A Facile Synthesis of *S*-(1-Chloroalkyl) Alkanesulfonothioates

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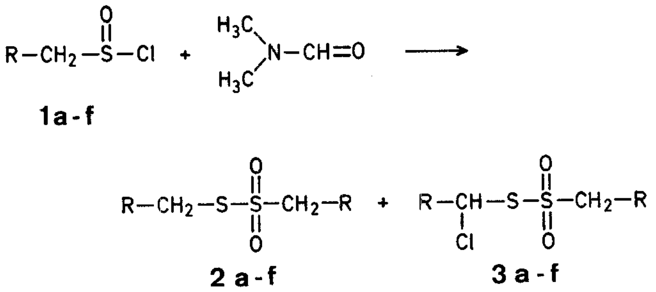
S-(1-Chloroalkyl) alkanesulfonothioates (**3**), which have bactericidal and fungicidal properties[1,2], and *S*-alkyl alkanesulfonothioates (**2**, thiosulfonates) are biologically important compounds as well as being synthetically useful substrates. Moreover, *S*-alkyl alkanesulfonothioates (**2**) are especially important as thioalkyl transfer agents[4-7]. Although there are scattered literature reports concerning the preparation of halogenated sulfonothioate *S*-esters, there are no systematic studies of the synthesis of *S*-(1-chloroalkyl) alkanesulfonothioates (**3**)[1,2,8,9].



1-3	R
a	H
b	CH_3
c	C_2H_5
d	n-C_3H_7
e	n-C_4H_9
f	n-C_7H_{15}

During our studies of the solvent effects on the reaction of activated zerovalent zinc and alkanesulfinyl chlorides (**1**)[3,10,11], we observed that *N*,*N*-dimethylmethanamide (DMF) reacted with alkanesulfinyl chlorides (**1**) to give *S*-alkyl alkanesulfonothioates (**2**) and *S*-(1-chloroalkyl) alkanesulfonothioates (**3**) in excellent overall yields.

The linear *S*-alkyl (**2**) and *S*-(1-chloroalkyl) alkanesulfonothioates (**3**) listed in Tables 1 and 2 were prepared in excellent yields from the reaction of alkanesulfinyl chlorides (**1**)[12,13] and anhydrous DMF. Although a product mixture of **2** and **3** is obtained, the sulfonothioate *S*-esters are easily separable via flash chromatography[3]. The yield of *S*-(1-chloroethyl) ethanesulfonothioate (**3b**) is higher than that reported for its synthesis from ethanesulfonyl chloride (four steps)[9] or from difficultly accessible thiirane oxide (ethylene episulfoxide)[9]. The ready availability of alkanesulfinyl chlorides (**1**)[12,13], the simplicity of experimental conditions, and the ease of product separation and purification make this method a useful synthetic procedure for the simultaneous preparation of *S*-alkyl alkanesulfonothioates (**2**, minor product) and *S*-(1-chloroalkyl) alkanesulfonothioates (**3**, major product).

Table 1. Yields of *S*-Alkyl (**2**) and *S*-(1-Chloroalkyl) (**3**) Alkanesulfonothioates from the Reaction of Linear Alkanesulfinyl Chlorides (**1**) and *N*,*N*-Dimethylmethanamide (DMF)[a].

No.	R	Product **2**		Product **3**		
		Yield [%][b]	b.p. [°C]/torr	Yield [%][b]	m.p. [°C]	Molecular Formula or Lit. b.p. [°C]/torr
a	H	11	114–116°/12[12]	63	37–38°	$C_2H_5ClO_2S_2$ (160.64)[c]
b	CH_3	18[f]	102–103°/1–2[3]	82[d]	oil	56°/0.03[2]
c	C_2H_5	13	112–114°/1–2[3]	87	oil	60°/0.02[2]
d	n-C_3H_7	15	128–130°/0.13[3]	85	oil	$C_8H_{17}ClO_2S_2$ (244.81)[e]
e	n-C_4H_9	14	176–180°/0.10[3]	81	oil	$C_{10}H_{21}ClO_2S_2$ (272.86)[f]
f	n-C_7H_{15}	5	oil[3]	90	oil	$C_{16}H_{33}ClO_2S_2$ (357.02)[g]

[a] Reaction performed with 1 eq of alkanesulfinyl chloride (**1**) and 3 eq of DMF at 22–24 °C for 24 h.

[b] Products isolated via flash chromatography.

[c] calc. C 14.95 H 3.14 Cl 22.07
found 14.94 3.10 22.01

[d] The mole ratio of ethanesulfinyl chloride (**1b**) to DMF is 1.65:1.

[e] calc. C 39.25 H 7.00 Cl 14.48
found 39.24 7.16 14.64

[f] calc. C 44.01 H 7.76 Cl 12.99
found 44.27 7.52 13.21

[g] calc. C 53.83 H 9.32 Cl 9.93
found 53.73 9.52 9.89

A reasonable pathway to *S*-(1-chloroalkyl) alkanesulfonothioates (**3**) probably involves alkanethial *S*-oxides (**4**) and *O*,*S*-(1-chloroalkyl) alkanesulfino-(thioperoxoates) (**5**, Scheme A). Nucleophilic attack by alkanethial *S*-oxide (**4**) on alkanesulfinyl chloride (**1**) leads to an intermediate which may rearrange to chlorosulfenyl sulfinate (**5**). Intramolecular rearrangement of chlorosulfenyl sulfinate **5** affords *S*-(1-chloroalkyl) alkanesulfonothioate **3**[2].

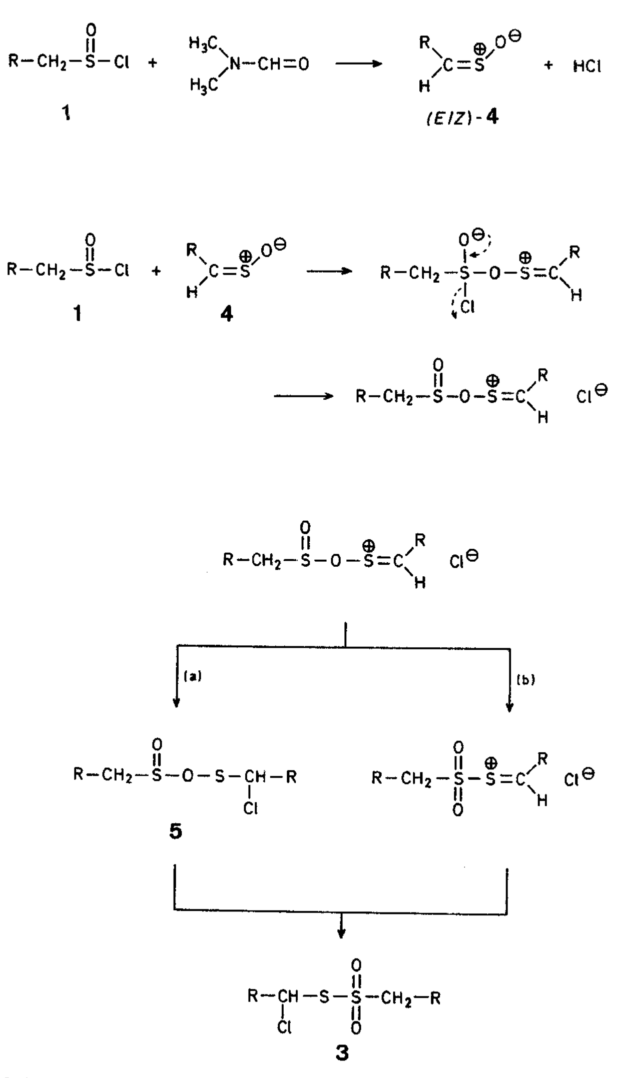
Table 2. I.R. and ^{13}C-N.M.R. Spectral Data of *S*-(1-Chloroalkyl) Alkanesulfonothioates (**3**)
$C(\varepsilon)-C(\delta)-C(\gamma)-C(\beta)-C(\alpha)-SO_2-S-C(\alpha')Cl-C(\beta')-C(\gamma')-C(\delta')-C(\varepsilon')$

Product	I.R. (CDCl$_3$) ν [cm^{-1}]		^{13}C-N.M.R. (CDCl$_3$/TMS)[a] δ [ppm]									
	asym-SO$_2$	sym-SO$_2$	C(α)	C(β)	C(γ)	C(δ)	C(ε)	C(α')	C(β')	C(δ')	C(γ')	C(ε')
3a	1331	1136	49.12					52.65				
3b	1331	1130	57.91	8.17				64.35	26.32			
3c	1327	1130	65.32	17.34	11.17			70.88	32.74	12.65		
3d	1330	1128	63.83	25.33	19.93	13.43		69.21	40.84	21.12	13.03	
3e	1329	1129	63.76	30.13	23.22	21.93	13.84	69.67	38.87	28.83	22.22	13.84
3f	1331	1128	63.87	31.88	29.10	29.10	28.08	69.75	39.19	31.88	29.10	28.78

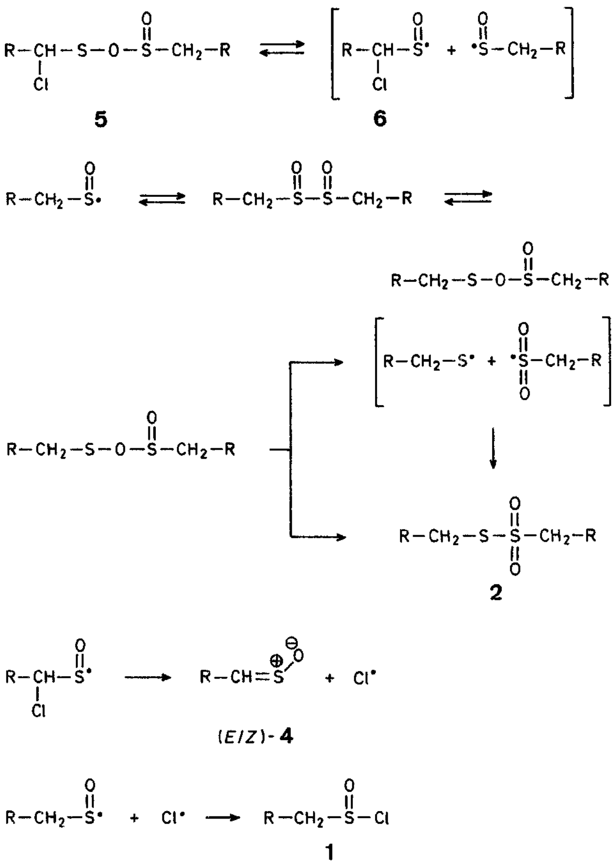
[a] Central solvent resonance at δ = 77.27 ppm at 22.63 MHz.

It is also interesting to note that the formation of *S*-(chloromethyl) methanesulfonothioate (**3b**) provides the first direct evidence for the intermediacy of methanethial *S*-oxide in solution[14-19].

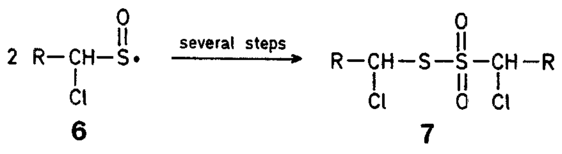
The formation of *S*-alkyl alkanesulfonothioates (**2**) probably involves free radicals (Scheme **B**)[20]. The loss of chlorine atom from the α-chloroalkyl sulfinyl radical [RCH(Cl)$\dot{S}$O, **6**] to give alkanethial *S*-oxide (**4**) precludes formation of *S*-(1-chloroalkyl) chlorosulfonothioate **7** (Scheme **C**).



Scheme A



Scheme B



Scheme C

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Robertson Laboratory, Florham Park, N.J. Mass spectra were obtained on a Finnigan GC/EI-CI mass spectrometer with a Nova 3 Data system. N.M.R. spectra were obtained on Perkin-Elmer EM-360, Varian FT-80A, Bruker WH-90, and Bruker WM-250 spectrometers. The Bruker WH-90 and WM-250 FT N.M.R. spectrometers were controlled by Bruker Model B-NC-12 and Bruker Aspect 2000 computers, respectively.

Nitrogen was dried by passing it through a column of Drierite and 5Å molecular sieves. *N,N*-Dimethylmethanamide (DMF) was predried over barium oxide, distilled from calcium hydride under reduced pressure, and stored under argon.

Analytical T.L.C. was performed on Analtech Uniplate 10 × 20 cm (250 μ thick) silica gel GF prescored glass plates which were developed in a solvent mixture of diethyl ether/hexanes (1:9 v/v) or ether/hexanes/dichloromethane (1:4:1 v/v). After the solvent had risen to the top, the plates were immersed in phosphomolybdic acid and charred.

Methane- (**1a**), ethane- (**1b**), propane- (**1c**), butane- (**1d**), pentane- (**1e**), and octanesulfinyl chloride (**1f**) were prepared according to literature procedures[3,12,13]. Their boiling points, and their I.R. ^{1}H-N.M.R., and ^{13}C-N.M.R. spectra agreed with literature values[3,21].

S-Alkyl (2) and S-(1-Chloroalkyl) Alkanesulfonothioates (3); General Procedure:

In a flame-dried, nitrogen flushed 25 ml round bottomed flask fitted with a septum is placed the alkanesulfinyl chloride **1** (10 mmol) via syringe under nitrogen flow. Dry DMF (2.2 g, 30 mmol) is added via syringe. The mixture is allowed to stir at 22–24 °C for 24 h, the solvent removed in vacuo, and the resulting dark brown solution is initially separated via flash chromatography as described below[3,22].

The product mixture containing *S*-alkyl (**2**) and *S*-(1-chloroalkyl) (**3**) alkanesulfonothioates is placed on a 46 cm × 5 cm diameter column which contained 15 cm of Mallinckrodt AR CC-4 100–200 mesh silica gel covered with 0.3 cm of sand. The *S*-alkyl (**2**) and *S*-(1-chloroalkyl) (**3**) alkanesulfonothioates are eluted with 500 ml of ether/hexanes (1:1 by volume) solution at a rate such that the eluant in the column fell ~ 2 cm/min. Fractions (50 ml) are collected and combined, based on T.L.C. analysis. Removal of solvent gives a mixture of *S*-alkyl (**2**) and *S*-(1-chloroalkyl) (**3**) alkanesulfonothioates.

The mixture of sulfonothioate *S*-esters (**2,3**) is subsequently separated via flash column chromatography on MCB Silica Gel 60 (particle size 0.040–0.063 mm; 230–400 mesh) using 1 liter of ether/hexane/dichloromethane (1:4:1 v/v) as eluant. Fractions (20 ml) are collected and combined, based on T.L.C. analysis. Removal of solvent gives the pure product.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation (CHE-82-19149) for support for this research. N.M.R. and mass spectra were determined at Irvine with spectrometers obtained with the assistance of the NSF instrumentation program. We also thank Kirk D. Robarge for this contributions to this project.

Received: September 30, 1983
(Revised form: December 15, 1983)

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[1] (a) S.S. Block, J.P. Weidner, *Dev. Ind. Microbiol.* **4**, 213 (1963).
(b) J.P. Weidner, S.S. Block, *J. Med. Chem.* **10**, 1167 (1967).
(c) T.P. Johnston, W.H.C. Rueggelberg, S.S. Block, *J. Agric. Food Chem.* **5**, 672 (1957).

[2] E. Block, A.A. Bazzi, *Tetrahedron Lett.* **23**, 4569 (1982).

[3] F. Freeman, M.C. Keindl, *Synthesis* **1983**, 913.

[4] T.F. Parsons, J.D. Buckman, D.E. Pearson, L. Field, *J. Org. Chem.* **30**, 1923 (1965).

[5] R.L. Autrey, P.W. Scullard, *J. Am. Chem. Soc.* **90**, 4917 (1968); **90**, 4924 (1968).

[6] L. Field, P.M. Giles, Jr., *J. Org. Chem.* **36**, 309 (1971).

[7] B.M. Trost, *Chem. Rev.* **78**, 363 (1978).

[8] During the course of our studies, Block and Bazzi[2] reported the preparation of **3b**, **3c**, and *S*-(1-chlorododecyl) dodecanesulfonothioate from the corresponding alkanesulfinyl chloride (**1**) and triethylamine.

[9] K. Kondo, A. Negishi, G. Tsuchashi, *Tetrahedron Lett.* **1969**, 2743.

[10] F. Freeman, C.N. Angeletakis, *Tetrahedron Lett.* **23**, 491 (1982).

[11] F. Freeman, C.N. Angeletakis, M.C. Keindl, *J. Org. Chem.* **49**, 454 (1984).

[12] I.B. Douglass, B.S. Farah, *J. Org. Chem.* **24**, 973 (1959).

[13] I.B. Douglass, R.V. Norton, *J. Org. Chem.* **33**, 2104 (1968).

[14] E. Block, in *Organic Sulfur Chemistry*, 9th International Symposium on Organic Sulfur Chemistry, Riga, USSR, June 9–14, 1980, R.Kh. Friedlina; E. Skosova, Eds., Pergamon Press, Oxford, 1981, pp 15–34; *C.A.* **95**, 96267 (1981).

[15] B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **101**, 1 (1982).

[16] Elimination of hydrogen chloride from methanesulfinyl chloride (**1a**) to produce methanethial *S*-oxide can be accomplished thermally, via the flash vacuum pyrolysis (FVP) technique[17,18].

[17] D.E. Powers, C.A. Arrington, W.C. Harris, E. Block, V.F. Kalasinsky, *J. Phys. Chem.* **83**, 1890 (1979).

[18] E. Block, H. Bock, S. Mohmand, P. Rosmus, B. Solouki, *Angew. Chem.* **88**, 380 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, 383 (1976).

[19] E. Block, R.E. Penn, R.J. Olsen, P.F. Sherwin, *J. Am. Chem. Soc.* **98**, 1264 (1976).

[20] (a) F. Freeman, C.N. Angeletakis, *J. Am. Chem. Soc.* **103**, 6232 (1981).
(b) F. Freeman, C.N. Angeletakis, *J. Am. Chem. Soc.* **104**, 5766 (1982).
(c) F. Freeman, C.N. Angeletakis, *J. Am. Chem. Soc.* **105**, 4039 (1983), and references therein.

[21] F. Freeman, C.N. Angeletakis, *Org. Magn. Reson.* **21**, 86 (1983).

[22] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).