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Reactions of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides with electrophilic agents

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Nitration, sulfonation, and iodination of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide and its derivatives with electron-releasing and electron-withdrawing substituents were studied. Electrophilic substitution in 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide occurs at position 5. The presence of electron-withdrawing substituents in this position hinders further substitution, while electron-releasing substituents in positions 5 and 6 direct an electrophile to position 4.

Key words: 1,3-dihydrobenzo[*c*]thiophene, 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides, nitration, sulfonation, halogenation.

Reactivity of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide and its derivatives is of great interest, because they are successfully used in organic synthesis, in particular, for syntheses of physiologically active compounds and pesticides.

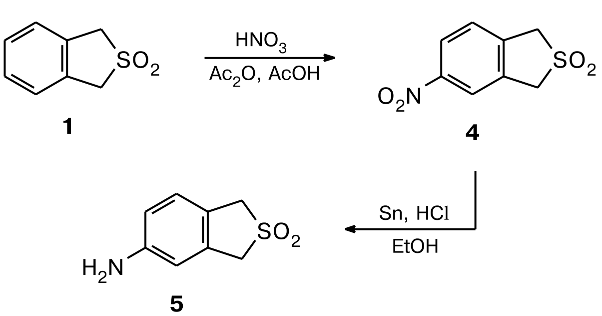
To extend the synthetic potential of these compounds, it seems promising to use their functionalization by substitution of hydrogen atoms of the benzene ring and heterocyclic moiety and reactions of the sulfono group.

In this work, we studied the benzene ring substitution of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides by different electrophilic agents.

Nitration. We used unsubstituted 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**1**), 5,6-dimethyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**), 5,6-ethylenedioxy-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**3**), and 5-nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**4**) as substrates.

Sulfone **1** has previously[1] been nitrated with fuming nitric acid to obtain nitro derivative **4** in moderate yield (55%). We developed conditions for the preparative synthesis of the latter by the action of fuming HNO_3 in a medium of 1 : 1 AcOH—Ac_2O mixture (10 °C, 5 h). As a result, compound **4** was obtained in high yield (81.2%), and its constants correspond to literature values[1] (Scheme 1).

Scheme 1



The IR spectrum of compound **4** contains absorption bands at 1540 and 1360 cm^{-1}, confirming the presence of a nitro group. The direction of nitration to position 5 of the heterocycle was also confirmed by the ^{1}H NMR spectrum of 5-amino-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**5**), which is the reduction product of nitro derivative **4** with tin in hydrochloric acid. The structure of amine **5** was proved by the IR and ^{1}H NMR spectral data. Its IR spectrum contains the characteristic absorption bands of the SO_2 group (1345 cm^{-1}). The ^{1}H NMR spectrum exhibits signals of protons of the methylene group of the heterocycle (δ 4.20 and 4.27) and amino group (δ 5.17). The signals of aromatic protons at δ 6.45 (s), 6.52 (d), and 6.95 (d) indicate that the amino group is in position 5.

Our attempt to introduce the second nitro group by the action of concentrated HNO_3 in Ac_2O and H_2SO_4 was unsuccessful, probably, because of the deactivating effect of the introduced nitro group on the benzene ring.

We have previously[2] studied the reaction of 5,6-dimethyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**) with nitric acid under different conditions. When benzothiophene dioxide **2** is treated with fuming HNO_3 or a mixture of HNO_3 and AcOH (1 : 5), or HNO_3 and H_2SO_4 (1 : 5), 5,6-dimethyl-4-nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**6**) is formed (Scheme 2). The reaction of compound **2** with fuming HNO_3 in the presence of Ac_2O produces only resinification products.

The reduction of compound **6** with tin in hydrochloric acid affords 4-amino-5,6-dimethyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**7**) in good yield. The struc-

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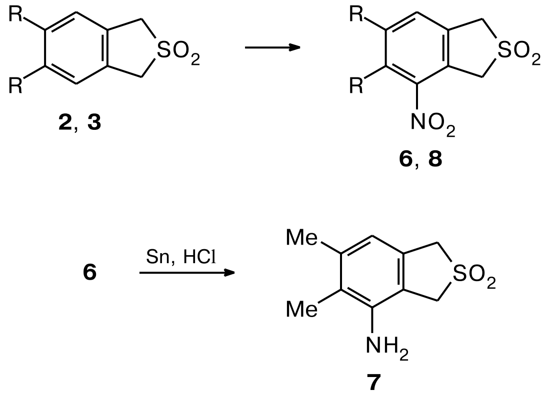
Scheme 2



R = Me (**2**, **6**); R + R = —OCH_2CH_2O— (**3**, **8**)

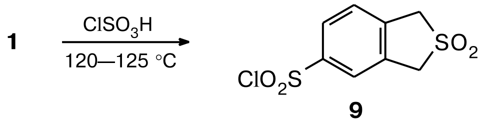
tures of nitro compound **6** and amine **7** were confirmed by data of the IR spectra.

It is known that the introduction of strong electron-releasing substituents (amino, hydroxy, and alkoxy groups) into the benzene ring enhances the reactivity of the molecule toward electrophilic agents. Therefore, we chose ethylenedioxy derivative **3** as an object.

As expected, compound **3** was successfully nitrated under mild conditions: with dilute nitric acid using slight heating. As a result, 5,6-ethylenedioxy-4-nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**8**) was obtained in good yield (see Scheme 2). The structure of compound **8** was confirmed by the data of its IR spectrum, which exhibits intense absorption bands at 1360 and 1530 cm^{-1} characteristic of the nitro group and bands at 1150 and 1330 cm^{-1} corresponding to the sulfono group.

Sulfonation. We studied the reactions of sulfones **1** and **2** with chlorosulfonic acid in a medium of the acid itself taken in a fivefold excess at 120—125 °C. As a result, 1,3-dihydrobenzo[*c*]thiophene-5-sulfochloride 2,2-dioxide (**9**)[3] was obtained in high yield (Scheme 3).

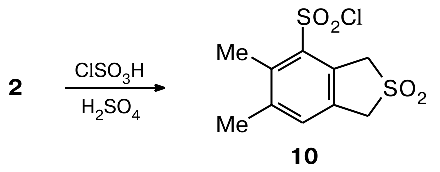
Scheme 3



The IR spectrum of compound **9** contains absorption bands of the sulfono group (1130 and 1325 cm^{-1}), aromatic ring (870 and 1580 cm^{-1}), and chlorosulfonyl group (1320 cm^{-1}). The ^1H NMR spectrum exhibits signals of protons of the methylene group (δ 4.76) and H(4), H(6) (δ 7.93 and 7.88), and H(7) protons (δ 7.63) of the aromatic fragment.

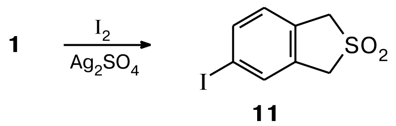
The presence of two Me groups in sulfone **2** enhances the reactivity of the molecule, and its reaction with chlorosulfonic acid occurs under milder conditions. For example, when a threefold excess of $ClSO_3H$ is used in H_2SO_4 at 100 °C, 5,6-dimethyl-1,3-dihydrobenzo[*c*]thiophene-4-sulfochloride 2,2-dioxide (**10**) is formed in high yield (Scheme 4).

Scheme 4



Halogenation. The chlorination and bromination of benzothiophene **1** in the presence of iron compounds were unsuccessful. The reaction of benzothiophene **1** with iodine in the presence of silver sulfate afforded 5-iodo-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**11**) in high yield, and its constants agree with literature data[4] (Scheme 5).

Scheme 5



The structure of derivative **11** was confirmed by the IR spectrum containing absorption bands at 820 and 900 cm^{-1} characteristic of the substituted benzene ring and intense bands at 1155 and 1320 cm^{-1} caused by the sulfono group. The absorption bands at 1455—1470 cm^{-1} can be assigned to vibrations of the methylene group of the heterocycle, and the absorption band of the C—I bond appears at 660 cm^{-1}.

Thus, electrophilic substitution in 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**1**) occurs at position 5 of the heterocycle, while the substitution occurs at position 4 in the case of its 5,6-disubstituted derivatives.

Experimental

IR spectra were recorded on a UR-20 spectrometer in KBr pellets. ^1H NMR spectra were obtained on a Tesla BS-487 instrument (80 MHz) using hexamethyldisiloxane as internal standard and acetone-d_6 as solvent. Reactions and purity of synthesized compounds were monitored by TLC on Silufol plates (iodine vapor detection). Melting points were determined on a Boetius heating microstage.

1,3-Dihydrobenzo[*c*]thiophene. A mixture of α,α′-dibromo-*o*-xylene[5] (132 g, 0.5 mol) and benzene (500 mL) was stirred until the dibromide dissolved completely. Then a solution of sodium sulfide nonahydrate (240 g, 1 mol) in water (200 mL) and benzyltriethylammonium chloride (0.5 g) were added to the mixture. The reaction mixture was stirred for 30 h at ~20 °C. After the end of the reaction, the mixture was distilled with water vapor. Benzene was distilled off first, and then the sulfide was collected under a water layer. The resulting sulfide was separated and cooled in a refrigerator. The yield of the product was 41—45 g (60.3—66.1%), m.p. 25—26 °C (*cf.* Ref. 6: 22.5—23.5 °C). The product was used without additional purification. ^{1}H NMR, δ: 4.46 (s, 4 H, CH_2); 7.14 (s, 4 H, CH).

1,3-Dihydrobenzo[*c*]thiophene 2,2-dioxide (1). A mixture of 1,3-dihydrobenzo[*c*]thiophene (40.8 g, 0.03 mol) and glacial AcOH (250 mL) was cooled in an ice bath at 5—10 °C, and a 30% solution of H_2O_2 (70 mL) was added dropwise for 1 h. Then the mixture was stirred for 1 h at ~20 °C and for 3 h at 90—95 °C. After the end of the reaction, the mixture was cooled, and precipitated crystals were filtered off, washed with water, dried in air, and recrystallized from EtOH. The yield of compound **1** was 45.1 g (89.5%), m.p. 152—153 °C (*cf.* Ref. 6: 150—151 °C). IR, ν/cm^{-1}: 1140, 1320 (SO_2). ^{1}H NMR, δ: 4.37 (s, 4 H, CH_2); 7.25 (s, 4 H, CH).

5,6-Dimethyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (2) was synthesized by a known procedure[2] in 90.0% yield, colorless needles, m.p. 172—173 °C. IR, ν/cm^{-1}: 720, 930, 1500 (arom.); 1100 (Me); 1140, 1320 (SO_2).

5,6-Ethylenedioxy-1,3-dihydrobenzo[*c*]thiophene. 6,7-Bis-chloromethyl-1,4-benzodioxane[7] (4.66 g, 0.02 mol) was added at 35—40 °C by portions with stirring in a nitrogen flow to a mixture of sodium sulfide nonahydrate (6.0 g, 0.025 mol), EtOH (200 mL), and water (40.0 mL). Then the mixture was stirred for 2 h at 60 °C, cooled to ~20 °C, and filtered. The filtrate was concentrated in a nitrogen flow, and the residue was dissolved in benzene (50 mL), washed with water, and dried with anhydrous $MgSO_4$. A benzene solution was filtered off, the solvent was evaporated, and the residue was recrystallized from MeOH. The yield of the product was 1.0 g (25%), m.p. 81—82 °C (*cf.* Ref. 8: m.p. 80—82 °C), R_f 0.63 (benzene). Found (%): C, 61.45; H, 5.07; S, 17.30. $C_{10}H_{10}O_2S$. Calculated (%): C, 61.94; H, 5.19; S, 16.50. ^{1}H NMR, δ: 4.06 (s, 4 H, CH_2); 4.16 (s, 4 H, CH_2O); 6.70 (s, 2 H, CH).

5,6-Ethylenedioxy-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (3). 28% Hydrogen peroxide (5 mL) was added with stirring at 30 °C to 5,6-ethylenedioxy-1,3-dihydrobenzo[*c*]thiophene (1.0 g, 0.005 mol) in glacial AcOH (15 mL). Then the reaction mixture was stirred for 8 h at 80 °C. After the end of the reaction, the contents of the flask was poured into a glass containing a mixture of ice and water, and the precipitate that formed was filtered off, dried, and recrystallized from EtOH. The yield of sulfone **3** was 0.92 g (90%), m.p. 220—222 °C (*cf.* Ref. 8: 220—221 °C), R_f 0.65 (benzene—acetone, 5 : 1). Found (%): C, 53.10; H, 4.75; S, 14.33. $C_{10}H_{10}O_4S$. Calculated (%): C, 53.10; H, 4.42; S, 14.16. IR, ν/cm^{-1}: 1140, 1310 (SO_2).

5-Nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (4). Nitric acid (40 mL, *d* = 1.50) was added dropwise at –5—–10 °C with stirring for 30 min to compound **1** (33.6 g, 0.2 mol) and a mixture of Ac_2O and AcOH (1 : 1) (240 mL). Stirring was continued for 5—8 h. During this time, sulfone was completely dissolved, a transparent solution formed, and then crystals precipitated. After the end of the reaction, the precipitate was filtered off on the Büchner funnel, washed with water and a dilute soda solution to the neutral reaction and again with water, and dried. Ice-cold water (500 mL) was added to the filtrate, and the precipitate that formed was filtered off, treated as the major product, and dried in air. The product was recrystallized from AcOH. The yield of sulfone **4** was 34.6 g (81.2%), m.p. 169—170 °C (*cf.* Ref. 1: 167—169 °C). IR, ν/cm^{-1}: 725, 955 (arom.); 1140, 1320 (SO_2); 1360, 1540 (NO_2).

5-Amino-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (5). Hydrochloric acid (120 mL) was added dropwise for 1 h to sulfone **4** (21.3 g, 0.1 mol), tin (21 g), and refluxing EtOH (500 mL). Then the mixture was refluxed for 8 h, cooled, and neutralized to a weakly alkaline reaction. A precipitate was separated and dried. The solid powdered product was extracted with chloroform and dried with anhydrous $MgSO_4$. The solvent was distilled off, and the residue was recrystallized from EtOH. The yield of amino derivative **5** was 14.9 g (81.4%), m.p. 199—201 °C (*cf.* Ref. 1: 194—196 °C). ^{1}H NMR, δ: 4.20, 4.27 (both s, 4 H, CH_2); 5.17 (s, 2 H, NH_2); 6.45 (s, 1 H, H(4)); 6.52, 6.95 (both t, 2 H, H(6), H(7), J = 7 Hz). IR, ν/cm^{-1}: 1345 (SO_2); 3490 (NH_2).

5,6-Dimethyl-4-nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (6) was synthesized similarly to a described procedure[2] in 82.9% yield, m.p. 170—171 °C.

4-Amino-5,6-dimethyl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (7). A mixture of nitro derivative **6** (1 g), tin (1 g), and concentrated hydrochloric acid (5 mL) was carefully heated in a water bath for 1 h to 80 °C. Then the mixture was stored at this temperature for 1 h, cooled, and neutralized with a 25% solution of potash. A precipitate was separated and dried. The solid powdered product was extracted with chloroform (4×30 mL), and the extracts were combined and dried with anhydrous $MgSO_4$. The solvent was distilled off, and the residue was recrystallized from EtOH. The yield of compound **7** was 0.35 g (40.0%), m.p. 195—196 °C. IR, ν/cm^{-1}: 1140, 1310 (SO_2); 3320 (NH_2).

5,6-Ethylenedioxy-4-nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (8). A mixture of HNO_3 (2.5 mL), water (2.5 mL), and sulfone **3** (0.226 g) was stirred first for 2 h at ~20 °C and then for 3 h at 60 °C. After the end of the reaction, the mixture was poured into a glass filled with ice (25 g). A precipitate was separated, dried, and recrystallized from formic acid. The yield of compound **8** was 0.228 g (84%), m.p. 231—233 °C, R_f 0.38 (benzene). Found (%): C, 44.37; H, 3.24; N, 5.10. $C_{10}H_9NO_6S$. Calculated (%): C, 44.28; H, 3.34; N, 5.16. IR, ν/cm^{-1}: 1150, 1330 (SO_2); 1445 (CH_2); 1360, 1530 (NO_2).

1,3-Dihydrobenzo[*c*]thiophene-5-sulfochloride 2,2-dioxide (9) was synthesized similarly to a known procedure[3] in 70.0% yield, m.p. 164—165 °C. ^{1}H NMR, δ: 4.76 (s, 4 H, CH_2); 7.63, 7.88, 7.93 (all s, 3 H, CH).

5,6-Dimethyl-1,3-dihydrobenzo[*c*]thiophene-4-sulfochloride 2,2-dioxide (10). Sulfone **2** (2 g, 0.01 mol) was dissolved in concentrated H_2SO_4 (10 mL), and freshly distilled chlorosulfonic acid (2.4 mL, 0.03 mol) was added with stirring. The mixture was stirred for 4 h at 100 °C and poured into a glass with ice-cold water (100 mL). A precipitate was separated and dried. The product was recrystallized from AcOH. The yield of compound **10** was 1.65 g (56%), m.p. 120—122 °C. Found (%): C, 41.10; H, 3.45; S, 21.15. $C_{10}H_{11}ClO_4S_2$. Calculated (%): C, 40.75; H, 3.76; S, 21.75. IR, ν/cm^{-1}: 870, 910, 1580 (arom.); 1140, 1320, 1325 (SO_2, SO_2Cl).

5-Iodo-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (11). A mixture was concentrated H_2SO_4 (20 mL), sulfone **1** (1.68 g, 0.01 mol), molecular iodine (6.35 g, 0.025 mol), and silver sulfate (1.55 g) was stirred for 32 h at 30—40 °C. Then the resulting mixture was poured into a glass with ice-cold water (50 mL), and a precipitate was separated, washed with water, dried, and recrystallized from EtOH. The yield of compound **11** was 1.8 g (65%), m.p. 120—122 °C. Found (%): C, 32.43; H, 2.51; S, 11.05. $C_8H_7IO_2S$. Calculated (%): C, 32.67; H, 2.40; S, 10.90. IR, ν/cm^{-1}: 820, 900 (arom.); 1155, 1320, 1320 (SO_2); 1455 (CH_2).

References

1. B. Iddon, *Adv. Heterocycl. Chem.*, 1972, **14**, 331.
2. G. A. Tashbaev and I. M. Nasyrov, *Izv. Akad. Nauk Tadzh. SSR. Otd. Fiz.-Mat., Khim. i Geol. Nauk* [*Bulletin of Academy of Sciences of Tadjik Republic, Department of Physical, Mathematical, Chemical, and Geological Sciences*], 1987, No. 3, 54 (in Russian).
3. G. A. Tashbaev, S. S. Dzhalolov, and I. M. Nasyrov, *Izv. Akad. Nauk Tadzh. SSR. Otd. Fiz.-Mat., Khim. i Geol. Nauk* [*Bulletin of Academy of Sciences of Tadjik Republic, Department of Physical, Mathematical, Chemical, and Geological Sciences*], 1987, No. 1, 41 (in Russian).
4. W. Oppolzer and A. Roberts, *Helv. Chim. Acta*, 1980, **63**, 1703.
5. *Organic Synthesis*, Ed. W. S. Johnson, J. Wiley and Sons, New York—London, 1954, **34**.
6. J. A. Oliver and P. H. Ongley, *Chem. Ind.*, 1965, **25**, 1024.
7. A. E. Agronomov and Yu. S. Shabarov, *Laboratornye Raboty v Organicheskom Praktikume* [*Laboratory Practical Works in Organic Chemistry*], Khimiya, Moscow, 1974, 178 (in Russian).
8. G. A. Tashbaev, I. M. Nasyrov, and S. S. Dzhalolov, *Dokl. Akad. Nauk Tadzh. SSR* [*Reports of Academy of Sciences of Tadjik Republic*], 1982, **25**, 732 (in Russian).

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