Chemistry of 1,3-Oxathianes. Synthesis and Conformation of 2-Substituted 1,3-Oxathianes[1,2]

Kaoru Fuji,*[3a] Masaru Ueda,[3a] Kenzo Sumi,[3a] Kanji Kajiwara,[3a] Eiichi Fujita,[3a] Takashi Iwashita,[3b] and Iwao Miura[3c]

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan, Suntory Institute for Bioorganic Research, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan, and Laboratory of Natural Products Chemistry, Otsuka Pharmaceutical Co., Ltd., Kawauchi-cho, Tokushima 771-01, Japan

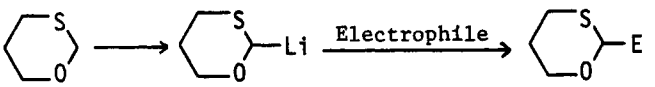
Received November 3, 1983

The reaction of 2-lithio-1,3-oxathiane with a variety of electrophiles including alkyl halides and carbonyl compounds affords substitution and addition products, respectively. Alkyl metal halides such as $(CH_3)_3SiCl$, $(CH_3)_3GeCl$, and $(CH_3)_3SnCl$, or alkyl metal acetate, $(CH_3)_3PbOAc$, reacted with 1,3-oxathianyl anion to give rise to the corresponding 2-(group 14)-substituted 1,3-oxathianes (**4**). 2-(Methylthio)- and 2-(methylseleno)-1,3-oxathianes (**6b** and **6c**) were prepared by a similar reaction of the anion with dimethyl disulfide and dimethyl diselenide, respectively. Other 1,3-oxathianes substituted with a 2-methoxy or 2-dimethylamino group at C-2 have been synthesized to investigate the orientation of heteroatoms. Examination of their ^1H and ^{13}C NMR spectra leads to the conclusion that group 14 metals and a dimethylamino group occupy the equatorial position, while methoxy and methylthio groups favor the axial disposition due to the anomeric effect. Conclusive evidence was not obtained from the available data to decide whether 2-(methylseleno)-1,3-oxathiane (**6c**) exhibits the anomeric effect or not.

Introduction

Umpolung[4] of the normal reactivity by modifying structural units has become one of the prevailing methods of choice in synthetic organic chemistry. Particularly, carbanions stabilized by adjacent sulfur atoms have been well documented,[5] since Corey and Seebach[6] first utilized 2-lithio-1,3-dithiane as an acyl anion equivalent. This contrasts with the limited use of metalated 1,3-oxathianes in synthetic organic chemistry. However, interesting differences in chemical reactivity between 1,3-dithane and 1,3-oxathiane derivatives have been reported. The metalated dithiane prepared from 2-furaldehyde was reported to be thermally unstable.[7] On the other hand, the corresponding oxathiane was stable enough to be a masked acyl anion.[8] The hydrogen atom at C(2) of the 1,3-dithiane prepared from 3-furaldehyde was easily removed by lithium diisopropylamide (LDA), while the corresponding 1,3-oxathiane was deprotonated by LDA or *n*-BuLi predominantly on the furan ring.[8] Some 1,3-oxathiane derivatives have been successfully used as chiral auxiliary reagents to synthesize (+)-atrolactic acid methyl ether,[9] (−)-mevalolactone,[10] optically active tertiary alcohols,[11] and secondary α-hydroxy acids[12] in high optical yields. It is a purpose of the present paper to describe the fundamental studies on the reactivity of 2-lithio-1,3-oxathiane (**2**) toward different electrophiles including heteroatoms. And also,

Scheme I



1 **2** **3**

we will discuss the conformation of 2-substituted 1,3-oxathianes. Especially, attention will be focused on the orientation of heteroatoms at C(2). The reactivity of 2-heterosubstituted 1,3-oxathianes toward the base will be a subject of the following paper.

Results

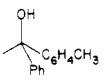
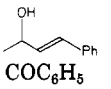
(1) Reaction of 2-Lithio-1,3-oxathiane (2) with Electrophiles. With an exception,[9b] the hydrogen atom at C(2) in 1,3-oxathiane derivatives is easily removed by *n*-BuLi or LDA. 1,3-Oxathiane (**1**) itself, however, resisted deprotonation under comparable conditions. Addition of *sec*-BuLi to a solution of 1,3-oxathiane (**1**) in tetrahydrofuran (THF) at −78 °C gave rise to a faintly yellow solution[13] which was quenched with D_2O. A ^1H NMR spectrum of the product **3** (E = D) purified by preparative gas–liquid chromatography (GLC) showed nearly 100% incorporation of deuterium at C(2) indicating quantitative formation of the anionic species **2**. 2-Lithio-1,3-oxathiane (**2**) was allowed to react with a variety of electrophiles including alkyl halides and carbonyl compounds to afford substitution and addition products, respectively. The results are summerized in Table I. Primary alkyl iodides gave an excellent yield of 2-alkylated 1,3-oxathianes (entries 1–3). But the reactions of **2** with bromides (entries 5 and 8) and isopropyl iodide (entry 4) gave a poor yield of the product under the given conditions. Benzyl bromide afforded a 20% yield of diphenylethane, which probably results from a Wurtz type reaction of benzyl bromide with benzyllithium formed by metal–halogen exchange. The yield of adducts from the nonenolizable ketones and aldehyde was satisfactory (entries 11, 12, and 14), while

(1) Chemistry of carbanions stabilized by sulfur. 1.
(2) A part of this work has been published in a preliminary form: Fuji, K.; Ueda, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1977**, 814.
(3) (a) Kyoto University. (b) Suntory Institute. (c) Otsuka Pharmaceutical Co., Ltd.
(4) (a) Seebach, D.; Kolb, M. *Chem. Ind. (London)* **1974**, 687. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(5) (a) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, *357*. (b) Field, L. *Synthesis* **1978**, 713. (c) Hase, T. A.; Koskimies, J. K. *Aldrichimica Acta* **1981**, *14*, 73.
(6) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.
(7) Taschner, M. J.; Kraus, G. A. *J. Org. Chem.* **1978**, *43*, 4235.
(8) (a) Reich, H. J.; Gold, P. M.; Chow, F. *Tetrahedron Lett.* **1979**, 4433. (b) Reich, H. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 3112.
(9) (a) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614. (b) Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598.
(10) Eliel, E. L.; Soai, K. *Tetrahedron Lett.* **1981**, *22*, 2859.
(11) (a) Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *22*, 2855. (b) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943.
(12) Ko, K.-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333.

(13) 1,3-Oxathianyllithium (**2**) is colorless. Complexation of *sec*-BuLi with THF gives a light yellow color which is an indication of a slight excess of *sec*-BuLi in THF. We, therefore, recommend the use of THF as a solvent when *sec*-BuLi is used as a base, because *sec*-BuLi is too active to get a reproducible titration value by conventional methods.

0022-3263/85/1950-0657$01.50/0

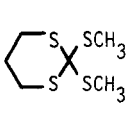
Table I. Reaction of 1,3-Oxathianyl Anion (2) with Electrophiles

entry	electrophile	product[a]	E	purification method[b]	% yield	IR ($CHCl_3$), cm^{-1}	anal.
1	CH_3I	**3a**	CH_3	A	99[c]	1090, 1075	($C_5H_{10}OS$) C, H
2	C_2H_5I	**3b**	C_2H_5	A	91[c]	1080, 1020	($C_6H_{12}OS$) C, H
3	n-C_3H_7I	**3c**	n-C_3H_7	A	83[c]	1080, 1010	($C_7H_{14}OS$) C, H
4	i-C_3H_7I	**3d**	i-C_3H_7	A	35[c,d]	1080, 1 020	($C_7H_{14}OS$) C, H
5	n-C_4H_9Br	**3e**	n-C_4H_9	A	25[c]	1230, 1210	($C_8H_{16}OS$) C, H
6	i-C_4H_9I	**3f**	i-C_4H_9	A	74[c]	1080, 1010	($C_8H_{16}OS$) C, H
7	t-C_4H_9Cl	**3g**	t-C_4H_9		0		
8	$C_6H_5CH_2Br$	**3h**	$CH_2C_6H_5$	A	26[c,e]	1095, 1080	($C_{11}H_{14}OS$) C, H
9	CH_3COCH_3	**3i**		B	53[f]	3575, 1080	($C_7H_{14}O_2S$) C, H
10	$C_6H_5COCH_3$	**3j**[g] (2:1)		C	51[f]	3590, 1080	($C_{12}H_{16}O_2S$)[h]
11	$C_6H_5COC_6H_5$	**3k**[i]		B	86[f]	3550, 1080	($C_{17}H_{18}O_2S$) C, H
12	$C_6H_5COC_6H_4CH_3$	**3l**[g] (1:1)		D	77[f]	3560, 1080	($C_{18}H_{20}O_2S$) C, H
13	CH_2=$CHCOCH_3$	**3m**[g] (1:1)		B	46[f]	3580, 1080	($C_8H_{14}O_2S$) C, H
14	C_6H_5CH=$CHCHO$	**3n**[g] (7:4)		B	78[f]	3575, 1070	($C_{13}H_{16}O_2S$) C, H
15	C_6H_5CN	**30**[j]	COC_6H_5	B	56[f]	1690, 1080	($C_{11}H_{12}O_2S$) C, H

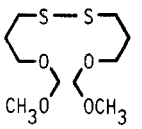
[a] Except for **3j**, all compounds gave satisfactory microanalyses. [b] A, preparative GLC using 5% FFAP; B, preparative TLC using Kieselgel 60 F254 (Merck, 2 mm plate); C, column chromatography over silica gel; D, column chromatography over alumina. [c] Determined by GLC. [d] Allowed to react for 6 days at −20 °C. [e] A 20% yield of 1,2-diphenylethane was isolated. [f] Isolated yield. [g] A mixture of threo and erythro isomers. [h] High-resolution mass spectrum, m/e 224.087; calcd for $C_{12}H_{16}O_2S$, 224.087. [i] mp 112–113.5 °C (ether–hexane). [j] mp 68–69 °C (ether–hexane).

enolizable ketones provided adducts in about 50% yield (entries 9, 10, and 13) due to the competitive enolization of starting ketones. Exclusive 1,2-addition of **2** to α,β-unsaturated carbonyl compounds was observed (entries 13 and 14), as in the case of 1,3-dithiane.[14] Unsymmetrically substituted carbonyl compounds exhibited poor kinetic threo and erythro product selection (entries 10 and 14) or no selection (entries 12 and 13).[15]

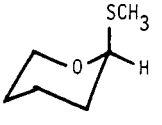
(2) Synthesis of 2-Heterosubstituted 1,3-Oxathianes. 2-(Group 14)-substituted[37] 1,3-oxathianes **4a–c** were prepared in reasonable yields by the reaction of **2** with pertinent metal chlorides. A reaction of anion **2** with trimethylplumbyl acetate afforded **4d** and **3** (E = $COCH_3$) in 70% and 16% yield, respectively. 2-(Methylthio)- and 2-(methylseleno)-1,3-oxathianes (**6b** and **6c**) were prepared by the reaction of **2** with dimethyl disulfide and dimethyl diselenide, respectively. It has been reported that a small amount of orthothiocarbonate **7** was formed by a reaction



7



8

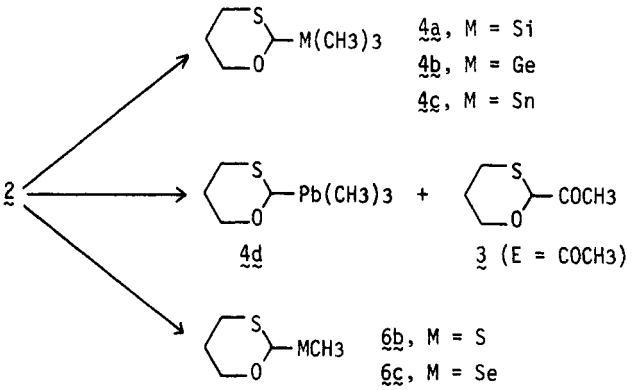


11

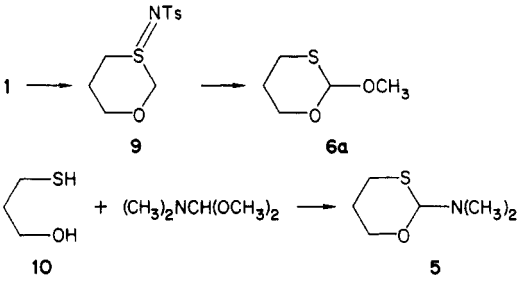
of 1,3-dithianyl anion with dimethyl disulfide,[16] because of increasing acidity of H(2) due to the introduction of the first methylthio group on C(2). However, this was not the case for 2-lithio-1,3-oxathiane (**2**).

Preparation of 2-chloro-1,3-dithiane by the reaction of 1,3-dithiane with *N*-chlorosuccinimide or sulfuryl chloride and the subsequent substitution reaction with nucleophiles have been reported.[17] Attempts to prepare 2-methoxy-

Scheme II



Scheme III



(14) It is known that the successful 1,4-addition of 2-lithio-1,3-dithiane to α,β-unsaturated carbonyl compounds can be achieved by the addition of hexamethylphosphoramide: (a) Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100. (b) El-Boug, M.; Wartski, L. *Tetrahedron Lett.* **1980**, *21*, 2897.

(15) Eliel, E. L.; Morris-Natschke, S. *J. Am. Chem. Soc.* **1984**, *106*, 2937.

(16) Woessner, W. D. *Chem. Lett.* **1976**, 43.

Table II. ^{1}H NMR Data for 2-Substituted 1,3-Oxathianes

	chemical shift, ppm (coupling constant, Hz)						
no.	2-H	4-axH[a]	4-eqH[b]	5-H	6-axH[a]	6-eqH[b]	others
3a	4.84 (q, 6)	3.04 (3.5, 12)	2.74 (12)	1.66–2.20	3.61 (2.5, 12)	3.98 (12)	CH_3 (1.45, d, 6)
3b	4.67 (t, 6)	3.03 (3.5, 10.5)	2.76 (10.5)	1.40–2.22[c]	3.59 (2.5, 12)	4.12 (12)	CH_3 (0.99, t, 7.5), CH_2 (1.40–2.22)[c]
3c	4.76 (t, 6)	3.02 (3.5, 11.5)	2.70 (11.5)	1.12–2.24[c]	3.55 (2.5, 12)	4.14 (12)	CH_3 (0.94, t, 6), CH_2CH_2 (1.12–2.24)[c]
3d	4.55 (d, 5.5)	3.02 (3.5, 11.5)	2.77 (11.5)	1.60–2.24[c]	3.58 (2.5, 12)	4.20 (12)	CH_3 (1.00, d, 7), CH_3 (1.01, d, 7), CH_3 (1.60–2.24)[c]
3e	4.72 (t, 6)	3.04 (2.5, 11.5)	2.72 (11.5)	1.04–2.20[c]	3.59 (2.5, 12)	4.16 (12)	CH_3 (0.88, t, 6), $CH_2CH_2CH_2$ (1.04–2.20)[c]
3f	4.76 (dd, 8)	3.06 (4, 12)	2.76 (12)	1.36–2.24	3.60 (2.5, 12)	4.16 (12)	CH_3 × 2 (0.92, d, 6)
3g[d,e]	4.47 (s)	3.01 (3.5, 13)	2.64 (13)	1.54–2.26	3.56 (3.5, 12)	4.16 (12)	(CH_3) × 3 (0.99, s)
3h	4.92 (t, 6)	2.56–3.28 (2 H, m)[c]		1.64–2.24	3.56 (2.5, 12)	4.16 (12)	C_6H_5 (7.24, s), CH_2 (2.56–3.28)[c]
3i	4.61 (s)	3.01 (4, 12)	2.82 (12)	1.50–2.20	3.62 (3, 12)	4.22 (12)	CH_3 × 2 (1.26, s) OH (2.48, bs)
3j[f]	4.88 (s)	2.52–3.12 (2 H, m)		1.60–2.28	3.04–3.84 (m)	4.04–4.44 (m)	CH_3 (1.62, s), CH_3 (1.64, s), C_6H_5 (7.08–7.68, m)
	4.98 (s)						
3k	5.65 (s)	3.02 (4, 12)	2.80 (12)	1.60–2.20	3.74 (3, 12)	4.23 (12)	C_6H_5 × 2 (7.00–7.68, m), OH (3.39, s)
3l	5.64 (s)	3.02 (4, 12)	2.78 (12)	1.64–2.16	3.73 (3, 12)	4.22 (12)	CH_3 (2.28, s), C_6H_5, C_6H_4 (6.96–7.56, m), OH (3.36, s)
3m[f]	4.86 (s)	3.00 (4, 12)	2.80 (12)	1.44–2.28	3.62 (12)	4.22 (12)	CH_3 (1.34, s), CH_3 (1.36, s), $CH{=}CH_2$ (5.00–6.20, m)
	4.65 (s)						
3n[f]	4.95 (d, 4)	3.06 (4, 12)	2.82 (12)	1.50–2.28	3.66 (3.5, 12)	4.12–4.56 (m)[c]	C_6H_5 (7.12–7.56, m), $C_6H_5CH{=}CH$ (6.74, d, 16), $C_6H_5CH{=}CH$ (6.20, dd, 7, 16) (6.28, dd, 7, 16), O*H*–OH (4.12–4.56),[c] OH (2.54, s)
	4.77 (d, 7)						
3o	6.09 (s)	3.20 (4, 12)	2.92 (12)	1.60–2.36	3.80 (2.5, 12)	4.36 (12)	C_6H_5 (7.28–8.12, m)
4a	4.65 (s)	3.01 (3.0, 12)	2.73 (12)	1.56–2.35	3.53 (2, 12)	4.12 (bd, 12)	CH_3 × 3 (0.10, s)
4b	4.83 (s)	3.01 (4, 12)	2.71 (12)	1.56–2.37	3.53 (3, 12)	4.10 (bd, 12)	CH_3 × 3 (0.25, s)
4c	5.09 (s) (16)[g]	3.01 (4, 12)	2.66 (12)	1.56–2.44	3.54 (3, 12)	4.00 (bd, 12)	CH_3 × 3 (0.20, s) (56)[g]
4d	5.51 (s) (16)[h]	2.94 (4, 12)	2.67 (12)	1.60–2.39	3.58 (3.5, 12)	3.98 (bd, 12)	CH_3 × 3 (0.88, s) (62)[h]
5	5.37 (s)	3.04 (4, 11)	2.80 (11)	1.50–2.12	3.67 (3.5, 12)	4.22 (bd, 12)	CH_3 × 2 (2.46, s)
6a	5.61 (s)	3.13 (m)	2.72 (m)	1.60–2.16	4.17 (m)	3.74 (m)	CH_3(3.46, s)
6b	5.76 (s)	3.14 (m)	2.82 (m)	1.76–2.06	4.32 (m)	3.70 (m)	CH_3(2.17, s)
6c	6.16 (s)	3.12 (m)	2.80 (m)	1.80–2.24	4.28 (m)	3.72 (m)	CH_3(2.07, s)

[a] All signals appeared as a dt unless otherwise cited. [b] All signals appeared as a broad doublet unless otherwise cited. [c] Overlapped signals. [d] Prepared by the reported method. Reference 21. [e] More precise values obtained by iterative computation have been reported. Reference 21. [f] A mixture of erythro and threo isomers. [g] Values in parentheses are ^{119,117}Sn couplings. [h] Values in parentheses are ^{207}Pb couplings.

Table III. ^{13}C Chemical Shifts for 2-Heterosubstituted 1,3-Oxathianes

	chemical shift, ppm				
no.	C(2)	C(4)	C(5)	C(6)	CH_3
4a	77.91	28.59	27.07	71.45	−3.82
4b	78.22	28.83	27.01	71.43	−3.98
4c[a]	75.56 (397.5, 416.0)	29.49 (31.3)	27.35	71.39 (39.1)	−10.47 (327.1, 341.8)
4d[b]	78.83	30.44 (43.9)	27.28	71.93 (51.3)	−1.26 (236.8)
5	98.67	27.77	25.66	69.73	+39.61
6a	102.91	25.05	24.51	62.98	+55.30
6b	82.78	26.65	25.25	64.82	+13.68
6c	75.33	26.71	25.48	64.58	+4.76
1	71.13	27.48	26.95	69.67	

[a] Values in parentheses are ^{117,119}Sn couplings in Hz, where resolved. [b] Values in parentheses are ^{207}Pb couplings in Hz, where resolved.

1,3-oxathiane (**6a**) through chlorination followed by methoxylation with sodium methoxide led to unidentifiable products. Bromination of **1** with *N*-bromosuccinimide followed by treatment with sodium methoxide afforded disulfide **8** instead of the expected product. 2-Methoxy-1,3-oxathiane (**6a**) was finally synthesized by a method similar to that reported by Yoshida et al. for the synthesis of 2-methoxy-1,3-dithiane.[18] Thus, conversion of 1,3-oxathiane (**1**) to the *N*-tosylsulfilimine **9** with chloramine-T (Aldrich) was followed by methanolysis to produce **6a** in 31% overall yield.

Transacetalization between 3-hydroxypropanethiol (**10**) and *N,N*-dimethylformamide dimethyl acetal resulted in the formation of **5** in 72% yield. ^{1}H NMR data for 2-substituted 1,3-oxathianes are summarized in Table II. Table III lists ^{13}C NMR data for 2-heterosubstituted 1,3-oxathianes.

Discussion

(1) 2-(Group 14)-Substituted 1,3-Oxathianes. A variety of alkylated 1,3-oxathianes have been synthesized[19,20] and their conformational aspects have been extensively studied.[21] Conformational energies of alkyl groups such as methyl, ethyl, and isopropyl at C(2) in

(17) (a) Arai, K.; Oki, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 553. (b) Kruse, C. G.; Broekhof, N. L. J. M.; Wijsman, A.; van der Gen, A. *Tetrahedron Lett.* **1977**, 885.

(18) Yoshida, H.; Yoshikane, M.; Ogata, T.; Inokawa, S. *Synthesis* **1976**, 551.

(19) (a) Friebolin, H.; Schmid, H. G.; Kabuss, S.; Faisst, W. *Org. Magn. Reson.* **1969**, *1*, 67. (b) Danneels, D.; Antheunis, M.; van Acker, L.; Tavernier, D. *Tetrahedron* **1975**, *31*, 327.

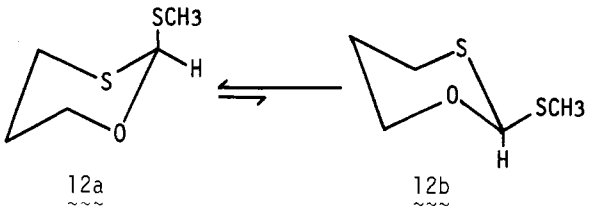
(20) (a) Pihlaja, K.; Pasanen, P. *Acta Chem. Scand.* **1970**, *24*, 2257. (b) Pasanen, P., Pihlaja, K. *Ibid.* **1971**, *25*, 1908.

(21) (a) Gelan, J.; Swaelens, G.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1970**, *79*, 321. (b) Gelan, J.; Anteunis, M. *Ibid.* **1968**, *77*, 423, 447. (c) de Wolf, N.; Buys, H. R. *Tetrahedron Lett.* **1970**, 551.

1,3-oxathianes were determined to be in the range of 3.25–3.55 kcal/mol.[22] Iterative computational analysis of 2-*tert*-butyl-1,3-oxathiane (**3g**) showed that this molecule exists in a chair conformation with 2-equatorial substituent.[23] However, surprisingly few numbers of 2-monoalkylated 1,3-oxathianes with no substituents at other positions have been reported so far. ^{1}H NMR data for 2-alkyl-1,3-oxathianes **3a–h** in Table II revealed that axial protons at C(4) and C(6) appeared as a doublet of triplet and equatorial protons were doublets with fine splittings. As has already been known for many six-membered cyclic sulfides,[19a,21b,24] the axial proton at the carbon atom next to the sulfur atom resonated at lower field than the equatorial proton in our case also.

The ^{1}H NMR pattern of 2-(trimethylsilyl)-1,3-oxathiane (**4a**) is extremely similar to that of 2-alkyl-1,3-oxathianes (**3**). No meaningful changes were observed in the spectrum at −50 °C, indicating the conformational homogeneity of this molecule in the $CDCl_3$ solution. Recently, ^{1}H and ^{13}C NMR spectra of 2-(group 14)-substituted 1,3-dithianes have been discussed in detail.[25] The conclusion drawn is that the group 14 substituents at C(2) prefer the equatorial orientation with a minimum of 2.15 kcal/mol for the A values for $Sn(CH_3)_3$ and $Pb(CH_3)_3$, which are much larger than the corresponding values in cyclohexane.[26] Analogous reasoning, including γ-effects,[27,28] leads to the equatorial orientation of the 2-(group 14)-substituents in 1,3-oxathianes. All parameters for 2-(trimethylsilyl)-1,3-oxathiane (**4a**) obtained by iterative computation at 400 MHz support the above conclusion.[29]

(2) 2-(Group 16)-Substituted 1,3-Oxathianes.[37] Iterative computation at 400 MHz afforded all parameters including chemical shifts and coupling constants for **6a**.[29] Several points are worthy of note. Not only the 4-axial proton but also the 6-axial proton are downfield from the corresponding equatorial ones. Zig–zag coupling[30] and coupling across the W-path through sulfur or oxygen ($J_{2,4eq}$ and $J_{2,6eq}$) are observed. These facts suggest that 2-methoxy-1,3-oxathiane (**6a**) exists in a chair conformation with the methoxy group largely in axial orientation due to the anomeric effect. Values[28] for the γ-effect on C(6) (−6.69 ppm) and C(4) (−2.43 ppm) correspond to the well-known γ gauche effect of a methoxy group, again supporting the above conclusion. Though 2-(methylthio)-1,3-oxathiane (**6b**) displays a pattern similar to that of **6a** in the ^{1}H NMR spectrum, the magnitude of the γ-effect on C(6) (−4.85 ppm) is considerably decreased from that of the standard compound **11** (−9.0 ppm), which indicates the existence of a conformational equilibrium between two conformational isomers **12a** and **12b**, where **12a** slightly predominates.[31] This was confirmed by the fact that coalescence of C(4) and C(6) was observed at −90 °C in the ^{13}C NMR spectrum.



12a 12b

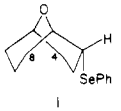
The ^{1}H NMR spectrum of 2-(methylseleno)-1,3-oxathiane (**6c**) is again similar to that of **6a**. A value of −0.77 and −5.09 for the γ-effect on C(4) and C(6), respectively, suggests axial disposition for the methylselenyl group. However, because of the lack of standard data for the γ-effect,[32] the preferred orientation of methylselenyl group in **6c** is an open question until the low temperature ^{1}H or ^{13}C NMR spectrum is measured.

(3) 2-(Dimethylamino)-1,3-oxathiane (5). 2-(Dimethylamino)-1,3-oxathiane (**5**) shows a similar ^{1}H NMR pattern to those of **3** and **4** in which the substituent on C(2) is in the equatorial position. Irradiation of the H(2) peak induced 4% and 5% NOE's on the axH(4) and axH(6) signals, respectively. Thus **5** does not display an anomeric effect. Similar observations have been reported for 2-amino-substituted tetrahydropyrans.[34]

Experimental Section

Melting points were determined with a Yanagimoto micro apparatus and uncorrected. Boiling points were determined on a microdistillation apparatus. Infrared spectra were recorded with a JASCO A-202 diffraction grating infrared spectrometer. ^{1}H NMR spectra were obtained with JEOL JNM-FX100, Nicolet NT-360, or Bruker HW-400 spectrometers. Chemical shifts are given in δ values relative to internal tetramethylsilane. Mass spectra were determined on a JEOL Model JMS-01SG double-focusing mass spectrometer. GLC analyses were performed on a Shimazu GC-4CM gas chromatograph. Preparative GLC was performed on a Varian aerograph Model 920 with a thermal conductivity detector. All reactions involving organolithium reagents were carried out in an atmosphere of dry nitrogen. THF was predistilled with NaOH and freshly distilled from sodium benzophenone ketyl.[35] *sec*-BuLi was prepared by the procedure of Gilman.[36]

(22) Pasanen, P.; Pihlaja, K. *Tetrahedron* **1972**, *28*, 2617.
(23) Bergesen, K.; Carden, B. M.; Cook, M. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 345.
(24) (a) Campaigne, E.; Chamberlain, N. F.; Edwards, B. E. *J. Org. Chem.* **1962**, *27*, 135. (b) Lambert, J. B.; Mixan, C. E.; Johnson, D. H. *J. Am. Chem. Soc.* **1973**, *95*, 4634. (c) Khan, S. A.; Lambert, J. B.; Hernandez, O.; Carey, F. A. *Ibid.* **1975**, *97*, 1468. (d) Eliel, E. L.; Rao, V. S.; Vierhapper, F. W.; Juaristi, G. Z. *Tetrahedron Lett.* **1975**, 4339. (e) Eliel, E. L.; Rao, V. S.; Riddell, F. G. *J. Am. Chem. Soc.* **1976**, *98*, 3583.
(25) Drew, G. M.; Kitching, W. *J. Org. Chem.* **1981**, *46*, 558.
(26) (a) Kitching, W.; Doddrell, D.; Grutzner, J. B. *J. Organometal. Chem.* **1976**, *107*, C5. (b) Kitching, W.; Olszowy, H.; Waugh, J.; Doddrell, D. *J. Org. Chem.* **1978**, *43*, 898. (c) Moder, T. I.; Hsu, C. C. K.; Jensen, F. R. *J. Org. Chem.* **1980**, *45*, 1008.
(27) The γ-effects of $M(CH_3)_3$ (M = Si, Ge, Su, Pb) are substantially downfield in anti arrangements and upfield in the gauche array: Kitching, W.; Marriott, M.; Adcock, W.; Doddrell, D. *J. Org. Chem.* **1976**, *41*, 1671.
(28) Comparison data on γ-effects of 2-heterosubstituted 1,3-oxathianes and other heterocycles are given in the supplementary material.
(29) Figures demonstrating the fit between the experimental and calculated spectra are included in the supplementary material.
(30) (a) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807. (b) Ramey, K. C.; Messick, J. *Tetrahedron Lett.* **1965**, 4423. (c) Gelan, J.; Anteunis, M. *Bull. Soc. Chim. Belg.* **1968**, *77*, 447.
(31) The anomeric effect of the RS group is somewhat smaller than that of the RO group. (a) Eliel, E. L.; Giza, C. A. *J. Org. Chem.* **1968**, *33*, 3754. (b) De Hoog, A. J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 972.
(32) Recently, γ-effects of phenylselenyl group on C(4) (γ anti) and C(8) (γ gauche) in 2-(phenylseleno)-9-oxabicyclo[3.3.1]nonane (**i**) were reported to be +2.0 and −4.2 ppm, respectively.[33] However, it is not appropriate to adopt these values as standard, because there should be appreciable difference in effect between SeMe and SePh groups; also the framework is quite different.



i

(33) Toshimitsu, A.; Aoai, T.; Uemura, S.; Okano, M. *J. Org. Chem.* **1981**, *46*, 3021.
(34) (a) Tesse, J.; Glacet, C.; Couturier, D. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 1525. (b) Barbry, D.; Couturier, D.; Ricart, G. *J. Chem. Soc., Perkin Trans 2* **1982**, 249.
(35) Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley-Interscience: New York, 1972; p 439.
(36) Gilman, H.; Moore, F. W.; Baine, O. *J. Am. Chem. Soc.* **1941**, *63*, 2479.

Table IV. Data for 2-Heterosubstituted 1,3-Oxathianes[a,b]

no.	bp, °C (mmHg)	yield, %	IR ($CHCl_3$), cm^{-1}	Anal.
4a	84–86 (18)	89	1250, 1070, 850	($C_7H_{16}OSSi$) C, H
4b		60	1065, 1020, 825	($C_7H_{16}OSGe$) C, H
4c	80–81 (4)	76	1065, 1015, 535	($C_7H_{16}OSSn$) C, H
4d		70	1055, 1010, 485	($C_7H_{16}OSPb$) C, H
5	98 (17)	72	1280, 1085, 1075	($C_6H_{13}NOS$) C, H
6a	63 (5)	31	1120, 1075, 950	($C_5H_{10}O_2S$), C, H
6b	75–78 (1)	82	1175, 1060, 1020	($C_5H_{10}OS_2$) C, H
6c	93–96 (3.5)	50	1135, 1055, 1020	($C_5H_{10}OSSe$) C, H

[a] Purified by preparative GLC (5% FFAP). [b] Overall yield from 1.

General Procedure for the Preparation of 2-Lithio-1,3-oxathiane (2) in THF. Preparation of 2-Deuterio-1,3-oxathiane (3, E = D). To a solution of 210 mg (2.0 mmol) of 1,3-oxathiane in 4 mL of THF was added a hexane solution of *sec*-BuLi at −78 °C until the solution was colored faint yellow. Nearly quantitative formation of **2** in this solution was confirmed as follows: After being stirred for a few minutes at −78 °C, the solution was introduced into deuterium oxide by means of a syringe at 0 °C followed by addition of brine and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered, and concentrated evaporatively to yield a crude oil. GLC analysis (5% PEG 6000) with *p*-methylanisole as an internal standard indicated quantitative recovery of the deuterated material. The crude material was purified by preparative GLC (5% FFAP). Integration of the proton at C(2) in the ^1H NMR spectrum of the purified material vs. any other well-defined and separated peaks of 1,3-oxathiane indicated nearly quantitative incorporation of deuterium at C(2).

Preparation of 3a. General Procedure. To a solution of 2-lithio-1,3-oxathiane (**2**) prepared from 105 mg (1.0 mmol) of 1,3-oxathiane (**1**) was added methyl iodide (143 mg, 1.0 mmol) followed by stirring at −78 °C for 1 h. The yield of 2-methyl-1,3-oxathiane (**3a**) was determined by GLC analysis (5% PEG 6000) with *p*-methylanisole as an internal standard. Extractive workup with dichloromethane and purification by preparative GLC (5% FFAP) gave pure **3a**.

Yields and data for **3** are summarized in Table I. ^1H NMR data for **3a–o** are given in Table II.

2-Heterosubstituted 1,3-oxathianes **4a–c**, **6b**, and **6c** were prepared in the same manner.

2-(Trimethylplumbyl)-1,3-oxathiane (4d) and 2-Acetyl-1,3-oxathiane (3, E = $COCH_3$). To a stirred solution of the anion **2** generated from 1.02 g (9.8 mmol) of 1,3-oxathiane (**1**) in THF (35 mL) was added 3.69 g (11.8 mmol) of trimethyllead acetate at −78 °C and the resulting mixture was maintained at the same temperature for 2 h with stirring. It was poured into ice–water. Extractive workup followed by preparative GLC gave 2.5 g (70%) of 2-(trimethylplumbyl)-1,3-oxathiane (**4d**) and 234 mg (16%) of 2-acetyl-1,3-oxathiane (**3**, E = $COCH_3$): IR ($CHCl_3$) 1725, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56–2.12 (2 H, m), 2.26 (3 H, s), 2.86 (1 H, br d, J = 12 Hz), 3.08 (1 H, dt, J = 4, 12 Hz), 3.64 (1 H, dt, J = 3.5, 12 Hz), 4.26 (1 H, br d, J = 12 Hz), 5.30 (1 H, s); high-resolution mass spectrum, m/e 146.041, calcd for $C_6H_{10}O_2S$ 146.040.

2-(Dimethylamino)-1,3-oxathiane (5). A mixture of 3-hydroxypropanethiol (1.19 g, 12.9 mmol) and *N,N*-dimethylformamide dimethyl acetal (3.59 g, 30.2 mmol) in anhydrous benzene (25 mL) was heated under reflux with continuous removal of water for 12 h. After benzene was distilled off, the residue was distilled under reduced pressure to afford 1.36 g (72%) of **5**. All data are given in Tables II, III, and IV together with other 2-heterosubstituted 1,3-oxathianes **4a–d** and **6a–c**.

***N*-Tosylsulfilimine 9.** Dry chloramine-T (3.64 g, 16 mmol) was added portionwise to a vigorously stirred solution of 1,3-oxathiane (1.51 g, 14 mmol) in anhydrous methanol at 0 °C. After being stirred for 15 min, the mixture was poured into ice–water to give crystals which were recrystallized from acetonitrile–CH_2Cl_2 (3.63 g, 91% yield): mp 132–134 °C; IR (KBr) 1265, 1135, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.2 (2 H, m), 2.36 (3 H, s), 2.80–3.56 (2 H, m), 3.56–4.04 (2 H, m), 4.54 (1 H, d, J = 10 Hz), 5.00 (1 H, d, J = 10 Hz), 7.20 (2 H, d, J = 8 Hz), 7.72 (2 H, d, J = 8 Hz). Anal. Calcd for $C_{11}H_{15}NO_3S_2$: C, 48.33; H, 5.53; N, 5.12. Found: C, 48.42; H, 5.65; N, 4.94.

2-Methoxy-1,3-oxathiane (6a). A suspension of **9** (3.0 g, 11 mmol) in a solution of KOH (6.0 g) in anhydrous methanol (60 mL) was stirred at room temperature until a clear solution was obtained (1 h). The solution was then poured into water and extracted with ether. The extract was dried ($MgSO_4$), filtered, and evaporated to afford an oily residue which was distilled under reduced pressure to give 0.5 g (34%) of pure 2-methoxy-1,3-oxathiane (**6a**).

Disulfide 8. To a stirred solution of 1,3-oxathiane (**1**) (505 mg, 4.9 mmol) in anhydrous benzene (5 mL) was added 712 mg (4 mmol) of NBS in anhydrous benzene (50 mL) at 0 °C under argon atmosphere. The ice bath was removed and stirring was continued for 4 h at room temperature. The reaction mixture was then poured into a sodium methoxide solution, prepared from 1.0 g (43.5 mmol) of sodium and anhydrous methanol (10 mL at 0 °C under argon atmosphere. After being stirred for 1.5 h, it was poured into ice–water and extracted with ether. The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford a residue, distillation of which gave 454 mg (69%) of **8** as a colorless oil: bp 130 °C (0.1 mmHg); IR ($CHCl_3$) 1120, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.4 (4 H, m), 2.83 (4 H, t, J = 8 Hz), 3.37 (6 H, s), 3.63 (4 H, t, J = 7 Hz), 4.60 (4 H, s).

Registry No. **1**, 646-12-8; **3** (E = D), 79144-10-8; **3** (E = $COCH_3$), 79144-07-3; **3a**, 19134-37-3; **3b**, 30098-77-2; **3c**, 66390-01-0; **3d**, 24699-59-0; **3e**, 66390-02-1; **3f**, 64548-32-9; **3g**, 58808-28-9; **3h**, 66390-00-9; **3i**, 94537-81-2; **3j** (isomer 1), 94537-82-3; **3j** (isomer 2), 94537-83-4; **3k**, 94537-84-5; **3l** (isomer 1), 94537-90-3; **3l** (isomer 2), 94596-29-9; **3m** (isomer 1), 94537-85-6; **3m** (isomer 2), 94537-86-7; **3n** (isomer 1), 94537-87-8; **3n** (isomer 2), 94537-88-9; **3o**, 86137-20-4; **4a**, 79143-99-0; **4b**, 79144-00-6; **4c**, 79144-01-7; **4d**, 79144-02-8; **5**, 79144-06-2; **6a**, 79144-05-1; **6b**, 79144-03-9; **6c**, 79144-04-0; **8**, 94537-89-0; **9**, 79143-98-9; **10**, 19721-22-3; $C_6H_5C(=O)C_6H_4CH_3$, 42343-24-8; CH_2=$CHCOCH_3$, 78-94-4; CH_3I, 74-88-4; C_2H_5I, 75-03-6; *n*-C_3H_7I, 107-08-4; *iso*-C_3H_7I, 75-30-9; 1-C_4H_9Br, 109-65-9; *iso*-C_4H_9I, 513-38-2; *t*-C_4H_9Cl, 507-20-0; $C_6H_5CH_2Br$, 100-39-0; CH_3COCH_3, 67-64-1; $C_6H_5COCH_3$, 98-86-2; C_6H_5CO-C_6H_5, 119-61-9; $C_6H_5COC_6H_4CH_3$, 104-55-2; C_6H_5CN, 100-47-0; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; chloramine-T, 127-65-1.

Supplementary Material Available: Table A giving all ^1H NMR parameters for **4a** and **6a** obtained by iterative computation at 400 MHz with a Bruker WH-400 spectrometer, Table B giving analytical data for **3a–f,h,i,k–o**, **4a–d**, **5**, and **6a–c**, Table C listing γ effect of 2-heterosubstituted 1,3-oxathiane and of 2-heterosubstituted heterocycles, and Figures A and B demonstrating the fit between the experimental and calculated spectra for **4a** and **6a** (5 pages). Ordering information is given on any current masthead page.

(37) The group notation is being changed in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is being eliminated because of wide confusion. Group I becomes groups 1 and 11, group II becomes groups 2 and 12, group III becomes groups 3 and 13, etc.