

CYCLISATIONS USING METHYL(BISMETHYLTHIO)SULPHONIUM SALTS. PART 6.¹
 SYNTHESIS OF 2-METHYLTHIOMETHYLATED TETRAHYDROFURANS

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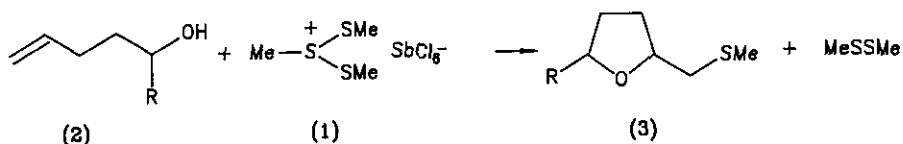
Abstract - The reaction of methyl(bismethylthio)sulphonium hexachloroantimonate (1) with δ -hydroxyalkenes (2) gives 2-methylthiomethyl-substituted tetrahydrofurans (3).

Cyclisations using sulphenylating agents of various nature have received much attention in recent years both for mechanistic interest and for the high synthetic potential of the ring systems obtained.²

Some time ago methyl(bismethylthio)sulphonium hexachloroantimonate (1) has been introduced as efficient methylthiolating agent towards functionalized alkenes and alkynes.^{1,3-6} In particular it was shown that 1 reacts with *o*-allylphenols to give 2-methylthiomethyl-dihydrobenzofurans in high yields.³

We now report that 1 can also be employed to obtain cyclofunctionalization of δ -hydroxyalkenes (2) to the tetrahydrofurans 3 (equation). Other efficient methods for similar sulphenooetherification of alkenols have been recently reported.⁷⁻⁹

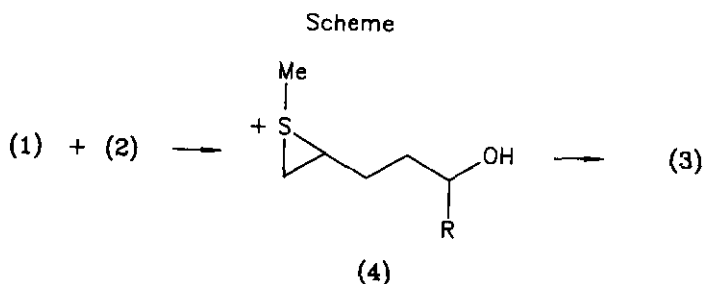
Equation



The alcohols (2) were prepared by using standard procedures (see experimental), from the Grignard reagent obtained from 4-bromobut-1-ene and the proper aldehydes or ketones. The reaction of 1 with 2 was easily performed by dropwise addition of

a methylene chloride solution of **1** to the solution of **2** in the same solvent at 0°C. After 30 minutes at this temperature and hydrolytic work-up (NaHCO₃ aqueous solution), the organic layer was separated and the product was isolated in good yield by column chromatography on silica gel. The five-membered ring structure of the products was assumed on the basis of mass spectrometry¹⁰ and nmr spectral data. The yields of the tetrahydrofurans obtained by this route are reported in the Table.

Formation of the 2-methylthiomethyltetrahydrofurans (**3**) likely arises from intramolecular nucleophilic attack of the oxygen atom at one carbon atom of the intermediate thiiranium ion (**4**)¹¹ (Scheme).



The five-membered ring closure of **4** to **3** always occurs regioselectively in an exo mode as it also happens in most of the similar cyclisations.^{2,3,7-9}

The cyclisation of **2b**, **2c**, **2d**, and **2e** was performed in order to verify whether steric hindrance at the 5-position of **2** could induce some stereoselection in the formation of **3**. In any case almost equimolar amounts of *cis* and *trans* tetrahydrofurans (**3**) were obtained. The ratio of the stereoisomers was determined by nmr or, when possible, by gas chromatography.

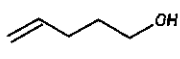
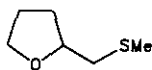
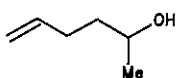
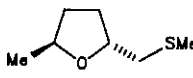
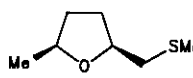
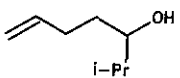
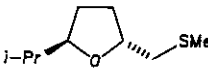
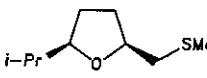
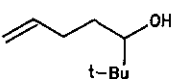
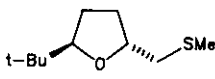
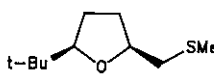
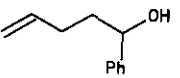
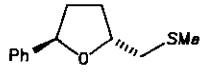
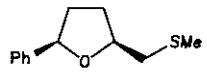
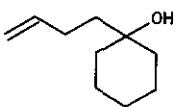
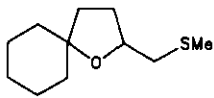
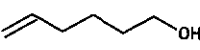
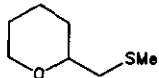
The cyclisation of **2b** was carried out at several temperatures from -78°C to +40°C, but detectable changes of the isomer ratio of the tetrahydrofurans (**3b**) were not observed.

Simple force field calculations performed by the Alchemy¹² program showed that the difference of the total energy of the *cis* and *trans* **3b-e** was 0.16, 0.45, 0.56, and 3.98 kcal/mol respectively, being always the *cis* the more stable isomer. Although these data have to be considered only indicative, they suggest that the cyclisation of the alkenols (**2**) is not a thermodynamically controlled process. In fact the so high calculated energy difference of the two isomeric phenyl substituted tetrahydrofurans (**3e**) would have given a strongly unbalanced mixture of stereoisomers.

The easiness of the preparation of **1**^{13,14} and of the overall procedure make this synthesis of substituted tetrahydrofurans a valid alternative to other

sulphenoetherification methods so far reported in the recent literature ⁷⁻⁹ since it is at least as simple as the other methods. Moreover this method might be of general application for the cyclisation of alkenols since we also found that the γ -alkenol (5) behaves like 2 and gives 2-methylthiomethyltetrahydropyran (6) in high yields (see Table).

Table
 Synthesis of cyclic ethers from alkenols in CH_2Cl_2 at 0 °C

Substrate	Products	Yields %	Isomer Ratio
 (2a)	 (3a)	82	—
 (2b)	 (3b) trans	72	1 : 0.9
	 (3b) cis		
 (2c)	 (3c) trans	81	1 : 0.9
	 (3c) cis		
 (2d)	 (3d) trans	36	1 : 1
	 (3d) cis		
 (2e)	 (3e) trans	82	1 : 1
	 (3e) cis		
 (2f)	 (3f)	53	—
 (5)	 (6)	67	—

Due to the importance of the presence of a tetrahydrofuran skeleton in many biological active compounds we are currently investigating the application of this reaction to the synthesis of some pharmacologically active compounds. Indeed preliminary experiments show that **3a**, **3c**, and **6** have some specific anti-thrombosis activity.

EXPERIMENTAL

^1H Nmr were recorded on a Varian VXR-300 spectrometer and the data reported for CDCl_3 solutions, TMS as internal standard, and coupling constants in Hz. GC-mass spectra were taken on a HP-5970-5790 system equipped with a SE-30, 25 m, capillary column.

Alkenols (**2a**) and (**5**) were purchased from Aldrich.

Compounds (**2b**)-(2f) were prepared by reaction of the Grignard reagent of the 1-bromo-but-3-ene and the appropriate carbonyl compounds and were characterized on the basis of literature data¹⁵.

The previously unreported alkenols (**2c**) and (**2f**) were purified by column chromatography on silica gel (eluant: (**2c**), light petroleum - diethyl ether 95:5 v/v; (**2f**), diethyl ether).

2-Methyl-3-hydroxyhept-6-ene (**2c**), bp 77-81°C at 50 mmHg, 39% yield. ^1H Nmr, δ 5.86 (m, 1H), 5.06 (m, 1H), 4.98 (m, 1H), 3.39 (m, 1H), 2.20 (complex m, 2H), 1.66 (m, 1H), 1.53 (complex m, 2H and OH), 0.93 (d, 3H, $J = 6.9$), and 0.92 (d, 3H, $J = 6.7$). Mass spectrum, m/z 128 (M^+), 110 ($M^+ - 18$), and 45 (base peak). Anal. Calcd for $\text{C}_8\text{H}_{16}\text{O}$; C, 74.94; H, 12.58. Found; C, 75.23; H, 12.37.

1-(3-Butenyl)cyclohexanol (**2f**) was further purified by bulb to bulb distillation at 50 mmHg (oil bath at 120°C); 43% yield. ^1H Nmr, δ 5.87 (m, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 2.16 (m, 2H and OH), 1.50 (m, 12H). Mass spectrum, m/z 154 (M^+), 136 ($M^+ - 18$), 55 (base peak). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}$; C, 77.87; H, 11.76. Found; C, 78.10; H, 11.53.

Cyclisation Reaction of (2a) - (2f) and (5) with Methyl(bismethylthio)sulphonium Hexachloroantimonate (1). General Procedure.-The appropriate alkenol (**2**) (2 mmol) in dry dichloromethane (5 ml) was cooled at 0°C and **1** (2 mmol) dissolved in the same solvent (10 ml) was added dropwise. After 30 min, 10% aqueous solution of Na_2CO_3 was added and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and washed with water to neutrality. The dichloromethane solution was dried (CaCl_2), the solvent was removed under vacuum, and the residue was chromatographed on silica gel column (eluant: (**3a**), light petroleum - diethyl ether 4:1; (**3b**), (**3d**), and (**3f**), light petroleum - ethyl

acetate 3:1; (3c) and (3e), light petroleum - ethyl acetate 9:1; (6), light petroleum - diethyl ether 9:1 v/v). The cyclic ethers (3) and (6) were further purified by vacuum distillation. 2-(Methylthiomethyl)tetrahydrofuran (3a); bp 36-37°C at 0.3 mmHg. $^1\text{H Nmr } \delta$ 4.047 (q, 1H, $J = 6.4$, H-2), 3.89 (m, 1H, H_A -5), 3.76 (m, 1H, H_B -5), 2.67 (A part of an ABX system, 1H, $J_{AB} = 13.24$, $J_{AX} = 6.07$, CH_ASMe), 2.59 (B part of an ABX system, 1H, $J_{BX} = 6.24$, CH_BSMe), 2.16 (s, 3H, SCH_3), 2.15 - 1.82 and 1.70 - 1.58 (complex m, 4H, H_3 and H_4). Mass spectrum, m/z 132 (M^+), 71 ($M^+ - \text{CH}_2\text{SMe}$, base peak). Anal. Calcd for $\text{C}_6\text{H}_{12}\text{OS}$; C, 54.50; H, 9.15. Found; C, 54.22; H, 9.31.

2-(Methylthiomethyl)-5-methyltetrahydrofuran (3b) was purified by bulb to bulb distillation at 35 mmHg, oil bath, 90°C. $^1\text{H Nmr } \delta$ 4.12 (m, 1H, H-2 or H-5), 4.01 (m, 1H, H-5 or H-2), 2.57 (m, 2H, CH_2SMe), 2.15 and 2.14 (two s, 3H, SCH_3), 2.10-1.90 and 1.70 - 1.40 (complex m, 4H, H-3 and H-4), 1.23 and 1.99 (two d, 3H, $J = 8.1$ and 8.1 , CH_3). Mass spectrum, m/z 146 (M^+), 85 ($M^+ - \text{CH}_2\text{SMe}$, base peak). Anal. Calcd for $\text{C}_7\text{H}_{14}\text{OS}$; C, 57.48; H, 9.65. Found; C, 56.94; H, 9.54.

2-(Methylthiomethyl)-5-isopropyltetrahydrofuran (3c) was purified by bulb to bulb distillation at 20 mmHg, oil bath, 130°C. $^1\text{H Nmr } \delta$ 4.13 and 4.04 (two m, 1H, H-2), 3.66 and 3.56 (two m, 1H, H-5), 2.51 - 2.73 (two m, 2H, CH_2SMe), 2.16 (s, 3H, SCH_3), 2.12 - 1.82 and 1.73 - 1.50 (two complex m, 5H, H-3, H-4 and CHMe_2), 0.95 and 0.86 (two d, 3H, $J = 6.5$ and 6.7 , isopropyl- CH_3), 0.94 and 0.85 (two d, 3H, $J = 6.5$ and 6.7 , isopropyl- CH_3). Anal. Calcd for $\text{C}_9\text{H}_{18}\text{OS}$; C, 62.02; H, 10.41. Found; C, 62.41; H, 10.63.

2-(Methylthiomethyl)-5-tert-butyltetrahydrofuran (3d), bp 115-118°C at 3 mmHg. $^1\text{H Nmr } \delta$ 4.09 and 4.02 (two m, 1H, H-2), 3.66 and 3.56 (two m, 1H, H-5), 2.72 - 2.47 (two m, 2H, CH_2SMe), 2.18 and 2.17 (two s, 3H, SCH_3), 2.10 - 1.90 and 1.85 - 1.57 (two complex m, 4H, H-3 and H-4), 0.89 and 0.88 (two s, 9H, $\text{C}(\text{CH}_3)_3$). Mass spectrum, m/z 188 (M^+), 127 ($M^+ - \text{CH}_2\text{SMe}$, 61%), 109 (base peak). Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{OS}$; C, 63.78; H, 10.70. Found; C, 64.10; H, 10.48.

2-(Methylthiomethyl)-5-phenyltetrahydrofuran (3e) was purified by bulb to bulb distillation at 0.2 mmHg, oil bath at 170°C. $^1\text{H Nmr } \delta$ 7.38 - 7.23 (m, 5H, Ph), 5.06 and 4.90 (two t, 1H, $J = 1.6$ and 7.1 , H-5), 4.44 and 4.26 (two m, 1H, H-2), 2.89 - 2.65 (m, 2H, CH_2SMe), 2.50 - 2.10 (complex m, 2H, H-4), 2.22 and 2.21 (two s, 3H, SCH_3), 1.85 (m, 2H, H-3). Mass spectrum, m/z 208 (M^+), 147 ($M^+ - \text{CH}_2\text{SMe}$, base peak). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{OS}$; C, 69.18; H, 7.74. Found; C, 69.54; H, 7.62.

2-Methylthiomethyl-1-oxaspiro[4.5]decane (3f) was purified by bulb to bulb distillation at 0.2 mmHg, oil bath at 150°C. $^1\text{H Nmr } \delta$ 4.11 (m, 1H, H-2), 2.67 (A part of an ABX system, 1H, $J_{AB} = 13.3$, $J_{AX} = 5.3$, CH_ASMe), 2.53 (B part of an ABX system, 1H, $J_{BX} = 6.7$, CH_BSMe), 2.14 (s, 3H, SCH_3), 1.80 - 1.20 (complex m,

14H, H-3, H-4, and cyclohexyl protons). Mass spectrum, m/z 200 (M^+), 139 ($M^+ - CH_2SMe$, 70%), 121 (base peak). Anal. Calcd for $C_{11}H_{20}OS$; C, 65.95; H, 10.06. Found; C, 66.33; H, 9.94. 2-(Methylthiomethyl)-tetrahydropyran (6); bp 45 -46 °C at 0.3 mmHg. 1H Nmr δ 4.01 (m, 1H, H-2), 3.44 (m, 2H, H-5), 2.62 (A part of an ABX system, 1H, $J_{AB} = 13.2$, $J_{AX} = 6.0$, $CH_A SMe$), 2.51 (B part of an ABX system, 1H, $J_{BX} = 4.8$, $CH_B SMe$), 2.15 (s, 3H, SCH_3) 1.90 - 1.20 (complex m, 6H, H-2, H-3, and H-4). Mass spectrum, m/z 146 (M^+), 85 ($M^+ - CH_2SMe$, base peak). Anal. Calcd for $C_7H_{14}OS$; C, 57.49; H, 9.65. Found; C, 57.58; H, 9.76.

ACKNOWLEDGEMENTS

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