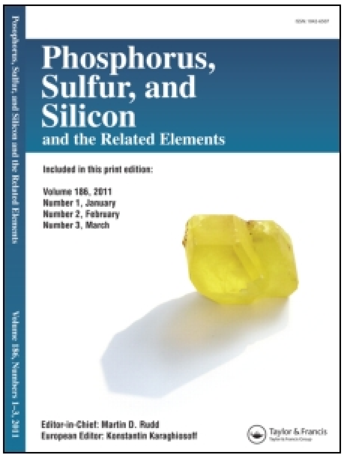

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Eric Block[a]; Venkatachalam Eswarakrishnan[a]
[a] Department of Chemistry, State University of New York at Albany, Albany, New York

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A SIMPLE SYNTHESIS OF 4-METHYLTHIO-1,2-DITHIOLANE: THE PHOTOSYNTHESIS INHIBITOR OF THE GREEN ALGA *CHARA GLOBULARIS*

ERIC BLOCK*† and VENKATACHALAM ESWARAKRISHNAN

Department of Chemistry, State University of New York at Albany,
Albany, New York 12222

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4-Methylthio-1,2-dithiolane, **1**, a photosynthesis inhibitor from *Chara globularis*, has been synthesized from allyl methyl sulfide in 76% overall yield. Derivatives of **1** which have also been prepared include 4-methylthio-1,2-dithiolane 1-oxide, 4-methylsulfonyl-1,2-dithiolane, and 4-methylsulfonyl-1,2-dithiolane 1,1-dioxide.

INTRODUCTION

In connection with a study of naturally occurring low molecular weight organosulfur compounds showing biological activity[1] we sought a simple synthesis of 4-methylthio-1,2-dithiolane (**1**), an odoriferous photosynthesis inhibitor found in the green alga *Chara globularis*.[2] A single synthesis of **1** has been reported[3] but suffers from low yield, from the use of the relatively inaccessible 1,2,3-propanetrithiol as starting material and from the need for chromatographic purification of the key intermediate. We wish to report a simple synthesis of both **1** and certain of its derivatives which takes advantage of the ready availability of 1,3-dibromo-2-(methylthio)propane (**2**).[4]

RESULTS AND DISCUSSION

Following the procedure of Stammer,[4] allyl methyl sulfide was treated with bromine giving **2** in quantitative yield. Since attempts to directly replace the bromine atoms of **2** by sulfur nucleophiles led to rearrangement, **2** was first oxidized with one equivalent of MCPBA to 1,3-dibromo-2-(methylsulfinyl)propane (**3**; 82% yield) (eq. 1). Treatment of **3** with sodium trithiocarbonate, acidification and reduction with lithium aluminum hydride afforded 2-methylthio-1,3-propanedithiol (**4**) in 93% yield from **3** (76% overall yield) and good purity. Treatment of **4** with iodine in ether as described previously[3] led cleanly to dithiolane **1** which was handled in solution due to its high reactivity (eq. 2).

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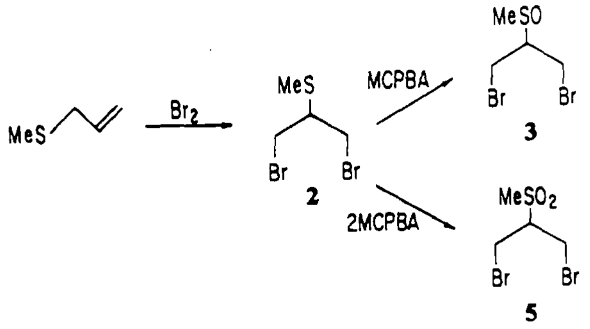
*Author to whom all correspondence should be addressed.
† Fellow of the John Simon Guggenheim Foundation, 1984–1985.



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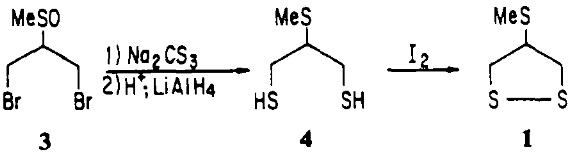

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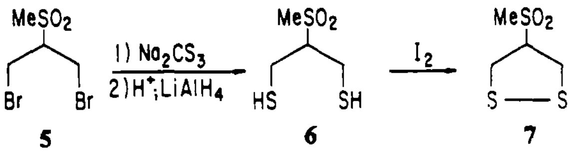

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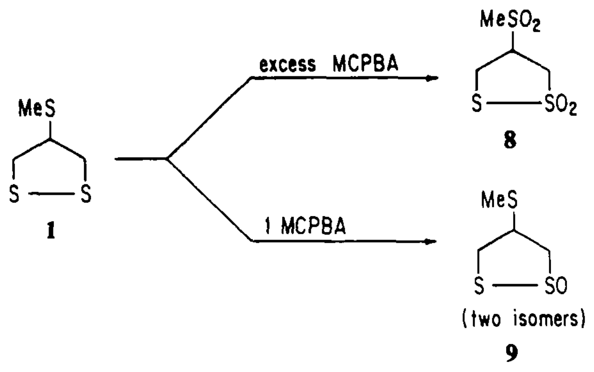
In a similar manner oxidation of **2** with two equivalents of MCPBA gave 1,3-dibromo-2-(methylsulfonyl)propane (**5**; 93% yield) which upon reaction with sodium trithiocarbonate, acidification and reduction as above gave 2-methylsulfonyl-1,3-propanedithiol (**6**) in 31% yield. This upon treatment with iodine gave 4-methylsulfonyl-1,2-dithiolane (**7**), a previously unknown derivative of **1** (eq. 3). In an effort to prepare 4-methylsulfinyl-1,2-dithiolane, the oxidation of dithiolane **1** was studied. We previously reported that oxidation of 1,2,4-trithiolane with *t*-BuOOH—V_2O_5 gave exclusively the antibiotic 1,2,4-trithiolane 4-oxide by oxidation of the sulfide rather than disulfide sulfur.[5,6] To our surprise exposure of **1** to the same oxidant gave only 4-methylthio-1,2-dithiolane 1-oxide (**9**) as a mixture of stereoisomers. Oxidation of **1** with excess MCPBA gave 4-methylsulfonyl-1,2-dithiolane 1,1-dioxide (**8**) (eq. 4).



(4)

EXPERIMENTAL

General. NMR spectra were recorded on a Bruker WH-90 or Varian EM360A or XL-300 spectrometer using tetramethylsilane as internal standard; abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet). Mass spectra were obtained on an AEI MS-902 mass spectrometer. Analytical gas chromatography (GC) was performed on a Perkin-Elmer Sigma 2B Gas Chromatograph interfaced to a Perkin-Elmer Sigma 10B Data Station. A 50 m OV-101 fused silica capillary column was used for all analyses. Melting points are corrected. Ultraviolet (UV) spectra were recorded on a Varian DMS 80 UV-visible spectrophotometer. Tetrahydrofuran and methylene chloride were dried by distillation from lithium aluminum hydride.

1,3-Dibromo-2-(methylsulfinyl)propane (**3**). A solution of *m*-chloroperbenzoic acid (85%; 8.2 g, 0.047 mol) in methylene chloride (100 mL) was added dropwise to a solution of 1,3-dibromo-2-(methylthio)propane (**2**) (10 g, 0.04 mol) in methylene chloride (100 mL) maintained at 0°C. When the addition was complete, the mixture was stirred for 20 min and then filtered to remove most of the *m*-chlorobenzoic acid which was washed with methylene chloride (50 mL). The combined filtrate was washed with 10% $NaHCO_3$ (50 mL), and water (50 mL) and dried ($MgSO_4$). Filtration and evaporation of solvent gave 8.64 g (82%) of **3** as an oil which solidified on standing. Recrystallization from methanol gave colorless crystals, mp 56–58°C, IR (neat) 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (dd, 1 H), 3.89 (dd, 1 H), 3.73 (d, 2 H), 3.3–3.18 (m, 1 H), 2.75 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 64.63, 36.75, 28.22, 27.22.

Anal. Calcd. for $C_4H_8SOBr_2$: C, 18.20; H, 3.05. Found: C, 18.05; H, 2.83.

2-Methylthio-1,3-propanedithiol (**4**). A solution of **3** (3.5 g, 0.013 mol) in methanol (5 mL) was added to an aqueous solution of sodium trithiocarbonate (31 mL, 1.7 M). The reaction mixture was stirred at 50°C for 5 h. Methanol was removed at reduced pressure, the aqueous solution was washed once with methylene chloride (8 mL), then acidified to pH 1 with concentrated sulfuric acid. Carbon disulfide and hydrogen sulfide liberated upon acidification were removed under reduced pressure. The aqueous solution was extracted with methylene chloride (3 × 50 mL) and the combined organic extracts washed with water, dried and concentrated giving an oil. The oil was dissolved in tetrahydrofuran (50 mL) and the solution was cooled to 0°C and treated with lithium aluminum hydride (1.3 g, 0.034 mol). The resulting slurry was stirred at room temperature for 15 h and then was poured slowly into a well-cooled solution of 10 mL water and 4 mL concentrated sulfuric acid. The aqueous solution was extracted with ether (3 × 10 mL) and the combined ether extracts were washed with water, dried and evaporated to give **4** as an oil (1.86 g, 93%), IR (neat) 2950, 2550, and 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09–2.68 (m, 5 H), 2.13 (s, 3 H), 1.72 (br t, 2 H); ^{13}C NMR ($CDCl_3$) δ 52.21, 27.07, 13.70; GC retention time (170°C) 3.82 min.

4-Methylthio-1,2-dithiolane (**1**). A solution of **4** (0.46 g, 3 mmol) in ether (15 mL) was added dropwise to a solution of iodine (1.5 g, 6 mmol) in ether (75 mL). After the addition the solution was stirred at room temperature for 5 min and was then decolorized by treatment with sodium thiosulfate (3 g) and sodium bicarbonate (30 mL of saturated aqueous solution). The ether layer was separated, washed with brine, dried and filtered. GC analysis indicated that the ether layer contained almost pure 4-methylthio-1,2-dithiolane. The ether solution was then diluted with carbon tetrachloride (10 mL) and the ether was removed at 0°C. A golden yellow solution of **1** in carbon tetrachloride was obtained; all analysis was done using this solution as pure **1** polymerizes rapidly; ^1H NMR (CCl_4) δ 3.8–2.8 (m, 5 H), 2.23 (s, 3 H); ^{13}C NMR (CCl_4) δ 50.95, 43.78, 15.10; GC retention time (170°C) 4.29 min.

1,3-Dibromo-2-(methylsulfonyl)propane (**5**). This compound was prepared from **2** by the same procedure used for the preparation of **3** above, except that 2 equiv. of *m*-chloroperbenzoic acid was used. From 1 g (0.004 mol) of **2**, 1.05 g (93%) of **5** was obtained as a white solid, mp 124–125°C (from ethanol); IR (KBr) 1320, 1280, 1270, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (dd, 4 H), 3.77–3.36 (m, 1 H), 3.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 65.96, 41.53, 26.48.

Anal. Calcd. for $C_4H_8SO_2Br_2$: C, 17.16; H, 2.88. Found: C, 17.25; H, 2.86.

2-Methylsulfonyl-1,3-propanedithiol (**6**). A suspension of **5** (2 g, 0.0071 mol) in methanol (8 mL) was added to an aqueous solution of sodium trithiocarbonate (17 mL, 0.029 mol). The reaction mixture was stirred at 50°C for 5 h. Methanol was removed *in vacuo* and the aqueous residue was washed once with methylene chloride (8 mL) and acidified to pH 1 with concentrated sulfuric acid. Liberated carbon disulfide and hydrogen sulfide were removed at reduced pressure. The aqueous solution was extracted with methylene chloride, the extract was washed with water, dried and concentrated to an oil. This oil was dissolved in tetrahydrofuran (30 mL) and treated with lithium aluminum hydride (0.8 g, 0.021 mol) and worked up as before giving dithiol **6** as an oil (0.41 g, 31%), IR 2550, 1320, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36–3.02 (m, 5 H), 2.98 (s, 3 H), 2.06–1.68 (t, 2 H); GC retention time (195°C) 4.74 min.

4-Methylsulfonyl-1,2-dithiolane (**7**). A solution of **6** (0.79 g, 0.0042 mol) is 2 : 1 ether : methylene chloride (15 mL) was added dropwise to a solution of iodine (2.16 g, 0.0085 mol) in ether (110 mL) and the solution was stirred for 5 min. Sodium thiosulfate (4.3 g) was added followed by a saturated solution of sodium bicarbonate (45 mL) and the mixture was stirred until colorless. The organic layer was separated, washed with brine, dried and filtered. Analysis by GC indicated that the solution contained a single higher boiling component different from **6** (retention time at 195°C, 5.46 min). The solution was concentrated at 0°C and $CDCl_3$ was added to give a golden yellow solution of **7**, ^1H NMR ($CDCl_3$) δ 4.46–3.26 (m, 5 H), 2.95 (s, 3 H).

4-Methylthio-1,2-dithiolane 1-oxide (**9**). A solution of **1** (0.456 g, 0.003 mol) in 1 : 1 *tert*-butanol : THF (2 mL) was cooled to −20°C (dry ice/CCl_4 bath) and treated dropwise with a 6% solution of hydrogen peroxide in *tert*-butanol (1.8 mL) containing 0.0037 g V_2O_5. The mixture was slowly warmed to room temperature and then concentrated to a green oil. Preparative TLC (silica gel, 9 : 1 methylene chloride : acetone) gave **8** (0.11 g, 22%) as a colorless solid, mp 71–73°C; IR 1070, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.54–2.74 (m, 5 H), 2.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 69.55, 66.59, 49.50, 47.61, 42.06, 41.46, 15.20. Analysis of the crude product prior to TLC by NMR spectroscopy indicated the presence of traces at most of 4-methylsulfinyl-1,2-dithiolane.

Anal. Calcd. for $C_4H_8S_3O$: C, 28.55; H, 4.79. Found: C, 28.74; H, 4.79.

4-Methylsulfonyl-1,2-dithiolane 1,1-dioxide (**8**). A solution of MCPBA (5.7 g, 85%, 0.033 mol) in methylene chloride (25 mL) was added dropwise to a solution of **1** (1.0 g, 0.0066 mol) in carbon tetrachloride (10 mL) at 0°C. When the addition was complete, the mixture was warmed to room temperature and stirred for 1 h. The solution was then washed with 10% sodium bicarbonate (30 mL), water (30 mL), dried and concentrated to a semisolid (0.74 g). This was washed with methylene chloride (4 × 5 mL) and concentrated *in vacuo* giving **8** as a solid (0.22 g; 15%), IR 1320, 1300, 1220, 1160, 1130 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.56–4.01 (m, 5 H), 3.19 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 59.58, 58.45, 40.22, 34.62; MS m/e 216 (0.01), 201 (0.04), 137 (0.4), 81 (72), 73 (89), 72 (100).

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