Notes

Synthesis of Unsymmetrical Sulfides from Alkyl Halides and Epoxides Using Borohydride Exchange Resin-Thiols in Methanol

Jae Hou Nah, Jaesung Choi, and Nung Min Yoon*

Department of Chemistry, Sogang University, Seoul 121-742, Korea

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Since organosulfur compounds have become increasingly useful and important in organic synthesis,[1,2] convenient preparation of appropriate sulfides especially those which carry other functional groups should be important.[3] Although phase transfer conditions have greatly improved the efficiency of sulfide synthesis from alkyl halides,[4,5] other new synthetic methods have also been developed continuously.[6~10]

Recently we have reported the synthesis of phenyl sulfides from alkyl halides and epoxides using borohydride exchange resin (BER)-diphenyl disulfide in methanol.[11] This is an excellent synthetic method of phenyl sulfides since it gives quantitative yields of products, exhibits good chemoselectivity, and has advantage of simple work up. We now wish to report an efficient method for the synthesis of unsymmetrical dialkyl sulfides from alkyl halides and epoxides using borohydride exchange resin and thiols in methanol.

As shown in Table 1, primary bromides and iodides reacted rapidly with stoichiometric amount of hexanethiol (1.05 eq) in methanol giving the corresponding unsymmetrical sulfides quantitatively in 3 h at 65 ℃ in the presence of 2.0 eq of BER and tosylates reacted somewhat slowly (9 h), but chlorides required 48 h (entries 1-6). In contrast, allyl, cinnamyl, propargyl and benzyl halides gave the corresponding sulfides quantitatively even at room temperature (entries 11-15). On the other hand, secondary halides such as 2-hexyl

Table 1. Synthesis of Unsymmetrical Sulfides from Alkyl Halides and Epoxides Using Borohydride Exchange Resin-Thiols in Methanol[a]

Entry	Substrate	Product	Temp. (℃)	Time (h)	Yield (%)[b]
1	octyl chloride	hexyl octyl sulfide	65	48	94[c]
2	octyl bromide	hexyl octyl sulfide	65	3	92
3	octyl iodide	hexyl octyl sulfide	25	18	94
4		hexyl octyl sulfide	65	3	91
5		cyclohexyl octyl sulfide	65	3	93
6	octyl tosylate	hexyl octyl sulfide	65	9	97
7	2-hexyl bromide	2-(hexylthio)hexane	65	12	83
8	2-octyl tosylate	2-(hexylthio)octane	65	24	86
9	cyclohexyl iodide	cyclohexyl hexyl sulfide	65	12	43
10	neopentyl bromide		65	24	nr
11	allyl chloride	allyl hexyl sulfide	25	6	89
12	*trans*-cinnamyl chloride	*trans*-cinnamyl hexyl sulfide	25	3	90
13		*trans*-cinnamyl cyclohexyl sulfide	25	3	91
14	propargyl bromide	hexyl propargyl sulfide	25	3	91
15	benzyl chloride	benzyl hexyl sulfide	25	12	94
16	3-chloro-2-butanone	3-(hexylthio)-2-butanone	25	3	85[d]
17	phenacyl bromide	hexyl phenacyl sulfide	25	1	96[d]
18		cyclohexyl phenacyl sulfide	25	1	99[d]
19	ethyl 2-chloropropionate	ethyl 2-(hexylthio)propionate	78	3	94[e]
20	ethyl 2-bromobutyrate	ethyl 2-(hexylthio)butyrate	25	3	90
21	1,2-decene oxide	2-hydroxy-1-(hexylthio)decane	65	6	98
22		2-hydroxy-1-(cyclohexylthio)decane	65	6	93
23	cyclohexene oxide	2-(hexylthio)cyclohexanol	65	12	91
24	styrene oxide	2-(hexylthio)-1-phenethyl alcohol	65	3	73 (75)
		1-(hexylthio)-2-phenethyl alcohol			18 (19)
25	1-bromo-4-chlorobutane	1-chloro-4-(hexylthio)butane	25	12	62 (66)
		1,4-di(hexylthio)butane			12 (14)

[a] Alkyl halides and epoxides (10 mmol) were reacted with borohydride exchange resin (20 mmol) and thiol (10.5 mmol) in methanol. [b] Isolated yields. GC yields are in parenthesis. [c] Reaction with 1.5 eq of hexanethiol. [d] Before the addition of substrate, BER and thiol were refluxed for 3.0 h to destroy the remaining hydride. [e] Reaction was carried out in ethanol instead of methanol.

Table 2. Competitive Reactions of Alkyl Halides with BER-Thiol in Methanol[a] and with Sodium Mercaptide-Phase Transfer Catalyst System in Water[b]

Entry	Substrate	Temp. (℃)	Time (h)	Product	Yield (%)[c]
1	octyl chloride	65	3.0	hexyl octyl sulfide	3 (6)[b]
	octyl bromide			hexyl octyl sulfide	97 (93)
2	benzyl chloride	25	6.0	benzyl hexyl sulfide	90 (68)
	octyl bromide			hexyl octyl sulfide	10 (32)
3	benzyl bromide	25	3.0	benzyl hexyl sulfide	100 (91)
	octyl bromide			hexyl octyl sulfide	0 (9)
4	*trans*-cinnamyl chloride	25	6.0	*trans*-cinnamyl hexyl sulfide	99 (85)
	octyl bromide			hexyl octyl sulfide	1 (15)
5	phenacyl bromide	25	1.0	hexyl phenacyl sulfide	100 (94)
	octyl bromide			hexyl octyl sulfide	0 (6)
6	ethyl 2-bromobutyrate	25	3.0	ethyl 2-(hexylthio)butyrate	98 (92)
	octyl bromide			hexyl octyl sulfide	2 (8)

[a] Mixtures of one mmol each of two alkyl halides were reacted with 1.0 eq of hexanethiol in the presence of 2.0 eq of borohydride exchange resin in methanol. [b] The mixtures of alkyl halides (organic phase) were reacted with aqueous solution of sodium hexylmercaptide (1.0 eq) in the presence of 0.033 eq of hexadecyltributylphosphonium bromide. See reference 4. [c] GC yields, number in parenthesis is with PTC system.

bromide, 2-octyl tosylate and cyclohexyl iodide reacted slowly accompanying elimination (entries 7-9). While neopentyl bromide, a more hindered halide, did not react at all even at 65 ℃ (entry 10). α-Halo ketones (3-chloro-2-butanone and phenacyl bromide) and α-halo esters (ethyl 2-chloropropionate and ethyl 2-bromobutyrate) reacted readily to afford α-alkylthio ketones and α-alkylthio esters (entries 16-20). 1-Bromo-4-chlorobutane gave a moderate yield (62%) of expected product, 1-chloro-4-(hexylthio)butane, together with the disubstituted product, 1,4-di(hexylthio)butane (12%) (entry 25). Of the epoxides tested, 1,2-decene oxide and cyclohexene oxide gave the corresponding β-hydroxy sulfides exclusively, showing the less hindered site attack (entries 21-23). However, styrene oxide gave two products, 2-(hexylthio)-1-phenethyl alcohol and 1-(hexylthio)-2-phenethyl alcohol in the ratio of 4.1 : 1 (entry 24).

Finally, in order to evaluate the chemoselectivity of this system, competitive reactions were carried out between octyl bromide and other halides using both present system and the phase transfer catalyst system (hexadecyltributylphosphonium bromide).[4] The selectivity was compared in Table 2. As shown in Table 2, this system shows much better selectivity than the PTC system. Thus octyl bromide was selectively reacted in the presence of octyl chloride at 65 ℃, the reactive halides such as benzyl bromide, *trans*-cinnamyl chloride, phenacyl bromide and ethyl 2-bromobutyrate were reacted almost exclusively with the present system leaving octyl bromide unaffected. As shown in general procedure, the reaction proceeds under essentially neutral conditions, and the work up procedure is very simple in most cases, giving essentially pure product by filtering the resin and evaporating the solvent.

In conclusion this method which involves two phase system is an excellent synthetic method for unsymmetrical dialkyl sulfides since it gives quantitative yields of products in most cases, exhibits good chemoselectivity, and has advantage of a simple work up.

Experimental Section

General Procedure for Preparation of Unsymmetrical Sulfides. The reaction of octyl bromide is representative. BER[12] (7.33 g, 20 mmol) was added to the methanol solution (100 mL) of octyl bromide (1.93 g, 10.0 mmol) and hexanethiol (1.24 g, 10.5 mmol), and the mixture was stirred under reflux for 3 h. Complete reaction was confirmed by GLPC. Then the resin was removed by filtration and the methanol was evaporated under reduced pressure to give the pure hexyl octyl sulfide (2.12 g, 92%): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 6H, J=5.7), 1.28-1.37 (m, 16H), 1.51-1.62 (m, 4H), 2.51 (t, 4H, J=7.3); MS m/z (relative intensity) (EI, 70 eV) 230 (M^+, 20) 146 (12) 145 (100) 118 (16) 117 (82) 112 (19) 87 (11) 85 (12) 84 (60) 83 (37) 70 (18) 61 (31) 57 (19) 56 (38) 55 (49).

Cyclohexyl octyl sulfide. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=6.4), 1.18-1.36 (m, 15H), 1.50-1.64 (m, 3H), 1.75-1.78 (m, 2H), 1.93-1.96 (m, 2H), 2.53 (t, 2H, J=7.4), 2.63 (m, 1H); MS m/z (relative intensity) (EI, 70 eV) 228 (M^+, 15) 145 (55) 115 (13) 87 (12) 83 (59) 82 (100) 81 (22) 71 (17) 69 (25) 67 (76) 61 (10) 57 (23) 56 (12) 55 (83) 54 (16).

2-(Hexylthio)hexane. ^{1}H NMR ($CDCl_3$) δ 0.86-1.02 (m, 6H), 1.24-1.38 (m, 12H), 1.46-1.61 (m, 5H), 2.44-2.55 (m, 2H), 2.72 (sxt, 1H, J=6.4); MS m/z (relative intensity) (EI, 70 eV) 202 (M^+, 29) 145 (100) 117 (51) 85 (25) 84 (74) 83 (41) 75 (58) 69 (30) 61 (27) 57 (20) 56 (60) 55 (69) 47 (11).

2-(Hexylthio)octane. ^{1}H NMR ($CDCl_3$) δ 0.79-0.91 (m, 6H), 1.07-1.49 (m, 16H), 1.52-1.74 (m, 4H), 2.45-2.55 (m, 1H), 2.68 (t, 2H, J=7.4), 3.23-3.31 (m, 1H); MS m/z (relative intensity) (EI, 70 eV) 230 (M^+, 15) 146 (10) 145 (100) 117 (39) 112 (25) 84 (28) 83 (55) 75 (49) 71 (29) 70 (50) 69 (35) 61 (22) 57 (59) 56 (49) 55 (71).

Cyclohexyl hexyl sulfide. ^{1}H NMR ($CDCl_3$) δ 0.82-0.93 (m, 5H), 1.19-1.46 (m, 11H), 1.56-1.75 (m, 5H), 2.53 (t, 1H, J=7.3), 2.69 (t, 2H, J=7.3); MS m/z (relative intensity) (EI, 70 eV) 200 (M^+, 12) 117 (47) 116 (16) 115 (16) 87 (12) 85

(19) 84 (11) 83 (60) 82 (100) 81 (24) 67 (62) 55 (56) 54 (13).

Allyl hexyl sulfide. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J= 6.5), 1.19-1.50 (m, 7H), 1.53-1.72 (m, 3H), 2.46 (t, 1H, J=7.2), 2.69 (t, 1H, J=7.2), 3.13 (d, 1H, J=7.2), 5.05-5.15 (m, 1H), 5.70-5.87 (m, 1H); MS m/z (relative intensity) (EI, 70 eV) 158 (M^+, 24) 117 (100) 87 (49) 85 (12) 83 (62) 75 (13) 74 (90) 73 (26) 69 (17) 61 (16) 60 (21) 59 (12) 56 (50) 55 (90) 53 (12) 47 (28) 46 (16) 45 (52).

***trans*-Cinnamyl hexyl sulfide.** ^{1}H NMR ($CDCl_3$) δ 0.85-0.92 (m, 3H), 1.22-1.42 (m, 5H), 1.52-1.66 (m, 3H), 2.50 (t, 2H, J=7.2), 3.31 (d, 2H, J=7.2), 6.19 (dt, 1H, J=15.8, 7.2), 6.44 (d, 1H, J=15.8), 7.18-7.41 (m, 5H); MS m/z (relative intensity) (EI, 70 eV) 234 (M^+, 5) 118 (9) 117 (100) 115 (23).

***trans*-Cinnamyl cyclohexyl sulfide.** ^{1}H NMR ($CDCl_3$) δ 1.13-2.01 (m, 10H), 2.65-2.70 (m, 1H), 3.35 (d, 2H, J=7.0), 6.24 (dt, 1H, J=15.8, 7.0), 6.47 (d, 1H, J=15.8), 7.23-7.40 (m, 5H); MS m/z (relative intensity) (EI, 70 eV) 232 (M^+, 10) 118 (10) 117 (100) 115 (24) 55 (8).

Hexyl propargyl sulfide. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.6), 1.26-1.44 (m, 6H), 1.62 (qui, 2H, J=7.2), 2.22 (t, 1H, J=2.6), 2.69 (t, 2H, J=7.2), 3.24 (d, 2H, J=2.6); MS m/z (relative intensity) (EI, 70 eV) 156 (M^+, 13) 117 (100) 85 (21) 83 (44) 72 (16) 71 (17) 69 (15) 56 (39) 55 (54) 47 (12) 45 (41).

Benzyl hexyl sulfide. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.2), 1.23-1.39 (m, 6H), 1.53-1.61 (m, 2H), 2.43 (t, 2H, J= 7.3), 3.72 (s, 1H), 7.24-7.34 (m, 5H); MS m/z (relative intensity) (EI, 70 eV) 208 (M^+, 6) 117 (21) 92 (14) 91 (100) 65 (11) 55 (15).

3-(Hexylthio)-2-butanone. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6.6), 1.23-1.30 (m, 5H), 1.35-1.40 (m, 2H), 1.46-1.67 (m, 3H), 2.27 (s, 3H), 2.39-2.47 (m, 1H), 3.34 (q, 1H, J=7.0); MS m/z (relative intensity) (EI, 70 eV) 188 (M^+, 15) 145 (88) 83 (36) 75 (100) 72 (18) 61 (37) 60 (11) 57 (12) 55 (54).

Hexyl phenacyl sulfide. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6.5), 1.23-1.40 (m, 6H), 1.56-1.64 (m, 2H), 2.57 (t, 2H, J=7.3), 3.78 (s, 2H), 7.44-7.58 (m, 3H), 7.96-8.01 (m, 2H); MS m/z (relative intensity) (EI, 70 eV) 236 (M^+, 2) 120 (39) 105 (100) 77 (25).

Cyclohexyl phenacyl sulfide. ^{1}H NMR ($CDCl_3$) δ 1.23-1.57 (m, 5H), 1.62 (m, 1H), 1.72-1.77 (m, 2H), 1.98-1.99 (m, 2H), 3.61 (m, 1H), 3.83 (s, 2H), 7.44-7.55 (m, 3H), 7.96-8.00 (m, 2H); MS m/z (relative intensity) (EI, 70 eV) 234 (M^+, 10) 120 (54) 115 (36) 114 (28) 105 (100) 83 (22) 81 (28) 77 (42) 55 (31) 51(14).

Ethyl 2-(hexylthio)propionate. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6.5), 1.23-1.39 (m, 9H), 1.43 (d, 3H, J=7.2), 1.51-1.62 (m, 2H), 2.48-2.66 (m, 2H), 3.40 (q, 1H, J=7.2), 4.19 (q, 2H, J=7.3); MS m/z (relative intensity) (EI, 70 eV) 218 (M^+, 8) 145 (13) 102 (100) 83 (16) 75 (28) 74 (20) 61 (14) 55 (23).

Ethyl 2-(hexylthio)butyrate. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.5), 1.00 (t, 3H, J=7.4), 1.26-1.94 (m, 13H), 2.54-2.69 (m, 2H), 3.15 (t, 1H, J=7.5), 4.20 (qui, 2H, J=7.2); MS m/z (relative intensity) (EI, 70 eV) 232 (M^+, 9) 159 (16) 117 (16) 116 (100) 101 (36) 89 (33) 88 (14) 83 (21) 75 (16) 73 (15) 55 (32).

2-Hydroxy-1-(hexylthio)decane. ^{1}H NMR ($CDCl_3$) δ 0.86-1.00 (m, 6H), 1.17-1.59 (m, 22H), 2.38-2.56 (m, 4H), 2.71-2.79 (m, 1H), 3.60-3.66 (m, 1H); MS m/z (relative intensity) (EI, 70 eV) 274 (M^+, 5) 138 (44) 110 (32) 109 (16) 97 (11) 96 (44) 95 (21) 87 (11) 83 (31) 82 (35) 81 (37) 69 (30) 68 (44) 67 (44) 61 (17) 57 (15) 56 (25) 55 (100) 54 (75) 53 (12).

2-Hydroxy-1-(cyclohexylthio)decane. ^{1}H NMR ($CDCl_3$) δ 0.85-0.91 (m, 3H), 1.17-1.48 (m, 14H), 1.57-1.97 (m, 10H), 2.38-2.84 (m, 4H), 3.59 (m, 1H); MS m/z (relative intensity) (EI, 70 eV) 272 (M^+, 5) 138 (14) 130 (56) 83 (59) 82 (100) 81 (18) 69 (19) 67 (31) 57 (12) 55 (60) 54 (12).

2-(Hexylthio)cyclohexanol. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=6.5), 1.29-1.49 (m, 10H), 1.51-1.79 (m, 5H), 2.05-2.13 (m, 2H), 2.30-2.43 (m, 1H), 2.55 (t, 2H, J=7.4), 3.25-3.30 (m, 1H); MS m/z (relative intensity) (EI, 70 eV) 216 (M^+, 7) 117 (42) 116 (19) 103 (12) 99 (29) 98 (94) 97 (13) 87 (25) 85 (15) 84 (20) 83 (31) 82 (17) 81 (100) 80 (85) 79 (43) 71 (15) 70 (39) 69 (25) 67 (19) 61 (19) 60 (14) 57 (25) 56 (27) 55 (51) 53 (12) 47 (13).

2-(Hexylthio)-1-phenethyl alcohol. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, J=6.6), 1.31-1.43 (m, 6H), 1.57-1.64 (m, 2H), 2.55 (t, 2H, J=7.1), 2.67-2.99 (m, 2H), 4.75 (q, 1H, J=4.3), 7.27-7.39 (m, 4H); MS m/z (relative intensity) (EI, 70 eV) 238 (M^+, 1) 133 (11) 132 (100) 117 (50) 107 (84) 105 (11) 104 (10) 103 (14) 91 (12) 84 (36) 79 (46) 77 (36) 69 (13) 61 (30) 56 (39) 55 (26) 51 (11) 48 (17).

1-Chloro-4-(hexylthio)butane. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=4.5), 1.25-1.42 (m, 6H), 1.52-1.93 (m, 6H), 2.44-2.56 (m, 4H), 3.56 (t, 2H, J=4.3); MS m/z (relative intensity) (EI, 70 eV) 210 (M^++2,8) 208 (M^+, 20) 131 (100) 124 (24) 117 (78) 91 (14) 88 (11) 83 (20) 61 (32) 56 (24) 55 (61) 47 (10).

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References

1. Solladie, G. *Synthesis of Sulfides, Sulfoxides and Sulfones.* In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 6, pp 133-170.
2. Ogura, K. *Sulfur Stabilization.* In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, U. K., 1991; Vol. 1, pp 505-539.
3. Peach, M. E. *Thiols as Nucleophiles.* In *The Chemistry of Thiol Groups*; Patai, S., Ed.;Wiley-Interscience: New York, U. S. A., 1974; Part 2, pp 721-784.
4. Landini, D.; Rolla, F. *Synthesis* **1974**, 565.
5. Herriott, A. W. *Synthesis* **1975**, 447.
6. Abel, E. W.; Armitage, D. A.; Bush, R. P. *J. Chem. Soc.* **1964**, 2455.
7. Tanigawa, Y.; Kanamaru, H.; Murahashi, S. *Tetrahedron Lett.* **1975**, *52*, 4654.
8. Degani, I.; Fochi, R.; Regondi, V. *Synthesis* **1983**, 630.
9. Khurana, J. M.; Sahoo, P. K. *Synth. Commun.* **1992**, *22*, 1691.
10. Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett* **1992**, 303.
11. Yoon, N. M.; Choi, J.; Ahn, J. H. *J. Org. Chem.* **1994**, *59*, 3490.
12. The preparation of BER is described in Choi, J.; Yoon, N. M. *J. Org. Chem.* **1995**, *60*, 3266.