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Supplementary Material Available: Full geometries and energies of all structures (19 pages). Ordering information is given on any current masthead.

Reaction of 3-Bromo-2,5-dimethylthiophene 1,1-Dioxide with Some Grignard Reagents. The Formation of a Heterotricycloheptane Derivative

Grigorios Nikitidis,† Salo Gronowitz,*,† Anders Hallberg,†,‡ and Claes Stålhandske§

Division of Organic Chemistry 1 and Division of Inorganic Chemistry 2, Chemical Center, University of Lund, P.O. Box 124, S-221 00 Lund, Sweden

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We have previously studied the reaction of 2,5-dialkyl-3-bromothiophene 1,1-dioxides with organolithium derivatives and found two competing reactions to occur with bromo derivatives. One reaction path, starting with halogen–metal exchange followed by ring opening, leads to lithium enyne sulfinates, which can be trapped with electrophiles such as benzyl bromide. The other path consists of a 1,6-Michael-type addition of the lithium reagent to the 5-carbon of the thiophene 1,1-dioxide, followed by ring opening and elimination of sulfur dioxide and lithium bromide to give enynes (Scheme I). When the same reaction conditions were applied to 3-chloro derivatives, the product was found to be a mixture of the enyne isomers, indicating that the latter reaction path was followed exclusively.[1-3]

We have now studied the reaction of 3-bromo-2,5-dimethylthiophene 1,1-dioxide with Grignard reagents.

The addition of ethylmagnesium bromide to an ethereal solution of 1 at −20 °C gave a compound in high yield with melting point 83–85 °C, which gave a correct analysis for $C_{14}H_{19}BrO_2S$. The number of carbon atoms indicated that it had been formed from 2 mol of the thiophene 1,1-dioxide and 1 mol of ethylmagnesium bromide. Its IR spectrum indicated the presence of a triple bond (2230 cm^{-1}). The presence of a methylacetylenic group was further confirmed by mercury(II) sulfate-catalyzed hydration[4] of the product to yield a carbonyl derivative with an acetonyl grouping.

A detailed NMR study was carried out on the product. DEPT (distortionless enhancement by polarization transfer) experiments showed the presence of five CH_3 groups with ^{13}C shifts at δ 3.75, 3.85, 6.34, 10.20, and 14.58. Two of the methyl groups (at δ 1.37 and 1.30) were singlets, and one (at 1.41) showed a very small coupling in the ^1H NMR spectrum, and therefore are most probably bound to quaternary carbons. In addition, the DEPT experiments showed one CH_2-carbon at δ 18.41, two CH-carbons at δ 44.66 and 52.65, and six carbons without hydrogens at δ 32.68, 40.52, 48.52, 64.16, 72.16, and 83.47.

Carrying out the reaction with 3-bromo-4-deuterio-2,5-dimethylthiophene 1,1-dioxide (2) led to a product in which the ^1H resonances at δ 3.12 and 2.67 had disappeared. In the ^2H NMR spectrum, the deuterium resonances were observed at δ 3.07 and 2.63. The NMR spectral investigation thus indicated a cage structure.

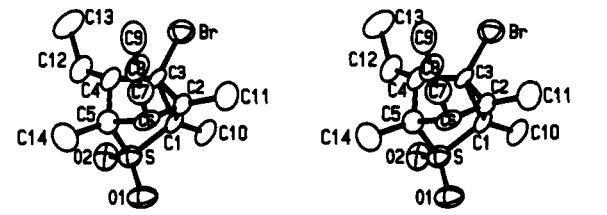


Figure 1. Stereoscopic view of one of the two independent molecules with atomic numbering.

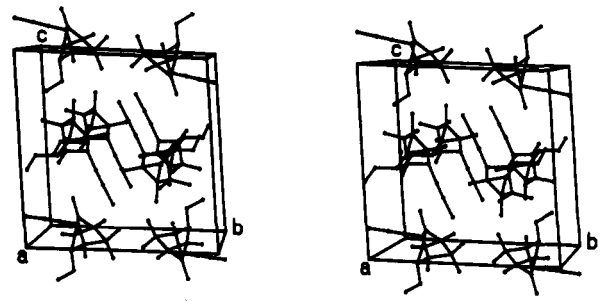


Figure 2. The packing of the molecules in the unit cell.

In order to prove the structure and to determine the stereochemistry of the compound, an X-ray crystallographic investigation was undertaken, the results of which clearly showed that the compound obtained from 1 was 2-bromo-*exo*-3-ethyl-1,4,6-trimethyl-*endo*-5-(1-propynyl)-7-thiatricyclo[2.2.1.$0^{2,6}$]heptane 7,7-dioxide (**6**). The NMR data are in complete accordance with this structure. The formation of **6** can probably be rationalized in the following way (Scheme II). 1,4-Michael addition of ethylmagnesium bromide to the 3-position of 1 gives the carbanion **3**,[5] which in Michael fashion adds to another molecule of 1 in the 3-position, giving the carbanion **4**. An intramolecular attack of this carbanion on the 4-position of the first sulfone molecule gives the carbanion **5**, which in a nucleophilic substitution attacks the 5-position with sulfinate as leaving group. Elimination of sulfur dioxide and bromide ion then gives **6**. This type of elimination leading to acetylenes has been observed by us in many reactions of thiophene 1,1-dioxides, for instance, the tandem cyclodimerization ring opening that leads to unsymmetrical highly substituted benzene derivatives.[6,7]

Reaction of the deuterated compound 2 provided compound **7**. *n*-Propylmagnesium chloride reacted similarly

† Division of Organic Chemistry 1.

‡ Present address: Department of Organic Pharmaceutical Chemistry, Box 574, Uppsala Biomedical Center, S-751 23 Uppsala, Sweden.

§ Division of Inorganic Chemistry 2.

(1) Karlsson, J. O.; Gronowitz, S.; Hallberg, A. *Chem. Scr.* **1982**, *20*, 37.

(2) Karlsson, J. O.; Gronowitz, S.; Hallberg, A. *Acta Chem. Scand. Ser. B* **1982**, *B36*, 341.

(3) Svensson, A.; Karlsson, J. O.; Hallberg, A. *J. Heterocycl. Chem.* **1983**, *20*, 729.

(4) According to the literature, the carbonyl group would be formed preferentially next to a secondary or tertiary carbon: March, J. *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*; Wiley-Interscience: New York, 1985; p 683.

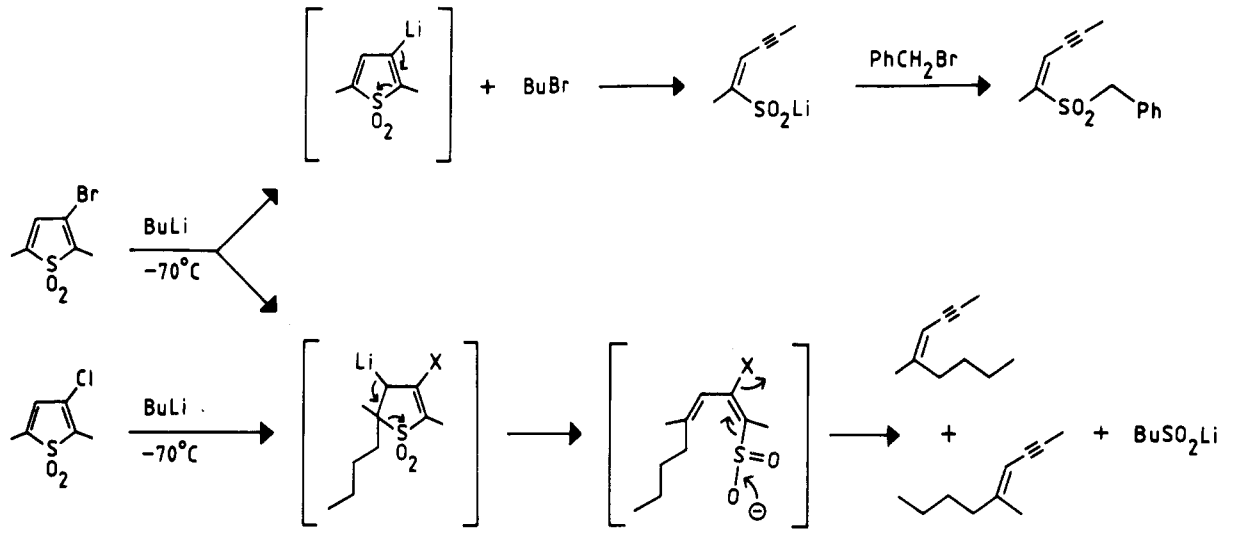
(5) Michael addition at the 3-position of thiophene 1,1-dioxides has been observed in the reaction with secondary amines in aqueous solution: (a) Wrobel, J. T.; Kabzinska, K. *Bull. Acad. Pol.* **1974**, *22*, 129. (b) Gronowitz, S.; Hallberg, A.; Nikitidis, G. *Tetrahedron* **1987**, *43*, 4793. In the reaction with thiolates and alkoxides: Gronowitz, S.; Nikitidis, G.; Hallberg, A. *Chem. Scr.* **1988**, *28*, 289. Organolithium derivatives prefer to attack the 5-position of the thiophene 1,1-dioxides in a 1,6-Michael-type addition reaction (see refs 1-3).

(6) Gronowitz, S.; Nikitidis, G.; Hallberg, A.; Servin, R. *J. Org. Chem.* **1988**, *53*, 3351.

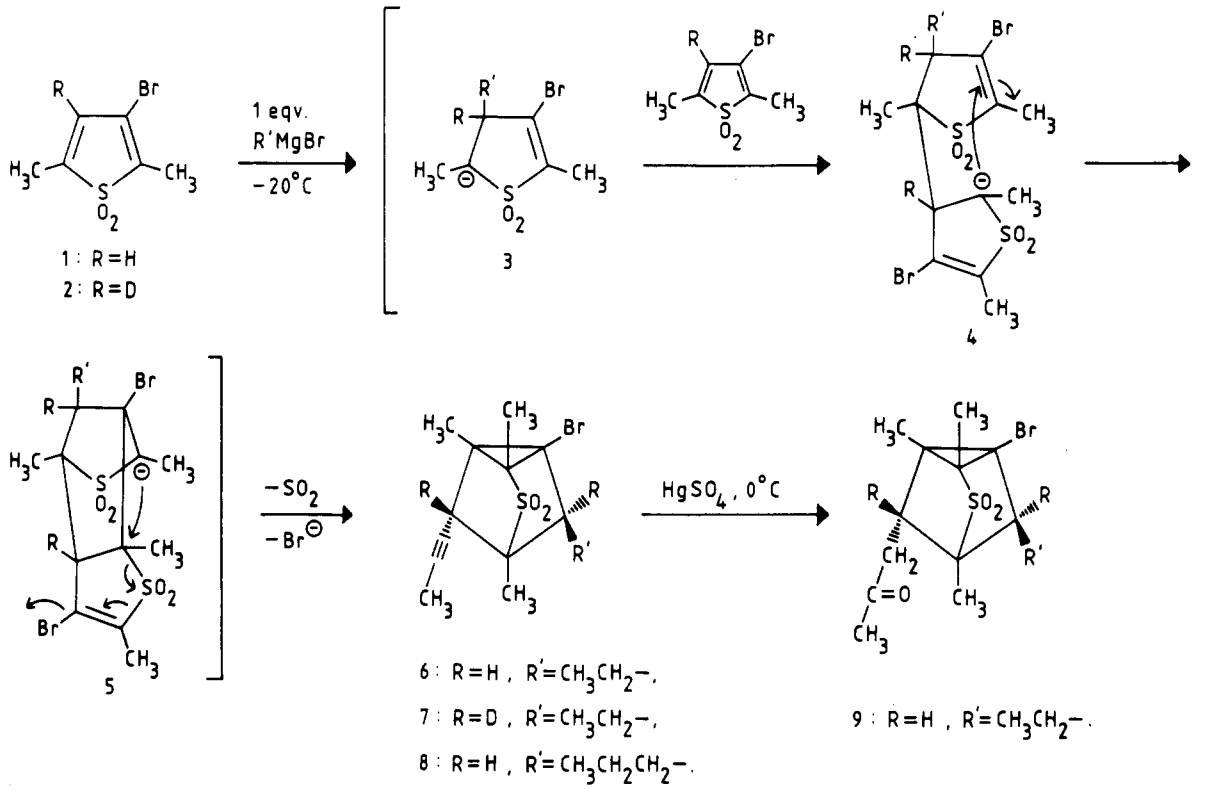
(7) Gronowitz, S.; Nikitidis, G.; Hallberg, A.; Stålhandske, C. *Acta Chem. Scand.*, in press.

0022-3263/91/1956-4064$02.50/0

Scheme I



Scheme II



with 1 and gave a 52% yield of 2-bromo-1,4,6-trimethyl-*exo*-3-propyl-*endo*-5-(1-propynyl)-7-thiatricyclo-[2.2.1.$0^{2,6}$]heptane 7,7-dioxide (8). All attempts to generalize the reaction by using methylmagnesium bromide or phenylmagnesium bromide have hitherto been unsuccessful.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer and were in accordance with the proposed structures. The NMR spectra (^{1}H, ^{13}C, HETCOR, selective decoupling, DEPT, and COSY; $CDCl_3$ as solvent) were recorded on a Varian XL 300 spectrometer. Quantitative gas chromatographic analyses were performed on a Varian 3300 gas chromatograph equipped with a 2-m column of 3% OV 17 on Gaschrom Q, 100–120 mesh, and a flame ionization detector. Mass spectra were obtained on a Finnigan 4021 (data system Incos 2100) gas chromatograph mass spectrometer operating at 70 eV and on a JEOL JMS-SX 102 spectrometer. Elemental microanalyses were performed at Dornis und Kolbe, Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany, and Mikro Kemi AB, Uppsala, Sweden. Column chromatography was carried out using Fluka Aluminum Oxide (Al_2O_3) type 507C neutral (100–125 mesh) and pentane/dichloromethane as eluent. The Grignard reagents, ethylmagnesium bromide and *n*-propylmagnesium chloride, were of 3 and 2.0 M solutions in diethyl ether, respectively, purchased from Aldrich Chemical Co., Inc. The purity of the 3-chloroperbenzoic acid used was 85%.

3-Bromo-4-deuterio-2,5-dimethylthiophene 1,1-Dioxide (2). To a stirred solution of 3-bromo-4-deuterio-2,5-dimethylthiophene (10; 19.2 g, 0.10 mol) in dichloromethane (400 mL) was added 3-chloroperbenzoic acid (64 g) in portions, and the solution was stirred 12 h at room temperature. Using the workup procedure of van Tilborg et al.[8,9] followed by recrystallization from ethanol

(8) van Tilborg, W. J. M. *Synthetic Commun.* **1976**, *6*, 583.

afforded the title product **2** (18.3 g, 82%, mp 97–99 °C): ^{1}H NMR ($CDCl_3$) δ 2.16 (q, 3 H, 2-CH_3, J = 0.8 Hz), 2.09 (q, 3 H, 5-CH_3, J = 0.8 Hz); ^{2}H NMR ($CHCl_3$) δ 6.33 (s, 1 D, 4-D); mass spectrum m/e 223/225.

2-Bromo-*exo*-3-ethyl-1,4,6-trimethyl-*endo*-5-(1-propynyl)-7-thiatricyclo[2.2.1.0^{2,6}]heptane 7,7-Dioxide (6). A solution of ethylmagnesium bromide in anhydrous diethyl ether (1.9 mL of 3.0 M, 5.5 mmol) was added dropwise to a stirred solution of 3-bromo-2,5-dimethylthiophene 1,1-dioxide[1] (1.12 g, 5 mmol), in anhydrous ether (20 mL), at −20 °C under nitrogen. After being stirred for 2 h, the reaction mixture was hydrolyzed with saturated ammonium chloride. The organic phase was separated, and the aqueous phase was extracted three times with ether (3 × 25 mL). The combined ethereal phase was washed twice with water (2 × 50 mL), dried over magnesium sulfate, and concentrated. Column chromatography followed by recrystallization from ethanol afforded **6** (0.6 g, 73%, mp 83–85 °C): IR 2230 (C≡C stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.12 (q, 1 H, 5-H, J = 2.4 Hz), 2.67 (b t, 1 H, 3-H, J = 5.9, 0.6 Hz), 1.97 (dsxt, 1 H, 3-CH_2, J = 15.0, 7.6, 5.9 Hz), 1.88 (d, 3 H, acetylenic CH_3, J = 2.4 Hz), 1.81 (dsxt, 1 H, 3-CH_2, J = 15.0, 7.6, 5.9 Hz), 1.41 (d, 3 H, 4-CH_3, J = 0.6 Hz), 1.37 (s, 3 H, 1-CH_3), 1.30 (s, 3 H, 6-CH_3), 1.08 (t, 3 H, 3-CH_3, J = 7.6 Hz); HETCOR (^{13}C-^{1}H NMR) δ 52.65–2.67, 44.66–3.12, 18.41–1.97 and 1.81, 14.58–1.08, 10.20–1.30, 6.34–1.37, 3.85–1.41, 3.75–1.88.

The multiplicity was confirmed by DEPT (five CH_3 carbons at δ 3.75, 3.85, 6.34, 10.20 and 14.58, one CH_2 carbon at δ 18.41, two CH carbons at δ 44.66 and 52.65, and six carbons without hydrogen at δ 32.68, 40.52, 48.52, 64.16, 72.16, and 83.47).

Irradiation at δ 3.12 resulted in a singlet at δ 1.88. Irradiation at δ 2.67 resulted in a sextet at δ 1.97 (J = 15.0 and 7.6 Hz), a sextet at δ 1.88 (J = 15.0 and 7.6 Hz), and a singlet at δ 1.41: mass spectrum m/e 330/332. Anal. Calcd for $C_{14}H_{19}BrO_2S$: C, 50.7; H, 5.8; Br, 24.1. Found: C, 50.5; H, 5.8; Br, 24.3.

2-Bromo-*endo*-3,*exo*-5-dideuterio-*exo*-3-ethyl-1,4,6-trimethyl-*endo*-5-(1-propynyl)-7-thiatricyclo[2.2.1.0^{2,6}]heptane 7,7-Dioxide (7). A solution of ethylmagnesium bromide in anhydrous diethyl ether (3.8 mL of 3.0 M, 12 mmol) was added dropwise to a stirred solution of 3-bromo-4-deuterio-2,5-dimethylthiophene 1,1-dioxide (**2**; 2.24 g, 10 mmol) in anhydrous ether (40 mL) at −20 °C under nitrogen. After being stirred for 2 h, the reaction mixture was hydrolyzed with 10% hydrochloric acid, washed with saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated. Column chromatography followed by recrystallization from ethanol afforded **7** (1.0 g, 60%, mp 82–83 °C): IR 2230 (C≡C stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96 (qv, 1 H, 3-CH_2, J = 15.0, 7.6 Hz), 1.88 (s, 3 H, acetylenic CH_3), 1.81 (qv, 1 H, 3-CH_2, J = 15.0, 7.6 Hz), 1.41 (s, 3 H, 4-CH_3), 1.37 (s, 3 H, 1-CH_3), 1.29 (s, 3 H, 6-CH_3), 1.08 (t, 3 H, 3-CH_3, J = 7.6 Hz); ^{2}H NMR ($CHCl_3$) δ 3.07 (s, 1 D, 5-D), 2.63 (s, 1 D, 3-D); mass spectrum m/e 332/334.

2-Bromo-1,4,6-trimethyl-*exo*-3-*n*-propyl-*endo*-5-(1-propynyl)-7-thiatricyclo[2.2.1.0^{2,6}]heptane 7,7-Dioxide (8). A solution of *n*-propylmagnesium chloride in anhydrous diethyl ether (11 mL of 2 M, 22 mmol) was added dropwise to a stirred solution of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (4.5 g, 20 mmol) in anhydrous ether (150 mL) at −20 °C under nitrogen. After being stirred for 2 h, the reaction mixture was treated as described previously for **7**. Column chromatography afforded **8** as an oil (1.8 g, 52%): IR 2230 (C≡C stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (q, 1 H, 5-H, J = 2.4 Hz), 2.73 (b t, 1 H, 3-H, J = 5.5 Hz), 1.86 (d, 3 H, acetylenic CH_3, J = 2.4 Hz), 1.9–1.3 (qm, 4 H, 3-CH_2CH_2), 1.39 (s, 3 H, 4-CH_3), 1.34 (s, 3 H, 1-CH_3), 1.28 (s, 3 H, 6-CH_3), 0.93 (t, 3 H, 3-CH_3, J = 7.3 Hz).

The multiplicity was confirmed by DEPT (five CH_3 carbons at δ 3.69, 3.83, 6.18, 10.21, and 14.14, two CH_2 carbons at δ 23.16 and 27.20, two CH carbons at δ 44.58 and 50.62, and six carbons without hydrogen at δ 32.68, 40.45, 48.74, 64.09, 72.18, and 83.44): mass spectrum m/e 344/346. Anal. Calcd for $C_{15}H_{21}BrO_2S$: C, 52.2; H, 6.1; Br, 23.1. Found: C, 52.1; H, 6.1; Br, 23.2.

2-Bromo-*exo*-3-ethyl-1,4,6-trimethyl-*endo*-5-acetonyl-7-thiatricyclo[2.2.1.0^{2,6}]heptane 7,7-Dioxide (9). 2-Bromo-*exo*-3-ethyl-1,4,6-trimethyl-*endo*-5-(1-propynyl)-7-thiatricyclo-[2.2.1.0^{2,6}]heptane 7,7-dioxide (**6**; 0.5 g, 1.5 mmol) was added to an ice-cooled suspension of mercury(II) sulfate[10] (50 mg, 0.17 mmol) in aqueous formic acid (10 mL, 85%) with vigorous stirring. After the solution was stirred overnight, saturated ammonium sulfate (50 mL) was added to the reaction mixture, which was then extracted with toluene (3 × 25 mL). The combined extracts were dried over magnesium sulfate and filtered through silica, the silica being subsequently washed with dichloromethane. Evaporation of the solvents and recrystallization from ethanol produced **9** (0.48 g, 91%): mp 113–118 °C; IR 1715–1720 (C=O stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.08 (dd, 1 H, 5-H, J = 7.5, 4.2 Hz), 2.54 (dd, 1 H, 5-CH_2, J = 18.0, 7.5 Hz), 2.44 (dd, 1 H, 5-CH_2, J = 18.0, 4.2 Hz), 2.24 (s, 3 H, 5-CH_3), 2.16 (t, 1 H, 3-H, J = 5.7 Hz), 1.99 (dsxt, 1 H, 3-CH_2, J = 15.0, 7.6, 5.7 Hz), 1.81 (dsxt, 1 H, 3-CH_2, J = 15.0, 7.6, 5.7 Hz), 1.42 (s, 3 H, 4-CH_3), 1.26 (s, 3 H, 1-CH_3), 1.09 (s, 3 H, 6-CH_3), 1.05 (t, 3 H, 3-CH_3, J = 7.6 Hz); mass spectrum m/e 348/350. Anal. Calcd for $C_{14}H_{21}BrO_3S$: C, 48.1; H, 6.1; Br, 22.9. Found: C, 48.3; H, 6.1; Br, 22.8.

3-Bromo-4-deuterio-2,5-dimethylthiophene (10). *n*-Butyllithium (107 mL, 2.06 N) in hexane was added dropwise to a solution of 3,4-dibromo-2,5-dimethylthiophene[11] (54.0 g, 0.2 mol) in anhydrous diethyl ether (500 mL) under a nitrogen atmosphere at −70 °C. After 30 min of vigorous stirring, deuterium oxide (30 mL) was added dropwise with continuous stirring at −70 °C for 1 h. The reaction mixture was allowed to reach room temperature, washed twice with water, and dried over magnesium sulfate. Distillation (85–86 °C (18 mmHg)) afforded **10** (34.2 g, 89%). According to ^{1}H NMR >98% deuteration occurred: ^{1}H NMR ($CDCl_3$) δ 2.40 (q, 3 H, 2-CH_3, J = 0.6 Hz), 2.33 (q, 3 H, 5-CH_3, J = 0.6 Hz); mass spectrum m/e 191/193; ^{2}H NMR ($CHCl_3$) δ 6.52 (s, 1 D, 4-D).

Acknowledgment. Grants from the Swedish Natural Science Research Council to S.G. and A.H. are gratefully acknowledged.

Supplementary Material Available: Tables of atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and complete descriptions of the X-ray structure determination of **6** (6 pages). Ordering information is given on any current masthead page.

(9) van Tilborg, W. J. M.; Smael, P.; Visser, J. P.; Kouvenhoven, C. G.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 85.

(10) Fieser & Fieser. *Reagents for Organic Synthesis*; John Wiley & Sons: New York 1967; Vol. 1, pp 658.

(11) Melles, J. L.; Backer, H. J. *Recl. Trav. Chim. Pays-Bas* **1953**, *72*, 314.

An Improved Synthesis of Isomerically Pure *cis*-1-Bromopropene

Carl E. Fuller and Donald G. Walker*

Bristol-Myers Squibb Company, Pharmaceutical Research Institute, Chemical Process Research, P.O. Box 4755, Syracuse, New York 13221-4755

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As a part of a program to develop new synthetic approaches to the oral antibiotic candidate cefprozil monohydrate,[1-4] we required multikilogram quantities of isomerically pure (>99%) *cis*-1-bromopropene (**3**). Apart from careful spinning band distillation of the commercial mixture (Z/E = 70/30)[5-7] or desilicobromination of a 1,2-di-

(1) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833.

(2) Baker, S. R.; Roth, G. P.; Sapino, C. *Synth. Commun.* **1990**, *20*, 2185.

(3) Kant, J.; Sapino, C.; Baker, S. R. *Tetrahedron Lett.* **1990**, *31*, 3389.

(4) Farina, V.; Baker, S. R.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 6043.

(5) Seyferth, D.; Vaughn, L. G. *J. Organomet. Chem.* **1963**, *1*, 138.

(6) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379.

0022-3263/91/1956-4066$02.50/0