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Preparation and Electrooxidative SO-Extrusion of Halogenated 7-Thiabicyclo[2.2.1]heptene 7-Oxides†

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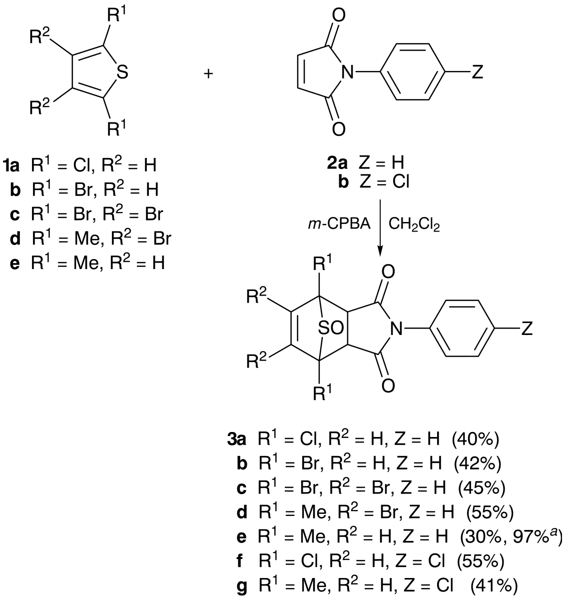
Halogenated thiophenes have been cycloadded oxidatively to maleimides to give halogenated thiabicyclo[2.2.1]heptene *S*-oxides which have been subjected to an electrochemical extrusion of SO to give various halogeno-substituted phthalimides.

Torssell[1] and Fallis and co-workers[2] have shown that oxidative cycloaddition occurs on treating alkyl-substituted thiophenes with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of an electron-poor dienophile. We have studied the reaction in greater detail and found it valuable to synthesize novel alkyl-substituted 7-thiabicyclo[2.2.1]heptene 7-oxides in connection with crown ether systems.[3] Recently, it was shown that the yield for the oxidative cycloaddition of alkyl-substituted thiophenes, proceeding *via* intermediate thiophene *S*-monoxides, could be greatly enhanced by adding $BF_3 \cdot Et_2O$ to *m*-CPBA.[4] While the uncatalysed reaction can be run at 0 °C to ambient temperature, the catalysed reaction is run typically at –78 °C. The greater stability of thiophene *S*-oxides towards further oxidation under catalysed conditions was demonstrated.[4,5] The further oxidation of thiophene *S*-monoxides to the *S*,*S*-dioxides is a main side reaction in the oxidative cycloaddition.

Oxidation of thiophenes at sulfur proceeds readily when the thiophenes are substituted with electron donors such as alkyl groups. Electron-withdrawing or more ambidentate substituents hinder the oxidation. For this reason the oxidative cycloaddition of halogenated thiophenes does not proceed well at room temperature. Nevertheless, at more elevated temperatures, 7-thiabicyclo[2.2.1]heptene *S*-oxides from readily in the reaction of 2,5-chlorinated or brominated thiophenes with such idenophiles as maleimides or maleic anhydride (Scheme 1). The products are not very soluble in dichloromethane and partly precipitate during the reaction. Further precipitation can be induced by addition of diethyl ether. Apart from diligent washing with diethyl ether, the products need no additional purification for a further transformation, although for analytical purposes column chromatography and recrystallization have been performed.

It has been found that the addition of $BF_3 \cdot Et_2O$ has no beneficial effect on the reaction, if the thiophene is halogenated at position 2 and/or 5. In the case of 3,4-dibromo-2,5-dimethylthiophene **1d**, however, an acceptable yield of the cycloadduct was obtained when the reaction was run at –20 °C in presence of $BF_3 \cdot Et_2O$.

In the cycloaddition five stereocentres are created. Nevertheless, only one isomer is isolated. Although no crystal structural analysis has been performed, it is thought to be the *endo*-product with the lone-electron pair of the sulfur directed to the newly formed olefinic bond. This is evidenced by comparison to compounds formed in cycloadditions with donor-substituted compounds.[3–5]



1a R^1 = Cl, R^2 = H
b R^1 = Br, R^2 = H
c R^1 = Br, R^2 = Br
d R^1 = Me, R^2 = Br
e R^1 = Me, R^2 = H

2a Z = H
b Z = Cl

3a R^1 = Cl, R^2 = H, Z = H (40%)
b R^1 = Br, R^2 = H, Z = H (42%)
c R^1 = Br, R^2 = Br, Z = H (45%)
d R^1 = Me, R^2 = Br, Z = H (55%)
e R^1 = Me, R^2 = H, Z = H (30%, 97%[a])
f R^1 = Cl, R^2 = H, Z = Cl (55%)
g R^1 = Me, R^2 = H, Z = Cl (41%)

Scheme 1 Oxidative cycloaddition of halogenated thiophenes. [a]For preparation, see ref. 4

Thiabicyclo[2.2.1]heptene *S*-oxides of type **3** are quite stable thermally and extrude SO only in excess of 150 °C.[6] On the other hand, **3** may be viewed as precursors for corresponding arenes. Photochemical[6] and oxidative extrusion[3] of SO in **3** has been found to proceed at much lower temperatures than the purely thermal extrusion. Nevertheless, the photochemical extrusion has synthetic limitations as to the reaction scale and in some cases gives a number of side products. The oxidative extrusions at ambient temperature, which are run under PTC conditions,[7] often require an excess of oxidizing agent ($KMnO_4$) and do not work well in all cases. The extrusion is thought ot proceed *via* an intermediate oxidation of the bridging sulfoxy group to a sulfone. For these reasons an electrochemical oxidative SO extrusion was tried. A number of electrochemical oxidations both of the thioether and of the sulfoxy moiety are known. Direct[8] and indirect[9] electrochemical oxidations have been reported. Moreover, oxidations of thioethers and sulfoxides often yield sulfones as by-products.[10]

First, the cycloadducts **3** were electrolysed in a medium containing NaCl or NaBr in a mixture of acetic acid in water AcOH–H_2O 4:1 (v/v).[11] For such systems it is known that the chloride or bromide ions are oxidized to the corre-

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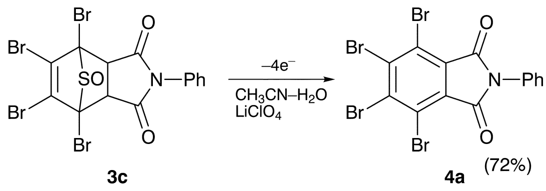

Scheme 2 Electrochemical SO-extrusion

sponding halogens, which disproportionate in aqueous acetic acid to give hypohalites.[12] These are the species responsible for the oxidation of the sulfoxides. This could be demonstrated as in a similar case in the literature by replacing sodium halide as electrolyte with sodium sulfate when no reaction took place. In the electrooxidation using NaCl or NaBr as electrolyte [Pt/Pt, 0.1 M NaX, AcOH–H_2O 4:1 (v/v)] the desired phthalimides **4** we found as the major products in the early phase of the reaction (up to 15% of conversion has been achieved) with a small amount of the corresponding cyclohexadienes as side products. As the reaction proceeds, however, the reaction mixture becomes more complex, and a number of products emerge. This can be attributed to halogenation of the methylidene carbon α to the carbonyl function of the imido moiety. Very slow addition of bromine to the thiabicyclo[2.2.1]heptene *S*-oxides leads to the formation of products identical to those found as side products in the electrooxidation. Thus, a second method of electrochemical oxidative SO extrusion was studied.

It is known that thioethers can be transformed to sulfoxides directly at platinum electrodes. Moreover, thioacetals are cleanly oxidatively cleaved to alkanones at such electrodes.[13] Interestingly, it could be shown that the cycloadducts **3** could be transformed to the corresponding phthalimides **4** under the same conditions [Pt/Pt, CH_3CN–H_2O (20:1 v/v) or dry CH_3CN, 0.5 M $LiClO_4$]. In these reactions the sulfur bridge is oxidized before it is extruded. A sulfone bridge in these molecules is much less stable than the corresponding sulfoxy bridge. Although it is believed that SO_2 itself is extruded from the molecules, the gas phase over the reaction solution has not yet been analysed for SO_2. For most systems tried, a satisfactory transformation could be achieved. Scheme 2 shows a typical example. In all cases a divided cell had to be used. The starting materials and the products are imides and can be reduced readily at the cathode. Furthermore, in many cases less material, product and starting material could be isolated from the anodic chamber with increasing reaction time. Thus, it became mandatory to shorten reaction times using the same set-up. Moreover, in almost all experiments a gradual blocking of the anode was observed. This may be due to oxidized sulfur species adsorbing on the electrode.[14] To circumvent blocking of the electrode and to shorten the reaction time of the oxidative extrusion, ultrasound was employed. Its use[15] during electrolysis increases mass transport of the substrate to the electrode and of the product from the electrode in many cases.[16] An increase in current at constant potential was noted when using ultrasound. The reaction time of the oxidative SO-extrusion can be shortened without altering the product distribution. The electrochemical cell was immersed in an ultrasonic bath (Bandelin Sonorex Super RK 510H). Typically, reaction times could be shortened by 30% (*e.g.* from 6 to 4 h). The yield of **4a** was increased to 87% upon application of sonication.

Experimental

Oxidative Cycloaddition of Halogenated Thiophenes with Phenylmaleimides.—A mixture of 2,5-dibromothiophene **1b** (2.42 g, 10 mmol), *N*-phenylmaleimide **2a** (1.8 g, 10.4 mmol), and *m*-chloroperbenzoic acid (7.3 g, 60 weight %, 25.4 mmol) in dichloromethane 60 cm^3) was refluxed for 48 h. Thereafter the solution was cooled, the precipitate formed filtered off, and the filtrate diluted with dry diethyl ether (100 cm^3). A second crop of crystalline precipitate formed and was filtered off. Further concentration of the filtrate *in vacuo* and addition of ether (100 cm^3) yielded further precipitate. The combined precipitate was washed with ether (2 × 20 cm^3) and dried. An analytical sample was recrystallized from dry ether to give **3b** as a pale yellow solid (1.73 g, 42%), mp 254 °C; IR (KBr) $\tilde{\nu}/cm^{-1} = 3100$, 3062, 2858, 1720, 1494, 1390, 1205, 1130, 963, 757, 733, 696, 682, 668. ^1H NMR (250 MHz, $CDCl_3$): δ 4.27 (2 H, s), 6.52 (2 H, s), 7.19–7.22 (2 H m, aromatic H), 7.42–7.47 (3 H, m, aromatic H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 52.78, 72.18, 126.25, 129.27, 130.92, 132.79, 135.10, 170.09 (C=O). MS (FAB, 3-nitrobenzyl alcohol): *m/z* (%) 434 ([$^{81}Br_2$]MH^+, 2.5), 432 ([$^{79}Br^{81}Br$]MH^+, 4.1), 430 ([$^{79}Br_2$]MH^+, 2.1), 394 ([$^{79}Br^{81}Br$]$MH^+ - SO$, 1.5). HRMS (FAB, 3-nitrobenzyl alcohol) ($C_{14}H_9Br_2NO_3S + H^+$): ($^{81}Br_2MH^+$) 433.8708 (calc.), 433.8698 (found); ([$^{79}Br^{81}Br$]MH^+) 431.8728 (calc.), 431.8729 (found); ($^{79}Br_2MH^+$) 429.8748 (calc.), 429.8746 (found).

Electrochemical SO-Extrusion.—Typically, a solution of a tetrabromothiabicyclo[2.2.1]heptene *S*-oxide (**3c**, 100 mg, 0.17 mmol) in acetonitrile–5 volume % water (16 cm^3) containing $LiClO_4$ (0.5 M, 8 mmol) was electrolysed in a divided cell equipped with a platinum-sheet anode (2 × 1 cm^2) at a constant current of 6 mA [cathode compartment: palladium-sheet cathode (2 × 1 cm^2), CH_3CN–10 volume % water (16 cm^3), 0.5 M $LiClO_4$]. The electrolysis was continued until most of the starting material had been consumed (TLC, until about 4.2 F mol^{-1} were passed). Then the anolyte was concentrated *in vacuo*, ether (15 cm^3) was added and the precipitate filtered off. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (eluent: chloroform) to yield *N*-phenyltetrabromophthalimide **4a** (66 mg, 72%) as colorless crystals, mp 278 °C (lit.,[17] 280 °C); IR (KBr) $\tilde{\nu}/cm^{-1}$ = 1705, 1490, 1385, 1335, 1277, 1122, 753, 735, 688, 663.

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