7, 139.3. MS: *m*/*z* (%) 252 (10) [M$^+$], 173 (25), 115 (23), 79 (100), 43 (95). IR (neat) ν 3421, 1588, 1071, 738 cm^{-1}. Anal. calcd for $C_{13}H_{13}ClOS$: C, 61.77; H, 5.18. Found: C, 61.5; H, 5.3.

2-(Phenylsulfanyl)cyclohexanol (5a).[4a] Colorless oil, bp 184–187 °C (4 mm Hg). R_f = 0.53 (EtOAc/hexane 2:8).

2-(4-Chlorophenylsulfanyl)cyclohexanol (5b).[23] Colorless oil, bp 176–179 °C (4 mm Hg). R_f = 0.49 (EtOAc/hexane 2:8).

2-(Naphthalen-2-ylsulfanyl)cyclohexanol (5c).[4a] Colorless oil, bp 219–220 °C (4 mm Hg). R_f = 0.41 (EtOAc/hexane 2:8).

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