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Photochemical and electrochemical behavior of thiophene-*S*-oxides

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ABSTRACT: The photochemical and electrochemical behavior of thiophene-*S*-oxides as a class was studied for the first time. It was shown that in both cases deoxygenation of the S—O functionality takes place. The outcome of the photoirradiation is very dependent on the substituent pattern of the starting material. Thiophene-*S*-oxides show different reduction behaviors in presence and absence of proton donors. In the absence of proton donors the reduction potential of the compounds is dependent on the substituents of the molecules. In the presence of proton donors, the substituents play a less significant role and a number of thiophene-*S*-oxides were reduced electrochemically to the corresponding thiophenes in presence of a 10-fold excess of benzoic acid. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: thiophene-*S*-oxides; thiophenes; electrochemistry; photochemistry; deoxygenation; cyclovoltammetry; reduction

INTRODUCTION

Thiophene-*S*-oxides are elusive molecules and only in recent times has it become possible to isolate and characterize them in their pure form.[1] For a long time they have been considered to be intermediates in the oxidation of thiophenes to thiophene-*S*,*S*-dioxides with peracids.[2] In the presence of a Lewis acid in this oxidation step thiophene-*S*-oxides can be isolated as, owing to the complexation of the Lewis acid with the oxygen of the thiophene-*S*-oxides, they are protected against further oxidation to the corresponding thiophene-*S*,*S*-dioxides. Thiophene-*S*-oxides have been used extensively as dienes in the [4 + 2]-cycloaddition.[3] Nevertheless, very little is known about their other chemical behavior.[4] As a preliminary study on the use of thiophene-*S*-oxides as complex ligands, we have become interested in the photochemical and electrochemical behavior of this class of molecules (although a number of efforts have been made, thus far metal complexes with a thiophene-*S*-oxide as ligand are unknown; see also Ref. 5).

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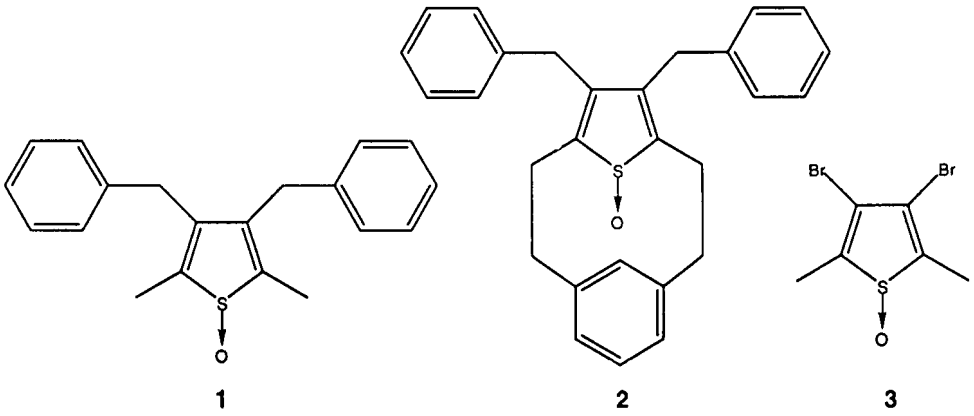
RESULTS AND DISCUSSION

Compounds **1**–**3** (Fig. 1) can be prepared from the corresponding thiophenes by oxidation with *m*-3-chloroperoxybentoic acid (*m*-CPBA) in the presence of $BF_3 \cdot Et_2O$ at low temperatures (Scheme 1). Side-products are the corresponding thiophene-*S*,*S*-dioxides. While it has been stated that voluminous groups at the positions 2 and/or 5 are advantageous for the stability of the thiophene-*S*-oxides,[6] tetra-substitution of the compounds leads equally to isolatable structures as one of the main reaction pathways of the thiophene-*S*-oxides, namely the self-condensation by cycloaddition, can be suppressed. In this case, simple methylation of positions 2 and 5 leads to stable products. Indeed, the thiophene-*S*-monoxides **1**–**3** are sufficiently stable for purification by column chromatography. Moreover, **1** has been stored at 0 °C for 2.5 years with only a very insignificant deterioration of the compound. Also, heating **1** in chloroform at 60 °C for 2 h leads only to a small amount of thiophene and an amount of more than 90% of the starting material can be reisolated. Nevertheless, the biological activity of some thiophene-*S*-oxides against a number of cancer cells might be attributable to a slight but continued deoxygenation of the compounds (there has also been a study showing that thiophene-*S*-monoxides can be metabolic intermediates of dietary thiophenes in rats).



1 2 3

Figure 1. Typical preparation of a thiophene-*S*-oxide

Photochemistry

Upon irradiation with light **1** deoxygenates rapidly. The two products **6** and **7** are produced (Scheme 2), where **5** could be formulated as an intermediate.

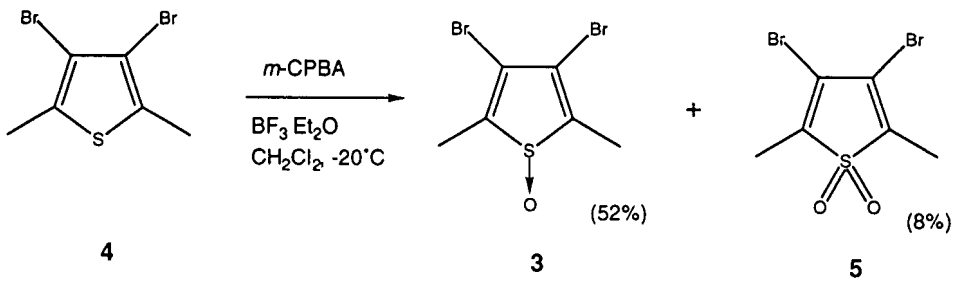
Generally, the exocyclic isomerization of double bonds in **1** and similar compounds could be observed under a number of other conditions, in both basic media (NaOMe, MeOH) and acidic media (*p*-TsOH, benzene). It also has been observed in a mass spectrometric experiment in the fast atom bombardment (FAB) mode that **3** adds one molecule of the matrix (*m*-nitrobenzyl alcohol), where again the corresponding intermediate of **5** can be formulated. *m*-Nitrobenzyl alcohol adds via Michael addition to **5**.

The irradiation of **3** leads to a number of products, where the progress of the reaction is much slower compared with **1** (Scheme 3). While an intermediate as discussed above may be formulated once again, here, bromo radicals are formed which lead to 2-bromomethyl-3,4-dibromo-5-methylthiophene (**8**) potentially as well as to **9** by addition of a bromo radical to **10** with subsequent cleavage of the bromohydrin. It is interesting that in the photoirradiation of **3** an appreciable amount of the thiophene **4** is formed by sole deoxygenation.

In the presence of compounds that can easily be oxidized, e.g. in the presence of amines or thiophenols, photoirradiation of a thiophene-*S*-oxide leads exclusively to the corresponding thiophene. [It is known that in the photoirradiation of dibenzothiophene-*S*-oxides an oxygen transfer occurs to xylene or cyclohexene, when used as solvents. Whether the oxygen is released from dibenzothiophene-*S*-oxides as molecular singlet oxygen, where a complex of two dibenzothiophene-*S*-oxides is involved or as an 'oxenoid' species, has been under discussion.[8] Dibenzothiophene-*S*-oxides resemble sulfoxy-bridged diaryls rather than dibenzo-annelated thiophene-*S*-oxides. They do not deoxygenate when photoirradiated under conditions used in this study ($\lambda > 320$ nm and in absence of a photosensitizer).] When *p*-methoxythiophenol was used as an additive in the photoirradiation, bis(*p*-methoxyphenyl) disulfide, a formal oxidation product of the thiophenol, could be isolated in amounts equal to the thiophene-*S*-oxide consumed. This reaction does not occur upon photoirradiation of the thiophenol alone and progresses very slowly when the thiophene-*S*-oxide and the thiophenol are reacted in the dark.

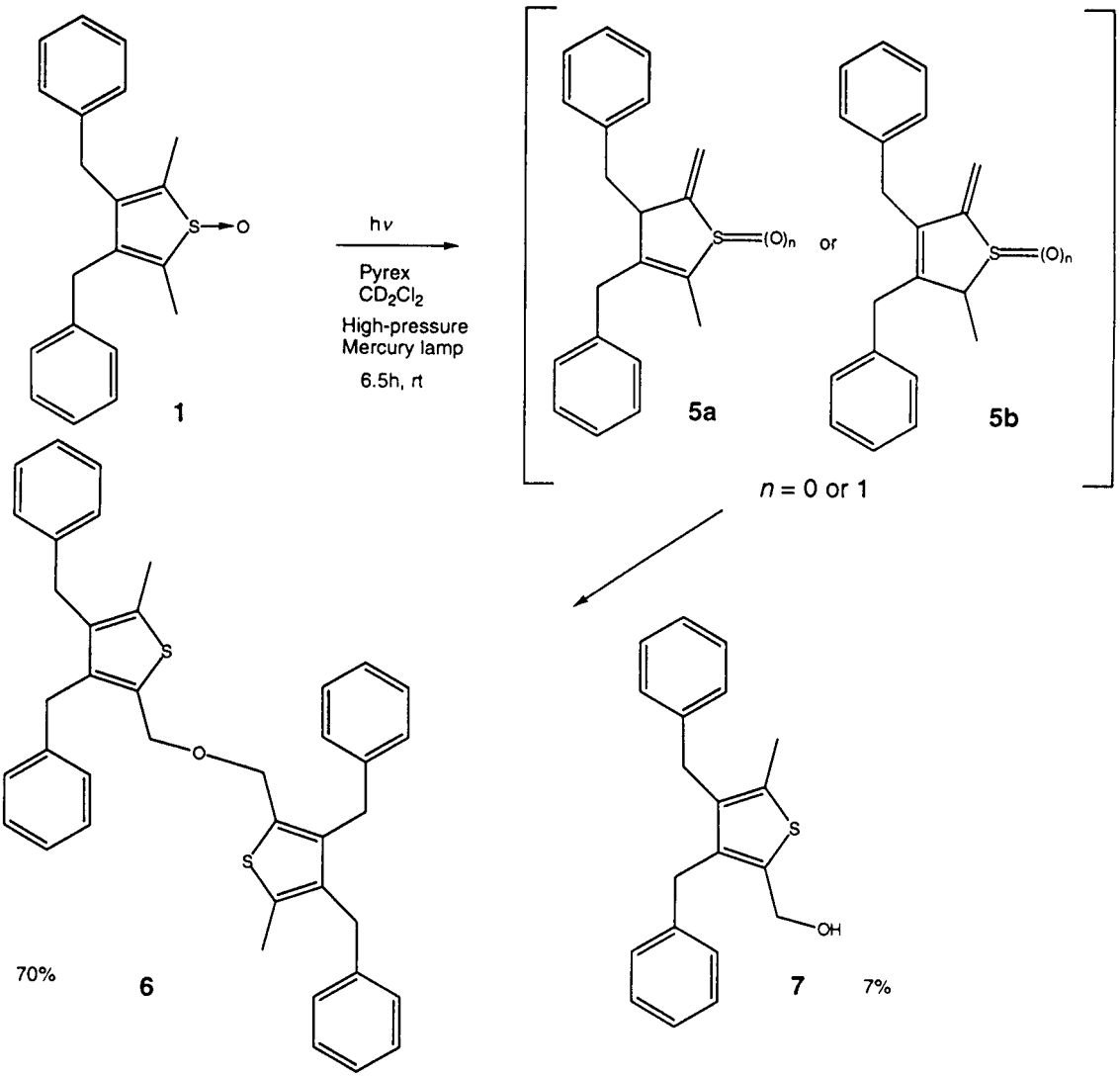
Electrochemistry

Thiophene-*S*-oxides **1**–**3** in acetonitrile (0.1 M NBu_4PF_6) show well-defined, chemically irreversible cyclic voltammetric reduction waves (see reduction process 1 in Table 1 and Fig. 3). In the absence of protons the



4 3 5

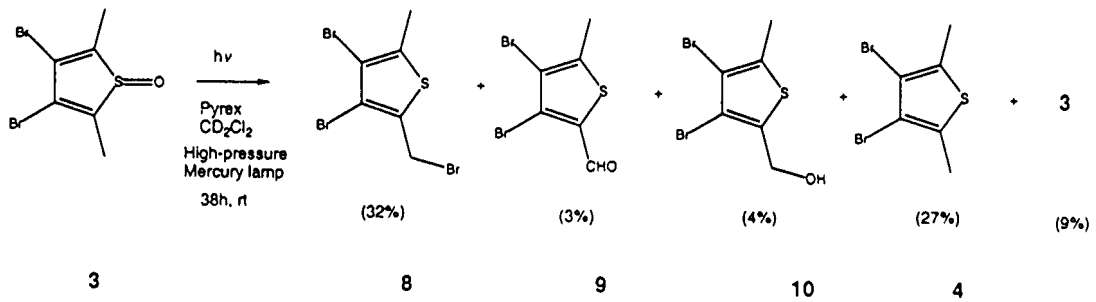
Scheme 1. Typical preparation of a thiophene-*S*-oxide



Scheme 2. Photoirradiation of thiophene-*S*-monoxide **1**

potential at which the reduction occurs is strongly affected by the substituents at the thiophene ring (see Table 1). The processes underlying this reduction are not yet clearly understood, although the observed peak currents indicate fast follow-up chemical steps and transfer of more than one electron.

In the presence of a proton donor the reduction responses of all thiophene-*S*-oxides **1**–**3** experience a marked shift to more positive potentials (Fig. 3), although again a certain dependence of the potential on the substituents of thiophene-*S*-monoxide remains. That this is a second process can be seen in the occurrence of two



Scheme 3. Photoirradiation of thiophene-*S*-monoxide **3**

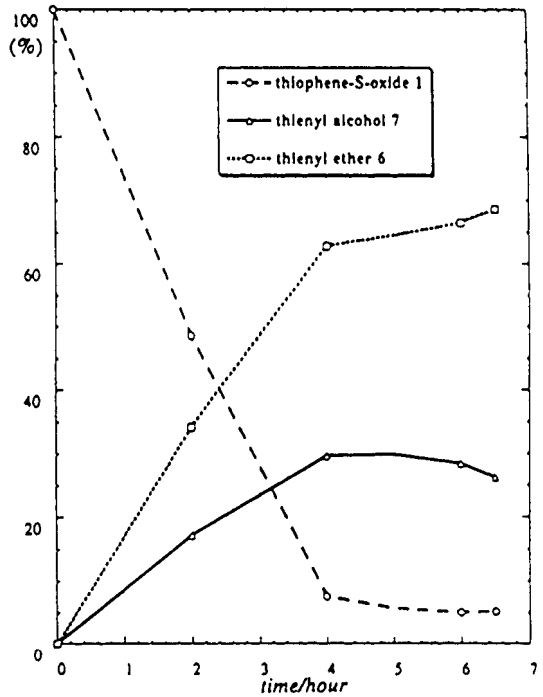


Figure 2. Photoirradiation of 3,4-dibenzyl-2,5-dimethylthiophene-*S*-oxide (**1**). Composition in mol% of the reactant and products after 2, 4, 6 and 6.5 h

reduction waves within a certain concentration range of the proton donor. In the presence of equimolar amounts of thiophene-*S*-oxide and benzoic acid, both processes can be seen to compete, which is indicative for the consumption of two equivalents of protons per thiophene-*S*-oxide molecule reduced. At higher concentrations of benzoic acid only the second process can be found, which is the two proton–two electron reduction of the thiophene-*S*-monoxide to the thiophene (Scheme 4). The authors believe that a protonation at oxygen of the thiophene-*S*-oxide occurs first with a subsequent single electron transfer to the cationic species. After a second protonation with a second electron transfer the thiophene is formed with elimination of water. Bulk electrolysis experiments have been carried out with **1**–**3** in the presence of a 10-fold excess of benzoic acid as proton source. In all cases the corresponding thiophenes (up to 90%) could be isolated. No other by-product could be detected by TLC, GC or ^{1}H NMR spectroscopy.

EXPERIMENTAL

General. Melting-points are uncorrected. IR spectra were measured with JASCO IR-700 and Nippon Denshi JIR-A2OM instruments. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer. The chemical shifts are relative to TMS. *J* values are given in hertz. Mass spectra were measured with a JMS-01-SG-2 spectrometer (electron ionization, 70 eV, direct inlet or GC–MS combination).

Photochemistry. For the irradiation a Rikoh–Kagaku–Sangyo RIKO 100 W high-pressure mercury lamp was used.

Electrochemistry. Benzoic acid (BDH), acetonitrile (dried and distilled, Fisons, after drying over activated alumina with a water content of ca 2mM) and tetrabutylammonium hexafluorophosphate (electrochemical grade, Fluka) were used as purchased. A conventional three-electrode electrochemical cell with argon degassing (BOC, Pureshield Argon) was used for voltammetric measurements. A saturated calomel electrode (SCE) (Radiometer, Copenhagen, Denmark) was the reference electrode (stored in acetonitrile–NBu_4PF_6), which allowed the ferrocene (Fc^+_0) redox couple to be detected at $E_{1/2}$ = 0.39 V vs SCE. A gold wire served as the counter

Table 1. Data obtained for the cyclic voltammetric reduction of different thiophene-*S*-oxides (2 mM) at a 3 mm diameter glassy carbon electrode in acetonitrile–0.1 M Bu_4NPF_6 (scan rate 0.1 V s^{-1}, $T = 20 \pm 2$ °C)

[BzCOOH] (mM)	Reduction: process 1			Reduction: process 2		
	$E_{1/2}$[a] (V vs SCE)	$E_{p,red}$[b] (V vs SCE)	$I_{p,red}$ (μA)	$E_{1/2}$[a] (V vs SCE)	$E_{p,red}$[b] (V vs SCE)	$I_{p,red}$ (μA)
3,4-Dibromo-2,5-dimethylthiophene-S-oxide (**3**):						
0	−1.27	−1.40	100	—	—	—
2	−1.26	−1.39	90	−0.91	−1.04	40
10	—	—	—	−0.91	−1.01	55
3,4-Dibenzyl-2,5-dimethylthiophene-S-oxide (**1**):						
0−1.95−2.02	85	—	—	—		
2	−1.95	−2.00	80	−1.40	−1.60	35
10	—	—	—	−1.36	−1.51	78
12, 13-Dibenzylmetacyclo[2](2,5)thiophenophane-S-oxide (**2**):0						
−1.65	−1.70	59	—	—	—	
2	−1.65	−1.70	59	−1.18	−1.34	30
10	—	—	—	−1.09	−1.22	55

[a] $E_{1/2}$ values correspond to the potential at half-height.
[b] E_p values correspond to the peak potential.

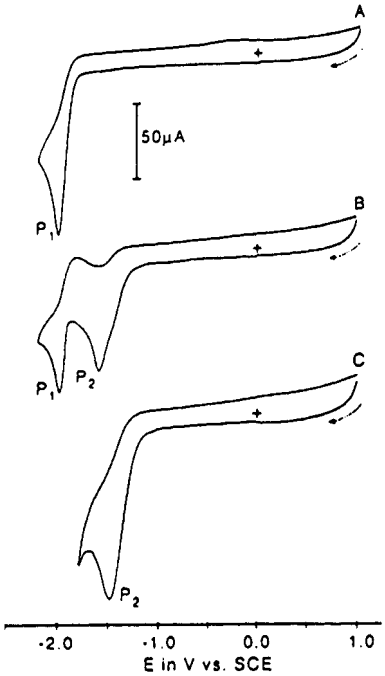


Figure 3. Cyclic voltammograms for the reduction of 2 mM 12,13-dibenzylmetacyclo[2](2,5)thiophenophane-*S*-oxide (**2**) in acetonitrile –0.1–M Bu_4NPF_6 at a 3 mm diameter glassy carbon electrode in the presence of (A) 0, (B) 2 and (C) 10 mM benzoic acid (scan rate 0.2 V s^{-1}, $T = 20 \pm 2$ °C)

electrode and the working electrode was a 3 mm diameter glassy carbon disc electrode (BAS, West Lafayette, IN, USA). A PGSTAT20 Autolab potentiostat (Eco Chemie, The Netherlands) was used.

Compounds **1**[3a] and **3**[3b] were prepared according to literature procedures.

*Synthesis of 3,4-dibromo-2,5-dimethylthiophene-S-oxide **(3)***. Boron trifluoride ether complex (2.0 ml, 15.8 mmol) was added slowly to solution of 3,4-dibromo-2,5-dimethylthiophene (**4**) (440 mg, 1.63 mmol) in dry CH_2Cl_2 (10 ml) at −20 °C under an inert (argon) atmosphere. After 10 min. a solution of *m*-CPBA (367 mg, 2.12 mmol) in CH_2Cl_2 (10 ml) was added dropwise to the reaction mixture at −20 °C and stirred at that temperature for 3 h. Thereafter, the reaction mixture was poured into a mixture of CH_2Cl_2 (30 ml) and a concentrated $NaHCO_3$ solution (50 ml). The resulting two-phase system was stirred for 20 min, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phase was washed with water (30 ml), dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel (eluent diethyl ether–hexane, 1:2) to yield **3** (244 mg, 0.85 mmol, 52%) as colorless crystals, R_f 0.29 (diethyl ether–hexane, 1:2); m.p. 104 –106 °C (diethyl ether–hexane); IR (KBr), 1591, 1431, 1372, 1198, 1151, 1123, 1056, 992, 774, 544, 474 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$), δ 2.33 (s, 6H, 2 CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$), δ 13.50, 122.71, 145.34; MS (FAB, 3-nitrobenzyl alcohol), *m/z* (%) 289 ($[^{81}Br_2]MH^+$, 23), 287 ($[^{81}Br^{79}Br]MH^+$, 29), 285 ($[79Br_2]MH^+$, 15); HRMS, found, 286.8559 (MH^+); calculated for $C_6H_7O^{79}Br^{81}BrS$, 286.8564; elemental analysis, found C, 25.36; H, 2.13; calculated for $C_6H_6OSBr_2$ (285.98), C, 25.20; H, 2.11%; and 3,4-dibromo-2,5-dimethylthiophene-*S*,*S*-dioxide (**5**) (38 mg, 0.13 mmol, 8%) as pale yellow crystals, *R*, 0.70, m.p. 98 –101 °C; IR (KBr), 1620, 1605, 1433, 1376, 1301, 1184, 1157, 1111, 559, 541, 458 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$), δ 2.19 (s, 6H, 2 CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$), δ 10.87, 124.31, 138.11; MS (70 eV), *m/z* (%) 303 ($[^{81}Br_2]M^+-H$, 20), 301 ($[^{81}Br^{79}Br]M^+-H$, 39), 299 ($[^{79}Br_2]M^+-H$, 20); HRMS, found, 301.8433; calculated for $C_6H_6O_2^{79}Br^{81}BrS$, 301.8435.

*Photoirradiation of **1***. Compound **1** (39.5 mg, 0.128 mmol) was placed in an NMR tube (Pyrex) and dissolved in CD_2Cl_2 (1.0 ml). The solution was purged with argon (loss of solvent led to a 1.6 M solution of **1** in CD_2Cl_2) and the tube was sealed under argon. The sample was photoirradiated. The composition of the solution was analyzed by ^1H NMR spectroscopy as the reaction progressed (see Fig. 1). After 6.5 h the tube was opened and the solution was directly subjected to column chromatography on silica gel (eluent diethyl ether–hexane, 1:1) to give bis-2-(3,4-dibenzyl-5-methyl-2-methylenethienyl) ether (**6**) (27 mg, 4.5×10^{-2} mmol, 70%) as pale yellow crystals; R_f 0.82 (diethyl ether–hexane, 1:1); m.p. 135–138 °C; IR (KBr), 3085, 3022, 2924, 2854, 1600, 1493, 1453, 1433, 1396, 1338, 1055, 981, 748, 696 cm^{-1}; ^1H NMR (270 MHz, CD_2Cl_2), δ 2.24 (s, 6H, 2 CH_3), 3.60 (ps, 8H, 4 CH_2), 4.56 (s, 4H, 2 CH_2—

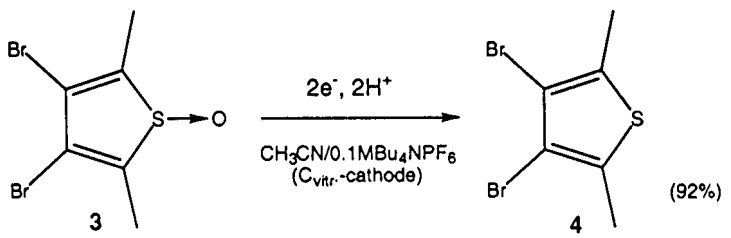


Figure 4. Preparative electrochemical reduction of a thiophene-*S*-oxide

O), 6.86–7.12 (m, 20H, Ar-H); ^{13}C NMR (67.8 MHz, CD_2Cl_2), δ 14.16, 33.18, 33.51, 65.37, 126.59, 126.63, 128.79, 129.00, 129.06, 129.09, 132.99, 135.33, 136.58, 138.87, 140.88, 140.91; MS (70 eV), *m/z* 598 (M^+); HRMS; found, M^+, 598.2364; calculated for $C_{40}H_{38}OS_2$, 598.2350; and 3,4-dibenzyl-2-hydroxymethylene-5-methylthiophene (**7**) [3 mg, 9.7×10^{-3} mmol, 7% (during the work-up an amount of compound **7** was lost: the reason for this is not known)] as colorless crystals; R_f 0.43 (diethyl ethen–hexane, 1:1); m.p. 99–102 °C; IR (KBr), 3412, 2910, 2852, 1601, 1493, 1453, 1431, 1333, 1288, 1221, 1194, 1134, 1072, 1041, 1028, 1009, 978, 743, 697 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$), δ 1.43 (s, 1H, OH), 2.26 (s, 3H, CH_3), 3.73 (s, 2H, CH_2), 3.79 (s, 2H), 4.67 (s, 2H, C*H*$_2$—O), 6.98–7.24 (m, 10H, Ar-H); ^{13}C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) [assignments of ^{13}C signals were aided by DEPT measurements; (+) denotes primary and tertiary, (−) secondary and $C_{(quat)}$ quaternary carbon atoms], δ 14.07 (+, CH_3), 33.03 (−), 33.20 (−), 58.56 (−), 126.38 (+, CH), 126.52 (+, CH), 128.30 (+, CH), 128.48 (+, CH), 128.84 (+, CH), 128.95 (+, CH), 134.75 (C_{quat}), 136.42 (C_{quat}), 137.84 (C_{quat}), 140.34 (C_{quat}), 140.61 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol), *m/z* 308 (M^+); HRMS, found, M^+ 308.1235; calculated for $C_{20}H_{20}OS$, 308.1228.

Electrochemical reduction of 3,4-dibromo-2,5-dimethylthiophene-S-oxide ***(3)***. Compound **3** (35 mg, 0.12 mmol) and benzoic acid (150 mg, 1.2 mmol) were dissolved in a degassed solution of 0.1 M Bu_4NPF_6 in acetonitrile (100 ml). For the experiment the counter electrode (gold) was kept in a separate compartment to avoid contamination of the product. As the working electrode a reticulated vitreous carbon electrode ($10 \times 10 \times 10$ mm) (Electrosynthesis Company, Lancaster, NY, USA) was used. The electrolysis was carried out at room temperature with stirring of the solution. After passing the equivalent of 2 C mol^{-1} charge at an applied potential of −1.4 V vs SCE, the electrolysis was stopped and the solvent was removed *in vacuo*. Thereafter, the mixture was taken up in water and extracted with chloroform. The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue on silica gel (diethyl ether–hexane, 1:1) gave **4** (30 mg, 92%) as a colorless solid, b.p. 37 –39 °C; IR (KBr), 2850, 1510, 1350, 1270, 1210, 1140, 1122, 1000 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$), δ 2.40 (s, 6H); ^{13}C NMR (67.9 MHz, $CDCl_3$), δ 15.78, 111.70, 131.50; MS (70 eV), *m/z* (%) 270 (M^+, 46). Elemental analysis, found, C, 26.71; H, 2.19; calculated for $C_6H_6Br_2S$ (269.98), C, 26.70; H, 2.24%.

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