Pergamon

Tetrahedron, Vol. 52, No. 38, pp. 12459-12464, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00725-9

Ring Substituted Thieno-*o*-quinodimethanes *via* Electrophilic Substitution Reactions of Thieno-3-sulfolene

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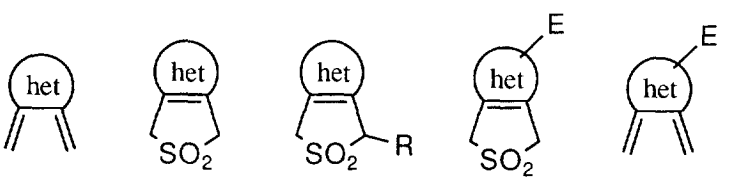
Abstract. Thieno-3-sulfolene **6** has been treated with several electrophiles at very mild temperatures to give substituted derivatives **7a-d**. Thermolysis of these substituted 3-sulfolenes at 170-210°C leads to the formation of the corresponding *o*-quinodimethanes **8a-d** which can be trapped as Diels-Alder cycloadducts.

Heteroaromatic *o*-quinodimethanes (HAQDM) **1** are a class of interesting compounds.[1] Because of their extremely high reactivity, they are usually generated as transient intermediates which are trapped as 1,4-adducts or [4+2] cycloadducts. The generation of HAQDM's can be achieved by several general methods including flash vacuum pyrolysis,[2] reductive 1,4-dehalogenation,[3] desilylation-induced 1,4-elimination,[4] and thermolysis of heteroaromatic-fused 3-sulfolenes **2**.[5] By most of the methods only one target HAQDM can be generated from one specific precursor so that derivatization and synthetic applications are essentially impossible. However, the use of fused 3-sulfolenes as precursors for *o*-quinodimethanes is ideal for synthetic applications because of the ease of introducing substituents at the α-positions of the sulfone group to yield **3** by deprotonation/alkylation reaction sequence.[6] Therefore, a great deal of work has been reported along this line.[5] In principle, it is possible to derivatize the heteroaromatic rings of the fused 3-sulfolenes by electrophilic substitution reactions so as to generate HAQDM's **5** from the 3-sulfolenes **4**. However, so far there is no report on this approach.[7]



1 **2** **3** **4** **5**

We have recently prepared thieno-3-sulfolene **6** by two different approaches[8] and demonstrated it to be a good precursor for the corresponding HAQDM. We have also found that the success of deprotonation/alkylation and subsequent inter- and intramolecular Diels-Alder reactions made compound **6** useful for the synthesis of multicyclic thiophenes. We now report the preparation of derivatives of **6** bearing substituents on the thiophene ring *via* electrophilic substitution reactions.

Treatment of **6** with five equivalents of bromine in CH_2Cl_2 under reflux for 1.5 days produced the monosubstituted product **7a** in 89% yield (Scheme I). Compound **7** could be treated with *t*-BuLi at -78°C to give back compound **6** *via* metal-halogen exchange process. The regiochemistry of the bromination reaction was confirmed by an NOE NMR experiment of compound **7**. A significant nuclear Overhauser effect was observed between H_3 (δ 6.96) and H_4 (δ 4.31), but no NOE between H_3 and H_6 (δ 4.25) was found. Such regioselectivity is consistent with those expected for electrophilic substitution reactions for thiophenes.[9] Attempts to accelerate the bromination reaction by increasing the reaction temperature was not successful. Treatment of **6** with excess of Br_2 in refluxing CCl_4 gave a complex mixture of polybrominated products from which SO_2 had been lost. It is unclear why Br_2 facilitates the extrusion of SO_2 from **6** significantly noticing that compound **6** remains unchanged after heating in refluxing CCl_4 for 1.5 days.

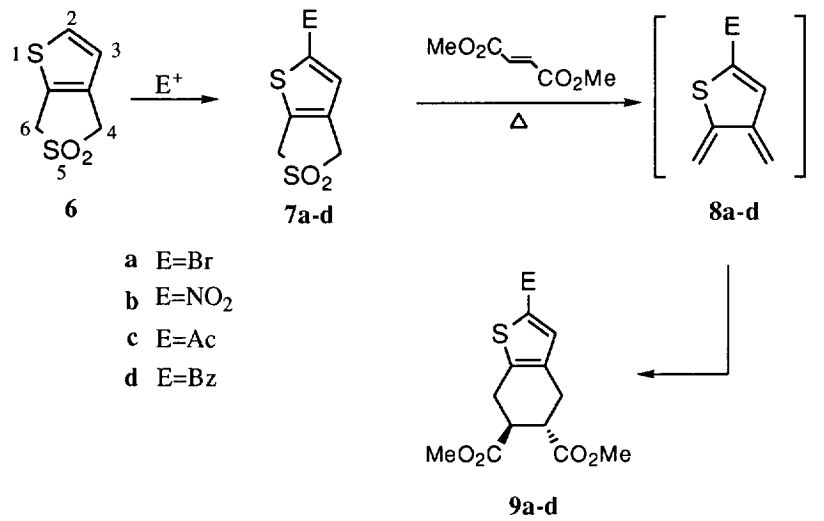
Nitration of compound **6** was accomplished by treatment with HNO_3/HOAc at room temperature. Compound **7b** was produced in nearly quantitative yield. It was also found that higher reaction temperatures resulted in poorer yield of **7b**.

Friedel-Crafts acetylation of **6** with acetyl chloride requires the use of Lewis acid. When the reaction was performed using $AlCl_3$ as the catalyst, the desired acetylated product **7c** was obtained, however only in poor yield. A large amount of decomposed material was observed. After several Lewis acids had been tested, $SnCl_4$ was found most effective for this reaction. Therefore, acetylation of **6** with AcCl in the presence of $SnCl_4$ in refluxing CH_2Cl_2 gave **7c** in 58% yield. Benzoylation with benzoyl chloride under the same condition gave **7d** in 82% yield. Attempts at Lewis acid catalyzed alkylation reactions of **6** have so far been unsuccessful.

In order to demonstrate that compounds **7a-d** are precursors for the ring-substituted thieno-QDM's **8a-d**, trapping reactions were performed by heating toluene solutions of these fused-3-sulfolenes with dimethyl fumarate in sealed tubes at 180-270°C. The corresponding [4+2] cycloadducts **9a-d** were produced without any difficulty (Scheme I).

In summary, we have prepared ring-substituted thieno-3-sulfolenes **7a-d** *via* aromatic electrophilic substitution reactions and proved that they are ideal precursors for the corresponding HAQDM's by thermolysis in the presence of dimethyl fumarate. This reaction sequence can conceptually be applied to other heteroaromatic-fused 3-sulfolenes. This, coupled with the well-established deprotonation/alkylation of 3-sulfolenes,[6] should provide an efficient route to a wide variety of substituted HAQDM's.

Scheme I



Experimental Section

2-Bromo-4,6-dihydrothieno[2,3-*c*]thiophene 5,5-Dioxide (7a)

To a CH_2Cl_2 solution (20 mL) of thieno-3-sulfolene **6**[8] (152 mg, 0.87 mmol) heated at reflux was added slowly a Br_2 solution (0.70g, 4.36 mmol) in CH_2Cl_2 (9 mL) through an additional funnel over a period of 30 min after which time the reaction mixture was heated for another 1.5 days. After evaporation of the volatiles under reduced pressure, the crude product was purified by column chromatography (silica gel, hexane/EtOAc, 4:1) to give **7a** as a white solid (89%): mp 163-165 °C; IR (KBr) 2944, 1728, 1432, 1303, 803 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 4.25 (s, 2H), 4.31 (s, 2H), 6,96 (s, 1H); MS (m/z) 254 (M^++1), 252, 190, 188, 109, 62, 45 (100). Anal. Calcd for $C_6H_5BrO_2S_2$: C, 28.47; H, 1.99. Found: C, 28.74; H, 1.97.

2-Nitro-4,6-dihydrothieno[2,3-*c*]thiophene 5,5-Dioxide (7b)

A solution of compound **6** (73.3 mg, 0.42 mmol), acetic anhydride (3.0 mL), acetic acid (1 mL), and concentrated HNO_3 (0.078 mL) was stirred at room temperature for 1 day after which time H_2O (10 mL) was added. The aqueous layer was extracted with EtOAc (20 mL x 3) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 2:1) to give **7b** as a white solid (98%): mp 163-165 °C; IR (KBr) 3111, 2952, 1325, 1177, 800 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 4.32 (s, 2H), 4.43 (s, 2H), 7.84 (s, 1H); MS (m/z) 219 (M^+), 155 (100), 109, 65. Anal. calcd for $C_6H_5NO_4S_2$: C, 32.87; H, 2.30; N, 6.39. Found: C, 33.18; H, 2.15; N, 6.04.

2-Acetyl-4,6-dihydrothieno[2,3-*c*]thiophene 5,5-Dioxide (7c)

A solution of compound **6** (45.0 mg, 0.26 mmol), acetyl chloride (110.4 mg, 1.41 mmol), and $SnCl_4$ (1 mmol as a 1M solution in CH_2Cl_2) in CH_2Cl_2 (5 mL) was heated at reflux for 10 h after which time H_2O (5 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:1) to give **7c** as a white solid (58%): mp 147-148 °C; IR (KBr) 2919, 1728, 1651, 1311, 1168 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.57 (s, 3H), 4.31 (s, 2H), 4.42 (s, 2H), 7.55 (s, 1H); MS (m/z) 216 (M^+), 190, 152 (100), 137, 109. Anal. Calcd for $C_8H_8O_3S_2$: C, 44.43; H, 3.73. Found: C, 44.74; H, 3.46.

2-Benzoyl-4,6-dihydrothieno[2,3-*c*]thiophene 5,5-Dioxide (7d)

A solution of compound **6** (51.2 mg, 0.29 mmol), benzoyl chloride (242.2 mg, 1.72 mmol), and $SnCl_4$ (1.5 mmol as a 1M solution in CH_2Cl_2) in CH_2Cl_2 (5 mL) was heated at reflux for 6 h after which time H_2O (5 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:1) to give **7d** as a white solid (82%): mp 184-186 °C; IR (KBr) 2897, 1626, 1294, 1168 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 4.33 (s, 2H), 4.47 (s, 2H), 7.46-7.70 (m, 4H), 7.80-7.89 (m, 2H). MS (m/z) 278 (M^+), 214 (100), 105, 77. Anal. Calcd for $C_{13}H_{10}O_3S_2$: C, 56.09; H, 3.62. Found: C, 55.70; H, 3.79.

General Procedure for Thermolysis of Fused 3-Sulfolenes 7a-d in the Presence of Dimethyl Fumarate to Yield the Cycloadducts 9a-d.

A solution of **7** (0.28 mmol) and dimethyl fumarate (2.80 mmol) in toluene (10 mL) in a sealed tube was heated for a period of time. The mixture was cooled to room temperature and then the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 5:1) to give the product **9**.

Dimethyl *trans*-2-Bromo-4,5,6,7-tetrahydrobenzothiophene-5,6-dicarboxylate (9a)

Compound **8a** was obtained by heating at 180 °C for 5 h as a white solid in 77% yield: mp 89-91 °C; IR (KBr) 2953, 1731, 1435, 1170 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.62–3.20 (m, 6H), 3.73 (s, 6H), 6.71 (s, 1H); MS (m/z) 334 (M^++1), 332, 303, 302, 301, 300, 274, 273, 215, 214, 134 (100). Anal. Calcd for $C_{12}H_{13}BrO_4S$: C, 43.26; H, 3.93. Found: C, 43.29; H, 3.58.

Dimethyl *trans*-2-Nitro-4,5,6,7-tetrahydrobenzothiophene-5,6-dicarboxylate (9b)

Compound **8b** was obtained by heating at 250 °C for 2 h as a pale yellow solid in 54% yield: mp 108-109 °C; IR (KBr) 2959, 1728, 1425, 1319, 1015 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.77-3.30 (m, 6H), 3.75

(s, 6H), 7.62 (s, 1H). MS (m/z) 299 (M^+), 268, 239, 180, 134 (100), 91. Anal. Calcd for $C_{12}H_{13}NO_6S$: C, 48.16; H, 4.38; N, 4.68. Found: C, 48.22; H, 4.22; N, 4.30.

Dimethyl *trans*-2-Acetyl-4,5,6,7-tetrahydrobenzothiophene-5,6-dicarboxylate (9c)

Compound **8c** was obtained by heating at 210 °C for 5 h as a white solid in 65% yield: mp 126-128 °C; IR (KBr) 2948, 1726, 1271, 1174, 996 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.50 (s, 3H), 2.72-3.30 (m, 6H), 3.74 (s, 6H), 7.36 (s, 1H); MS (m/z) 296 (M+), 264, 236, 177, 134, 91, 59, 43 (100). Anal. Calcd for $C_{14}H_{16}O_5S$: C, 56.74; H, 5.44. Found: C, 56.47; H, 5.45.

Dimethyl *trans*-2-Benzoyl-4,5,6,7-tetrahydrobenzothiophene-5,6-dicarboxylate (9d)

Compound **8d** was obtained by heating at 270 °C for 5 h as a white solid in 70% yield: mp 105-107 °C; IR (KBr) 3074, 2949, 1731, 1618, 1434, 1225 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 2.76-3.40 (m, 6H), 3.74 (s, 3H), 3.75 (s, 3H), 7.30 (s, 1H), 7.44-7.65 (m, 3H), 7.78-7.89 (m, 2H); MS (m/z) 358 (M^+), 326, 298, 239, 149, 105 (100), 77. Anal. Calcd for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06. Found: C, 63.43; H, 4.77.

Acknowledgement. We thank the National Science Council for financial support. We also thank Ms.Su-Ching Lin for performing the NOE NMR experiment of compound **7a**.

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(*Received in China* 28 *May* 1996; *revised* 13 *June* 1996; *accepted* 9 *July* 1996)