CYCLISATIONS USING METHYL(BISMETHYLTHIO)SULPHONIUM SALTS. PART 6.[1] SYNTHESIS OF 2-METHYLTHIOMETHYLATED TETRAHYDROFURANS

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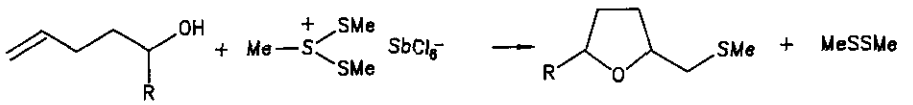
Abstract - The reaction of methyl(bismethylthio)solphonium hexachloroantimonate (1) with δ-hydroxyalkenes (2) gives 2-methylthiomethyl-substituted tetrahydrofurans (3).

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-methylthiomethyldihydrobenzofurans 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 sulphenoetherification of alkenols have been recently reported.[7-9]

Equation



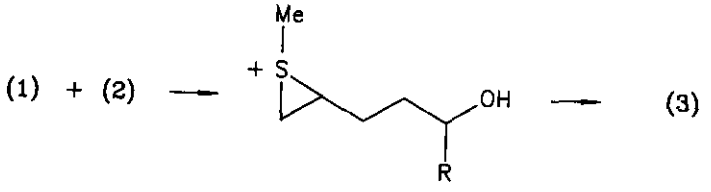
(2) (1) (3)

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 ($NaHCO_3$ 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 spectrometry[10] 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).

Scheme



(4)

The five-membered ring closure of 4 to 3 always occurs regiospecifically 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.

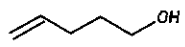
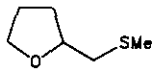
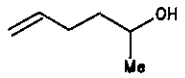
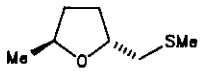
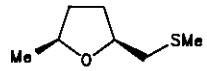
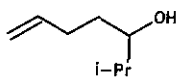
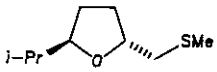
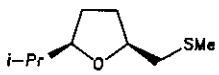
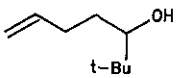
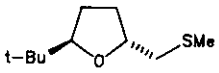
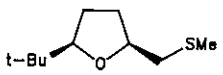
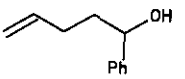
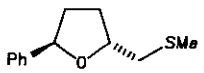
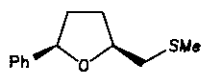
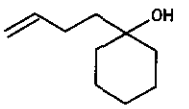
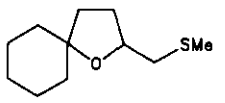
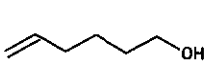
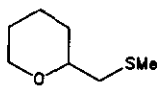
Simple force field calculations performed by the Alchemy[12] program showed that the difference of the total energy of the cis and trans 3b-e was 0.16, 0.45, 0.56, and 3.98 kcal/mol respectively, being always the cis the more stable isomer. Although these data have to be considered only indicative, they 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  (3b) cis	72	1 : 0·9
 (2c)	 (3c) trans  (3c) cis	81	1 : 0·9
 (2d)	 (3d) trans  (3d) cis	36	1 : 1
 (2e)	 (3e) trans  (3e) cis	82	1 : 1
 (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

^{1}H 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 data[15].

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. ^{1}H 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 $C_8H_{16}O$; 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. ^{1}H 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 $C_{10}H_{18}O$; 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 dichlomethane 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 furter purified by vacuum distillation. 2-(Methylthiomethyl)tetrahydrofuran (3a); bp 36-37°C at 0.3 mmHg. ^{1}H Nmr δ 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^+ - CH_2SMe, base peak). Anal. Calcd for $C_6H_{12}OS$; 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}H Nmr δ 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^+ - CH_2SMe, base peak). Anal. Calcd for $C_7H_{14}OS$; 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}H Nmr δ 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 $C_9H_{18}OS$; C, 62.02; H, 10.41. Found; C, 62.41; H, 10.63. 2-(Methyltiomethyl)-5-tert-butyltetrahydrofuran (3d), bp 115-118°C at 3 mmHg. ^{1}H Nmr δ 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, $C(CH_3)_3$). Mass spectrum, m/z 188 (M^+), 127 (M^+ - CH_2SMe, 61%), 109 (base peak). Anal. Calcd. for $C_{10}H_{20}OS$; 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}H Nmr δ 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^+ - CH_2SMe, base peak). Anal. Calcd for $C_{12}H_{16}OS$; C, 69.18; H, 7.74. Found; C, 69.54; H, 7.62. 2-Methylthiomethyl-1-oxaspiro[4.5]décane (3f) was purified by bulb to bulb distillation at 0.2 mmHg, oil bath at 150°C. ^{1}H Nmr δ 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. ^{1}H 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_ASMe), 2.51 (B part of an ABX system, 1H, J_{BX} = 4.8, CH_BSMe), 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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REFERENCES AND NOTES

1. Part 5, G. Capozzi, R. Ottana', and G. Romeo, Heterocycles, 1987, 26, 39.
2. For a recent review on the argument, see F. Capozzi, G. Capozzi, and S. Menichetti, 'Reviews on Heteroatom Chemistry' vol. 1, ed. by S. Oae, Myu, Tokyo, 1988, p. 178 and references cited therein.
3. G. Capozzi, F. Marcuzzi, and G. Modena, J. Chem. Soc., Perkin Trans. I, 1981, 3106.
4. G. Capozzi, C. Caristi, and M. Gattuso, J. Chem. Soc., Perkin Trans. I, 1984, 255.
5. G. Capozzi, R. Ottana', G. Romeo, and G. Valle, J. Chem. Research (S), 1986, 200.
6. G. Capozzi, R. Ottana', and G. Romeo, Heterocycles, 1986, **24**, 583.
7. G. J. O'Malley and M. P. Cava, Tetrahedron Letters, 1985, 26, 6159.
8. S. M. Tuladhar and A. G. Fallis, Tetrahedron Letters, 1987, **28**, 523.
9. P. Brownbridge, J. Chem. Soc., Chem. Commun., 1987, 1280.
10. A. Sturaro, P. Traldi, and G. Capozzi, Org. Mass. Spectrom., 1987, 22, 179.
11. G. Capozzi, O. DeLucchi, V. Lucchini, and G. Modena, Tetrahedron Letters, 1975, 2603.
12. Alchemy is a Tripos Inc. trade mark.
13. G. Capozzi, V. Lucchini, G. Modena, and F. Rivetti, J. Chem. Soc., Perkin Trans. 2, 1975, 900.
14. R. Weiss and C. Schlierf, Synthesis, 1976, 323.
15. V. Speziale, J. Roussel, and A. Lattes, J. Heterocycl. Chem., 1974 11, 771.

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