J. Chem. Research (S), 1998, 216–217†

Solid–Liquid Phase-transfer Catalytic Synthesis of Chiral Glycerol Sulfide Ethers Under Microwave Irradiation†

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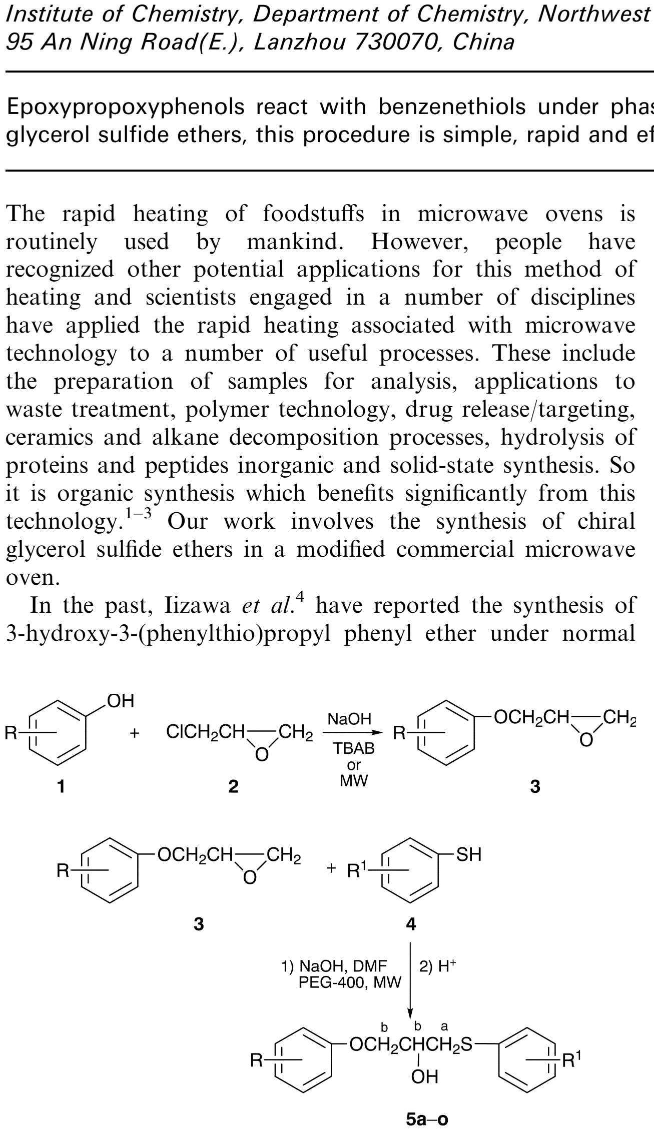
Epoxypropoxyphenols react with benzenethiols under phase-transfer catalysis and microwave irradiation to give chiral glycerol sulfide ethers, this procedure is simple, rapid and efficient.

The rapid heating of foodstuffs in microwave ovens is routinely used by mankind. However, people have recognized other potential applications for this method of heating and scientists engaged in a number of disciplines have applied the rapid heating associated with microwave technology to a number of useful processes. These include the preparation of samples for analysis, applications to waste treatment, polymer technology, drug release/targeting, ceramics and alkane decomposition processes, hydrolysis of proteins and peptides inorganic and solid-state synthesis. So it is organic synthesis which benefits significantly from this technology.[1–3] Our work involves the synthesis of chiral glycerol sulfide ethers in a modified commercial microwave oven.

In the past, Iizawa *et al.*[4] have reported the synthesis of 3-hydroxy-3-(phenylthio)propyl phenyl ether under normal conditions. However, they have synthesied only one isomer and since these compounds can be separated into two kinds of chiral compounds, they may have some biological activity, so it is very interesting to investigate these compounds. We have now found that chiral glycerol sulfide ethers can be obtained from epoxypropoxyphenols and benzenethiols using microwave irradiation. This method is simple, rapid and affords good yields. It takes only 8 min for the reaction to finish (compared to 5 h for the synthesis by Iizawa *et al.*[4]). The reactions are shown in Scheme 1 and the results are summarized in Table 1.



5a R = H, R^1 = H
b R = H, R^1 = 4-Me
c R = 4-Me, R^1 = Me
d R = H, R^1 = 2,3-[CH=CH]$_2$
e R = 2,3-[CH=CH]$_2$, R^1 = 2,3-[CH=CH]$_2$
f R = 2,3-[CH=CH]$_2$, R^1 = 2-CO$_2$H
g R = 4-Me, R^1 = 2,3-[CH=CH]$_2$
h R = H, R^{1}Ph = PhCH$_2$
i R = 2,3-[CH=CH]$_2$, R^1 = H
j R = 4-Me, R^{1}Ph = PhCH$_2$
k R = 4-Me, R^1 = H
l R = 2,3-[CH=CH]$_2$, R^1 = 4-Me
m R = H, R^1 = 2-CO$_2$H
n R = 2,3-[CH=CH]$_2$, R^{1}Ph = PhCH$_2$
o R = 4-Me, R^1 = 2-CO$_2$H

Scheme 1

Since atomic sulfur is easily polarized, the effect of the R^1 groups of substituted benzenethiols is important in determining the yield of the chiral glycerol sulfide ethers. When the substituted benzenethiol contains an eletron-releasing group such as Me, the yield of the corresponding glycerol sulfide ether is high (73%), and when the substituent is an electron-withdrawing group such as NO$_2$ the yield of the corresponding glycerol sulfide ether is low.

Using the reaction of PhCH$_2$SH with epoxypropoxyphenol as an example, we investigated the effect of phase-transfer catalysts (PTC) on the reaction. When PEG-400 (or PEG-600) was used as a phase-transfer catalyst, the yield of the glycerol sulfide ether is high (89.3%) whereas the yield is only 67.6% without any PTC. The efficiency of several PTCs studied is in the order PEG-400 ≈ PEG-600 > Bu$_4$NBr > Me$_4$NI.

The effect of various solvents used in the formation of chiral glycerol sulfide ethers was studied and DMF was found to be the best solvent for the reactions. This is because DMF is a polar solvent and it's boiling point is high, it can efficiently absorb microwave energy, also sodium aryl thiolates are soluble in DMF. Other solvents were studied for these reactions and their suitability are in the order DMF > EtOH > butanol > acetone. Power and reaction time also influence the yield of the glycerol sulfide ethers which is greatest at 750 W and 8 min.

Experimental

Infrared spectra were measured as KBr discs (or liquid film) using an Alpha Centauri FT-IR spectrophotometer, ^{1}H NMR spectra (80 MHz) were recorded in CDCl$_3$ [or (CD$_3$)$_2$CO] using an FT-80 spectrometer, mass spectra were obtained on a Nippon Shimadzu QP-1000 GC-MS spectrometer. Microwave irradiations are carried out in a modified Galanz WP 750B commercial microwave oven at 2450 MHz.

General Procedure.—In a typical experiment, the benzenethiol (5.4 mmol), sodium hydroxide (0.4 g, 9.6 mmol), PEG-400 (0.1 g) and DMF (10 ml) were added in a bottle (100 ml), and then refluxed under microwave irradiation with 100% power (750 W). After 1 min a mixture of the epoxypropoxyphenol[5,6] (5.8 mmol) and DMF (2 ml) was added dropwise over a period of 1.5 min and irradiated continuously for 5.5 min. The solid was filtered off and the filtrate taken to dryness under reduced pressure. The residue was acidified with dilute HCl and extracted with diethyl ether and the solution dried over MgSO$_4$. After filtration, the diethyl was evaporated to yield crude product which was chromatographed on silica gel

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Preparation of chiral glycerol sulfide ethers (**5a**-**o**)

Compound	Reaction time/min	Mp/°C	Yield (%)	Molecular formula	Found (calcd) (%)				ν_{max}/cm^{-1} (KBr)	δ_H ($CDCl_3$, Me_4Si)	MS (m/z)
					C	H	O	S			
5a	8	Oil	92	$C_{15}H_{16}O_2S$	69.46 (69.23)	6.19 (6.15)	12.04 (12.31)	12.44 (12.31)	3426, 2926, 1599, 1244, 690	2.49 (s, 1 H, OH), 3.21 (m, 2 H, H^a), 4.09 (m, 3 H, H^b), 6.81–7.49 (m, 10 H, aromatic)	260 (M^+)
5b	8	Oil	73	$C_{16}H_{18}O_2S$	70.06 (70.07)	6.30 (6.57)	12.20 (11.68)	11.44 (11.68)	3426, 2923, 1599, 1588, 690, 2871	1.26 (s, 1 H, OH), 3.13 (m 2 H, H^a), 4.04 (m, 3 H, H^b), 6.81–7.92	274 (M^+)
5c	8	53.2–53.9	90	$C_{17}H_{20}O_2S$	70.82 (70.83)	6.68 (6.94)	11.39 (11.11)	11.11 (11.11)	3575, 2919, 1610, 1585, 1243, 631	2.28 (d, 6 H, CH_3), 2.72 (s, 1 H, OH), 3.17 (m, 2 H, H^a), 4.01 (s, 3 H, H^b), 6.71–7.38, (m, 8 H, aromatic)	288 (M^+) 289 ($M + 1$)
5d	8	Oil	91	$C_{19}H_{18}O_2S$	73.37 (73.55)	5.72 (5.81)	10.40 (10.32)	10.51 (10.32)	3427, 2926, 1590, 1564, 1244, 690	2.72 (s, 1 H, OH), 3.28 (m, 2 H, H^b), 4.04 (s, 3 H, H^a), 6.77–8.50, (m, 12 H, aromatic)	310 (M^+)
5e	8	Oil	79	$C_{23}H_{20}O_2S$	76.61 (76.67)	5.61 (5.56)	8.71 (8.89)	9.07 (8.89)	3406, 2927, 1595, 1580, 1241, 665	2.37 (s, 1 H, OH), 3.35 (m, 2 H, H^a), 4.21 (m, 3 H, H^b), 6.65–8.51, (m, 14 H, aromatic)	360 (M^+)
5f	8	121–122	88.9	$c_{20}H_{18}O_4S$	67.79 (67.80)	5.04 (5.08)	18.08 (18.08)	9.11 (9.04)	3445, 1690, 1596, 1580, 2930, 1243, 645	3.37 (m, 2 H, H^a), 4.41 (m, 3 H, H^b), 4.95 (s, 2 H, $CO_2H + OH$), 6.75–8.81 (m, 11 H, aromatic)	354 (M^+)
5g	8	Oil	75	$C_{20}H_{20}O_2S$	74.19 (74.07)	5.99 (6.17)	9.77 (9.88)	10.05 (9.88)	3427, 2023, 1587, 1613, 1382, 601	2.26 (s, 3 H, CH_3), 2.43 (s, 1 H, OH), 3.26 (m, 2 H, H^a), 3.26 (m, 2 H, H^a), 6.67–8.49 (, 11 H, aromatic)	324 (M^+)
5h	8	54.5–55.2	89.3	$C_{16}H_{18}O_2S$	69.92 (70.07)	6.53 (6.57)	11.74 (11.68)	11.81 (11.68)	3394, 2926, 1599, 1587, 1492, 1244, 687	1.63 (s, 1 H, OH), 2.74 (m, 2 H, H^a), 3.78 (m, 2 H, H^a), 4.01 (s, 3 H, H^b), 6.84–7.40 (m, 10 H, aromatic)	274 (M^+)
5i	8	Oil	67	$C_{19}H_{18}O_2S$	73.25 (73.55)	5.80 (5.81)	10.53 (10.32)	10.40 (10.32)	3422, 2927, 1595, 1580, 1241, 690	2.56 (s, 1 H, OH), 3.31 (m, 2 H, H^a), 4.23 (m, 3 H, H^b), 6.70–8.27 (m, 12 H, aromatic)	310 (M^+)
5j	8	55–55.9	70	$C_{17}H_{20}O_2S$	70.96 (70.83)	6.69 (6.94)	11.14 (11.11)	11.21 (11.11)	2920, 1613, 1585, 1512, 1379, 1242, 700	1.60 (s, 1 H, OH), 2.29 (s, 3 H, CH_3), 2.69 (m, 2 H, H^a), 3.76 (s, 2 H, H^b), 3.98 (s, 3 H, H^b), 6.73–7.31 (m, 9 H, aromatic)	288 (M^+)
5k	8	52–52.6	97	$C_{16}H_{18}O_2S$	70.19 (70.07)	6.56 (6.57)	11.43 (11.68)	11.82 (11.68)	3574, 2917, 1582, 1611, 1608, 1386, 1244, 688	2.28 (s, 3 H, CH_3), 2.48 (s, 1 H, OH), 3.20 (m, 2 H, H^a), 6.71–7.41 (m, 9 H, aromatic)	264 (M^+)
5l	8	Oil	82.4	$C_{20}H_{20}O_2S$	74.12 (74.07)	6.08 (6.17)	10.11 (9.88)	9.69 (9.88)	3419, 2873, 2923, 1596, 1580, 572	2.28 (s, 3 H, CH_3), 3.25 (m, 2 H, H^a), 4.21 (s, 3 H, H^b), 6.67–8.29 (m, 11 H, aromatic)	324 (M^+)
5m	8	111–111.7	94	$C_{16}H_{16}O_4S$	62.92 (63.16)	4.98 (5.26)	21.53 (21.05)	10.57 (10.53)	3191, 2923, 1690, 1587, 1563, 1496, 685	3.30 (m, 2 H, H^a), 4.26 (m, 3 H, H^b), 5.75 (s, 2 H, $CO_2H + OH$), 6.85–8.11 (m, 9 H, aromatic)	304 (M^+)
5n	8	62–62.5	80	$C_{20}H_{20}O_2S$	74.46 (74.07)	5.96 (6.17)	9.51 (9.88)	10.07 (9.88)	3500, 2926, 1620, 1595, 1580, 1243, 700	2.48 (s, 1 H, OH), 2.81 (m, 2 H, H^a), 3.79 (s, 2 H, H^a), 4.18 (m, 3 H, H^b), 6.74–8.22 (m, 12 H, aromatic)	324 (M^+)
5o	8	113–114	66.7	$C_{17}H_{18}O_4S$	64.21 (64.15)	5.57 (5.66)	20.41 (20.13)	9.81 (10.06)	3503, 2925, 1674, 1588, 1563, 1514, 1256, 690	2.28 (s, 3 H, CH_3), 3.28 (m, 2 H, H^a), 4.10 (m, 3 H, H^b), 5.45 (s, 2 H, $CO_2H + OH$), 6.75–8.14 (m, 8 H, aromatic)	318 (M^+)

[eluent: light petroleum (bp 60–90 °C)–ethyl acetate (16:1 v/v)] or crystallized.

Received, 10th November 1997; Accepted, 12th January 1998
Paper E/7/08058A

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