Dimerization Reactions of Some Thiophene 1,1-Dioxides. Preparation of Benzo[*b*]thiophene 1,1-Dioxides

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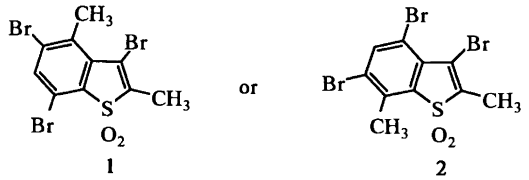
Heating of 3,5-dibromo-2-methyl- and 3,5-dibromo-2-phenyl-thiophene 1,1-dioxide, and of 4-bromo-2-methylthiophene 1,1-dioxide, in alcohol leads to dimerization followed by elimination of hydrogen bromide to give benzo[*b*]thiophene 1,1-dioxides.

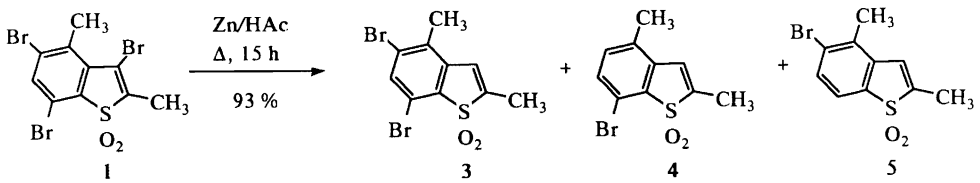
We have recently shown that some 3-halo-2,5-dialkylthiophene 1,1-dioxides undergo a tandem dimerization ring-opening reaction, which provides a short and convenient method for the synthesis of unsymmetrically pentasubstituted benzenes.[1] We have recently found that other bromo-substituted thiophene 1,1-dioxides react differently and eliminate hydrogen bromide after cycloaddition to give benzo[*b*]thiophene 1,1-dioxides. Refluxing of 3,5-dibromo-2-methylthiophene 1,1-dioxide in *t*-butyl alcohol for 120 h gave a tribromodimethylbenzo[*b*]thiophene 1,1-dioxide in 65 % yield, which depending upon the relative orientations of the diene and dienophile, could be either 3,5,7-tribromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide (**1**) or 3,4,6-tribromo-2,7-dimethylbenzo[*b*]thiophene 1,1-dioxide (**2**). Only the monosubstituted side reacts as the dienophile.



1 **2**

It was not possible to differentiate between **1** and **2** by simple ^1H and ^{13}C spectroscopy, and the solubility of the compound was not sufficient to permit INADEQUATE experiments. The product was proved to be **1** in the following way. Debromination of **1** with zinc dust in glacial acetic acid gave one dibromo derivative and two monobromo derivatives (Scheme 1) in the proportions 52:38:10, which were separated by HPLC. The dibromo derivative was shown to be 5,7-dibromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide (**3**) by the observation of nuclear Overhauser effects (NOE) on both methyl groups when the thiophenic proton in the 3-position was irradiated. If the primary product had been **2**, the dibrominated product would have been 4,6-dibromo-2,7-dimethylbenzo[*b*]thiophene 1,1-dioxide, and should only show an NOE effect at one methyl group.

^1H NMR spectroscopy showed that the two monobromo derivatives obtained upon zinc debromination of **1** were 7-bromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide (**4**) and 5-bromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide (**5**). The key structural proof was the presence of a long-range coupling of 0.7 Hz between the 4-methyl group and the 5-hydrogen of **4**.



1 **3** **4** **5**

52 : 38 : 10

Scheme 1.

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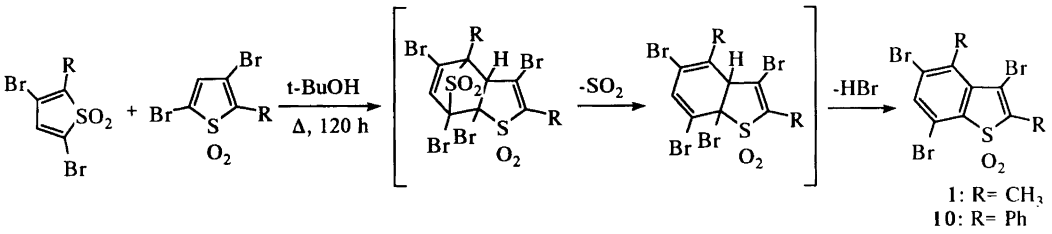


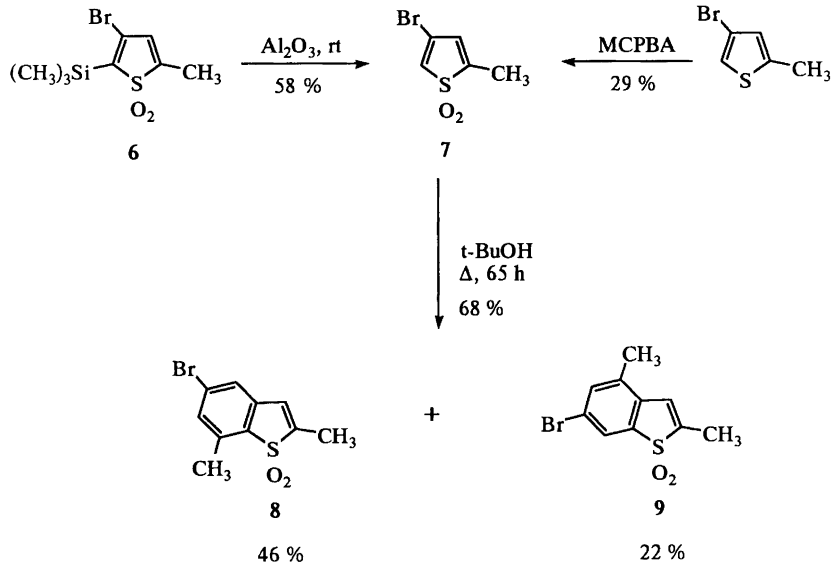
Scheme 2.

The cycloaddition of 3,5-dibromo-2-methylthiophene 1,1-dioxide thus occurs with high regioselectivity and, as observed previously,[1] a dienophile with one electron-withdrawing group and an unsymmetrical diene with a 2-substituent are expected to react in such a way that the two substituents are *para*-oriented.[2] It is also interesting to note that the formation of the benzo[*b*]thiophene 1,1-dioxides occurs through a *cis*-elimination of hydrogen bromide[3] (Scheme 2).

In order to investigate the scope of this benzo[*b*]thiophene 1,1-dioxide synthesis, we studied the reaction of 4-bromo-2-methylthiophene 1,1-dioxide (**7**). In this connection, we found a more convenient method for its preparation. A yield of only 29 % was obtained when 4-bromo-2-methylthiophene was oxidized in the usual way with 3-chloroperbenzoic acid, probably due to the instability of the product. However, when 4-bromo-2-methylthiophene was treated with LDA, followed by trimethylsilyl chloride,[4] it was transformed into 3-bromo-5-methyl-2-trimethylsilylthiophene, which could easily be oxidized to give 3-bromo-5-methyl-2-trimethylsilylthiophene 1,1-dioxide (**6**) in 85 % yield. Desilylation on Al_2O_3 provided 4-bromo-2-methylthiophene 1,1-dioxide (**7**) in 58 % yield.

Refluxing of **7** for 65 h in *t*-butyl alcohol gave two products, which were separated by HPLC in 46 and 22 % yield, respectively. NOE experiments clearly showed that the compounds formed by dimerization and elimination of hydrogen bromide were 5-bromo-2,7-dimethylbenzo[*b*]thiophene 1,1-dioxide (**8**) (NOE effect on the hydrogen at 7.33 ppm when the methyl group at 2.59 ppm was irradiated) and 6-bromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide (**9**) (NOE effect on hydrogens 3 and 5 when the methyl group at 2.37 ppm was irradiated) (Scheme 3). Furthermore, the ^1H NMR spectrum of compound **9** contained a long-range coupling of 0.6 Hz between the 3- and 7-hydrogens. Thus, the dienophilic part of 7 was the 3-bromo side; no selectivity, however, in the mode of addition to the diene was observed. In contrast with 3,5-dibromo-2-methylthiophene 1,1-dioxide, the isomeric 2,3-dibromo-5-methylthiophene 1,1-dioxide did not undergo dimerization even after reflux for 10 days.

When 3,5-dibromo-2-phenylthiophene was oxidized, both the dioxide and its dimerization product were formed. Reflux of an alcohol solution of the crude product gave 3,5,7-tribromo-2,4-diphenylbenzo[*b*]thiophene 1,1-dioxide (**10**) in 86 % yield. The structure assignment is based on comparison with the analogous methyl compound.



Scheme 3.

Experimental

Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer and were in accordance with the proposed structures. The NMR spectra (^1H, ^{13}C, selective decoupling, COSY and NOE experiments, $CDCl_3$ as the 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. High resolution mass spectra were recorded 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 aluminium oxide type-507 C neutral and pentane–dichloromethane (1:1) as the eluent. The purity of the 3-chloroperbenzoic acid used was 85 %.

3,5,7-Tribromo-2,4-dimethylbenzo[b]thiophene 1,1-dioxide (**1**). To a solution of 3-chloroperbenzoic (40.6 g, 0.2 mol) in 1,2-dichloroethane (350 ml), 3,5-dibromo-2-methylthiophene[4] (20.45 g, 0.08 mol) was added, and the solution was heated on an oil bath at 90 °C for 24 h. 3-Chlorobenzoic acid was filtered from the cooled solution, and the filtrate was washed twice with a saturated sodium hydrogencarbonate solution. The solution was dried over magnesium sulfate, treated with activated charcoal, filtered, and evaporated at room temperature. The crude product, consisting of 3,5-dibromo-2-methylthiophene 1,1-dioxide (according to the mass spectrum) (ca. 18 g, 78 %), was dissolved in *t*-butyl alcohol (100 ml) and was refluxed for 5 days (120 h). During the reaction, dark crystals were formed. This mixture was washed with dichloromethane (50 ml), and the organic solvents were evaporated. The remaining product was washed with pentane and recrystallized from ethanol to give 8.75 g (51 %) of the title compound as yellow crystals, m.p. 185–186 °C. ^1H NMR ($CDCl_3$): δ 7.87 (s, 1 H, 6-H), 2.87 (s, 3 H, 4-CH_3), 2.25 (s, 3 H, 2-CH_3). MS: *m/z* 428/430/442/434. Anal. $C_{10}H_7Br_3O_2S$: C, H, Br.

5,7-Dibromo-2,4-dimethylbenzo[b]thiophene 1,1-dioxide (**3**), *7-Bromo-2,4-dimethylbenzo[b]thiophene 1,1-dioxide* (**4**) *and 5-Bromo-2,4-dimethylbenzo[b]thiophene 1,1-dioxide* (**5**). To a suspension of dry zinc powder[5] (481 mg, 7.5 mmol) in glacial acetic acid (10 ml) was added, 3,5,7-tribromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide (**1**) (431 mg, 1.0 mmol). The reaction mixture was refluxed for 15 h. The remaining zinc powder was filtered from the cooled suspension, and the filtrate was diluted in water and extracted with dichloromethane (3×25 ml). The combined organic phase was washed with a saturated sodium hydrogencarbonate solution and dried over magnesium sulfate. Removal of the solvent afforded 280 mg (93 %) of a residue, which consisted of three isomers according to GLC in the ratio 52:38:10. According to the mass spectrum, 52 % of the residue was the dibromo isomer **3** and 48 % of the monobromo isomers **4** and **5**. The three isomers were separated by HPLC [RI detector (128) column packed with Nucleosil OH 7 μm 250×1/2", heptane and ethyl acetate (7:3) as the eluent, flow 2.5 ml min^{-1}] to give 110 mg (31.3 %) of **3**, m.p. 172–172.5 °C, 20 mg (7.3 %) of **4**, m.p. 149–152 °C and 75 mg (27.5 %) of **5**, m.p. 141–141.5 °C. ^1H NMR ($CDCl_3$) for **3**: δ 7.75 (s, 1 H, 6-H), 6.85 (q, 1 H, 3-H, J = 1.8 Hz), 2.39 (s, 3 H, 4-CH_3), 2.27 (d, 3 H, 2-CH_3, J = 1.8 Hz). **4**: δ 7.39 (d, 1 H, 6-H, J = 8.1 Hz), 7.16 (dq, 1 H, 5-H, J = 8.1, 0.7 Hz), 6.81 (q, 1 H, 3-H, J = 1.8 Hz), 2.33 (br s, 3 H, 4-CH_3), 2.24 (d, 3 H, 2-CH_3, J = 1.8 Hz). **5**: δ 7.65 (d, 1 H, 6-H, J = 8.0 Hz), 7.41 (br d, 1 H, 7-H, J = 8.0 Hz), 6.94 (m, 1 H, 3-H, J = 1.8, 0.9 Hz), 2.44 (s, 3 H, 4-CH_3), 2.25 (d, 3 H, 2-CH_3, J = 1.8 Hz). To confirm the structure, NOE experiments were carried out on **3**. Irradiation at δ 6.85 resulted in NOE effects at 2.39 and 2.27 ppm (thus supporting the assignment of the proposed structure). MS: *m/z* for **3** 350/352/354, and for **4** and **5** 272/274. Anal. $C_{10}H_8Br_2O_2S$ (**2**): C, H, Br. Anal. $C_{10}H_9BrO_2S$ (**4** and **5**): C, H, Br.

3-Bromo-5-methyl-2-trimethylsilylthiophene 1,1-dioxide (**6**). To a vigorously stirred suspension of 3-chloroperbenzoic acid (10.1 g, 44.0 mmol) and solid sodium hydrogencarbonate (as an acid acceptor; 4.2 g, 50.0 mmol), in dichloromethane (150 ml) was added 3-bromo-5-methyl-2-trimethylsilylthiophene[6] (5.0 g, 20.0 mmol). The reaction suspension was stirred at room temperature for 72 h. (If no sodium hydrogencarbonate was added, desilylation occurred for 20–25 % of the starting material and the oxidation was complete within 2–3 h.) The 3-chloroperbenzoic acid precipitated when the reaction was cooled to −50 °C and was filtered off.

The filtrate was washed twice with saturated sodium carbonate solution, and several times with water. The organic phase was dried over magnesium sulfate, filtered, and evaporated at 0 °C. The crude product, 4.89 g (87 % more than 90 % pure) of **6**, was stored in a sealed bottle in the refrigerator. (It was unstable when concentrated; one month at 10 °C gave considerable decomposition, but in cooled dichloromethane solution it was stable for longer periods: > two years.) ^1H NMR ($CDCl_3$): δ 6.27 (q, 1 H, 4-H, J = 1.92 Hz), 2.15 (d, 3 H, 5-CH_3, J = 1.92 Hz), 0.42 [s, 9 H, 2-Si(CH_3)$_3$]. MS: *m/z* 280/282. Peak matching on M^+. Calc. for $C_8H_{13}BrO_2SSi$: 279.9589. Found: 279.9600.

4-Bromo-2-methylthiophene 1,1-dioxide (**7**). When 3-bromo-5-methyl-2-trimethylsilylthiophene[6] (5.0 g, 20.0 mmol) was oxidized as described above, the title compound (**7**) was formed during column chromatography of 3-bromo-5-methyl-2-trimethylsilylthiophene 1,1-dioxide on aluminium oxide. Recrystallization of the product from ethanol gave 2.45 g (58 %) of **7**, m.p. 89.5–90.5 °C. By

direct oxidation of 4-bromo-2-methylthiophene[7] as described above (but without sodium hydrogencarbonate), the title compound (**7**) was obtained in 29 % yield. ^{1}H NMR ($CDCl_3$): δ 6.78 (d, 1 H, 5-H, J = 1.2 Hz), 6.30 (dq, 1 H, 3-H, J = 1.9, 1.2 Hz), 2.16 (d, 3 H, 2-CH_3, J = 1.9 Hz). MS: *m/z* 208/210. Anal. $C_5H_5BrO_2S$: C, H, Br.

*5-Bromo-2,7-dimethylbenzo[*b*]thiophene 1,1-dioxide* (**8**) *and 6-Bromo-2,4-dimethylbenzo[*b*]thiophene 1,1-dioxide* (**9**). A solution of 4-bromo-2-methylthiophene 1,1-dioxide (1.46 g, 7.0 mmol) in *t*-butyl alcohol (30 ml) was refluxed with vigorous stirring. After 65 h two isomers were formed. Removal of the solvent and purification of the crude product by HPLC [RI detector (128), column packed with Nucleosil OH 7 μm 250×1/2″, heptane–ethyl acetate (7:3) as the eluent, flow 2.0 ml min^{-1}] afforded 435 mg (46 %) of **8**, m.p. 169–170 °C, and 210 mg (22 %) of **9**, m.p. 114–116 °C. ^{1}H NMR ($CDCl_3$): for **8**: δ 7.33 (br m, 1 H, 6-H, J = 1.2, 0.7 Hz), 7.19 (br d, 1 H, 4-H, J = 1.2 Hz), 6.66 (q, 1 H, 3-H, J = 1.8 Hz), 2.59 (br d, 3 H, 7-CH_3, J = 0.7 Hz), 2.19 (d, 3 H, 2-CH_3, J = 1.8 Hz). ^{13}C NMR ($CDCl_3$): for **8**: δ 9.13, 16.67, 123.34, 124.80, 127.58, 133.27, 133.65, 133.76, 136.56 and 142.38. NOE (CD_2Cl_2): Irradiation at 2.59 ppm resulted in an NOE effect at 7.33 ppm. ^{1}H NMR ($CDCl_3$): for **9**: δ 7.65 (dd, 1 H, 7-H, J = 0.8, 0.6 Hz), 7.49 (dq, 1 H, 5-H, J = 0.8, 0.7 Hz), 6.86 (dq, 1 H, 3-H, J = 1.8, 0.6 Hz), 2.37 (br d, 3 H, 4-CH_3, J = 0.7 Hz), 2.21 (d, 3 H, 2-CH_3, J = 1.8 Hz). ^{13}C NMR ($CDCl_3$): for **9**: δ 9.26, 17.09, 122.38, 123.10, 123.30, 128.70, 135.14, 137.63, 137.98 and 140.54. NOE (CD_2Cl_2): irradiation at 2.37 ppm resulted in an NOE effect at 7.49 and 6.86 ppm. MS: *m/z* 272/274. Anal. $C_{10}H_9BrO_2S$ (**8** and **9**): C, H, Br.

*3,5,7-Tribromo-2,4-diphenylbenzo[*b*]thiophene 1,1-dioxide* (**10**). To a solution of 3-chloroperbenzoic acid (1.3 g, 6.0 mmol) in 1,2-dichloroethane (30 ml) was added 3,5-dibromo-2-phenylthiophene[8] (0.64 g, 2.0 mmol) and the solution was heated on an oil bath at 90 °C for 22 h. 3-Chlorobenzoic acid was filtered from the cooled solution, and the filtrate was washed three times with a saturated sodium carbonate solution. The water phases were extracted with dichloromethane (2×50 ml), and the combined organic phases were washed twice with water and dried over magnesium sulfate, treated with activated charcoal, filtered, and evaporated at room temperature. The crude mixture, consisting of 3,5-dibromo-2-phenylthiophene 1,1-dioxide and **10** in a 4:1 ratio, was dissolved in ethyl alcohol (100 ml) and was refluxed for 3 days (72 h). During the reaction dark crystals were formed. This mixture was cooled with ice–water and the crystals were filtered off, washed with ice-cooled 99.5 % ethyl alcohol, and recrystallized from ethyl acetate to give 0.48 g (86 %) of **10**, m.p. 223–227 °C. ^{1}H NMR ($CDCl_3$): δ 8.08 (s, 1 H, 6-H), 7.65–7.21 (m, 10 H, 2,4-diphenyl). MS: *m/z* 552/554/556/558. Anal. $C_{20}H_{11}Br_3O_2S$: C, H, Br.

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