ORGANIC LETTERS

2003
Vol. 5, No. 11
1883−1885

Thiophene Isosteres of 9,10-Dithioanthraquinone

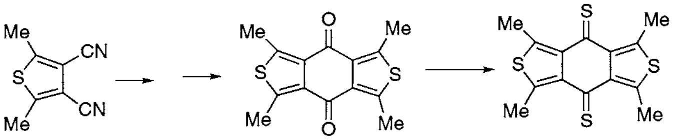
Yvette A. Jackson,[†] Desikan Rajagopal, Jackie Bendolph,[‡] Melanie Guillory,[‡]
M. V. Lakshmikantham, Jongtae Yang, and Michael P. Cava*

Department of Chemistry, University of Alabama, P.O. Box 870336,
Tuscaloosa, Alabama 35487

mcava@bama.ua.edu

Received March 10, 2003

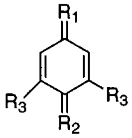
ABSTRACT



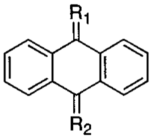
The preparation of 1,3,5,7-tetramethyl-4,8-dihydrobenzo[1,2-c:4,5-c′]dithiophene-4,8-dione and its conversion to the corresponding mono- and dithione are described.

In contrast to the volume of literature, reviews, and monographs on *p*-benzoquinone, very little is known about sulfur analogues of quinones. The mono and dithio analogues **1a** and **1b** of *p*-benzoquinone have been generated and characterized spectroscopically in an argon matrix.[1] Recently, compound **1c** was isolated and found to be relatively stable in the solid state.[2] Monothioanthraquinone **2a** was synthesized by Raasch from diazaanthrone and elemental sulfur in refluxing DMF[3] and also by reaction of anthrone with a sulfur-transfer reagent.[4] In comparison to the benzoquinone analogue **1a**, monothioanthraquinone **2a** is very stable. Formation of the dithione **2b** of anthraquinone, however, has not met with much success. There has been one report of generation of a compound thought to be **2**b, but it was also reported that the experiment could not be reproduced.[5]

In 1986, we reported our results of thionation of anthraquinone.[6] We isolated traces of monothione from the reaction of anthraquinone with Lawesson's reagent in varying solvents and succeeded in obtaining polydisulfide **5** in good yield (80%) when boiling solutions of anthraquinone and Lawesson's reagent were quickly mixed under nitrogen and the mixture was heated at reflux for 3 h. We also confirmed the intermediacy of the monothioanthraquinone **2a** in this reaction by subjecting it to thionating conditions, which led to polydisulfide **5**. In fact, even when monothioanthraquinone was subjected to the reactions as shown in Scheme 1 and the thionated adduct **4** subjected to retro-Diels−Alder conditions, the polydisulfide **5** was obtained in good yield.[6]



1a R_1 =S, R_2 =O, R_3 =H
1b $R_1 = R_2$ =S, R_3 = H
1c R_1 = S, R_2 = O, R_3 =t-Bu



2a R_1 = O, R_2 = S
2b R_1 = R_2 = S

The relative stability of monothione **1c** over **1a** was attributed to steric protection by the bulky *t*-butyl groups.[2] Annelation of two benzene rings to *p*-benzoquinone also allowed for a more stable monothione (**2a** over **1a**), but anthraquinone dithione is still very reactive, and it polymerizes to **5** upon formation. Our objective was to choose appropriate structural modifications to facilitate the isolation

---

[†] Present address: University of the West Indies, Mona, Kingston 7, Jamaica, West Indies.

[‡] Participants of the Summer Undergraduate Research Program (Summer 1999).

(1) Bock, H.; Mohmand, S.; Hirabayashi, T.; Maier, G.; Reiseauer, H. P. *Chem. Ber*. **1983**, *116*, 273.

(2) Suzuki, R.; Matsumoto, K.; Kurata, H.; Oda, M. *J. Chem. Soc., Chem. Commun*. **2000**, 1357.

(3) Raasch, M. A. *J. Org. Chem*. **1979**, *44*, 632.

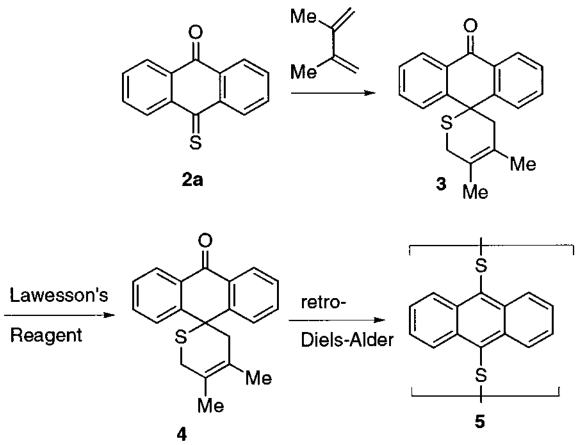
(4) Huang, N. Z.; Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem*. **1987**, *52*, 169.

(5) Heilbron, I. M.; Heaton, J. S. *J. Chem. Soc*. **1923**, *123*, 1735.

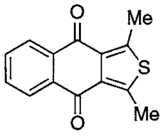
(6) Lakshmikantham, M. V.; Levinson, M.; Menachery, M.; Cava, M. P. *J. Org. Chem*. **1986**, *51*, 411.

10.1021/ol034419g CCC: $25.00

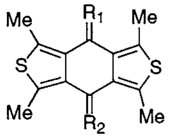
Scheme 1



of a dithione. In this regard, the annelation of thiophene rings to benzoquinones was considered. The substrates of choice appeared to be the thiophene isosteres **6** and **7a**, in view of the fact that the starting materials were readily prepared.



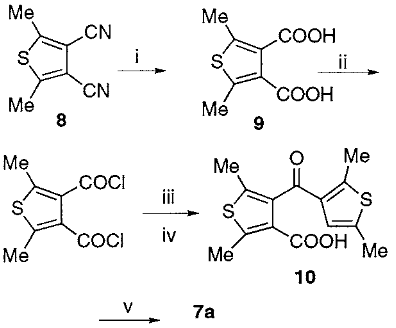
6



7a $R_1 = R_2 = O$
7b $R_1 = S$, $R_2 = O$
7c $R_1 = R_2 = S$

Synthesis of compounds **6** and **7a** was accomplished by extension of MacDowell's method.[7] When phthaloyl dichloride in 1,2-dichloroethane was treated with aluminum chloride followed by 2,5-dimethylthiophene, we obtained the desired diketone **6** in 80% yield as fluffy yellow needles. Compound **7a** was obtained by the pathway shown in Scheme 2. Hydrolysis of the readily prepared **8**[8] with potassium hydroxide in refluxing ethylene glycol[7] produced the dicarboxylic acid **9** (90%). This was treated with thionyl chloride, and the resulting bis acid chloride was subjected to Friedel–Crafts reaction with 2,5-dimethylthiophene. Unlike the case with phthaloyl dichloride, the diketone was not obtained directly, but ketoacid **10** was isolated. Finally, ring closure of **10** to **7a** was achieved quantitatively by treatment with phosphorus pentoxide in methanesulfonic acid.

Scheme 2[a]



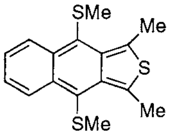
[a] Reagents: (i) KOH/ethylene glycol, reflux 4 h; (ii) $SOCl_2$; (iii) $AlCl_3/Cl(CH_2)_2Cl$; (iv) dimethylthiophene; (v) $P_2O_5/MeSO_3H$.

Thionation of **7a** was attempted using Lawesson's reagent and Davy reagent methyl. The latter was found to give more consistent and reproducible results. Treatment of **7a** with 1.2 molar equiv of Davy reagent methyl for 2 h in refluxing toluene produced, after chromatography, the monothione **7b** as a fluffy emerald-green solid in 42% yield. (Unreacted starting material (15%) was also recovered.) When the reaction time was increased to 12 h, **7b** was obtained in 40% yield, no starting material was recovered, and dithione **7c** was isolated (5%). Dithione **7c** is a very dark green, microcrystalline compound showing λ_{max} at 428 nm (log e 3.36) and a low intensity absorption maximum in dichloromethane solution at 636 nm. Unfortunately, the compound did not give crystals that were suitable for single-crystal X-ray analysis.

Direct thionation of monothione **7b** was attempted. The reaction required extended time. After 18 h, there was still starting material present and dithione was produced in only 16% yield. On recovery of the dithione, the remaining brown solid of unknown constitution was stirred overnight with aqueous 2 M sodium hydroxide to give diketone **7a** in 25% yield based on starting monothione.

In an effort to prepare more dithione **7c**, we also attempted Diels–Alder reaction of monothione **7b** with 2,3-butadiene, with a view to thionation and retro-Diels–Alder reaction.[6] Compound **7b**, however, did not react with 2,3-butadiene in chloroform at room temperature or even with excess diene at reflux. The thione moiety may be too crowded for Diels–Alder reaction to occur. Steric factors may also be inhibiting formation of the dithione.

We turned our investigation to diketone **6**, but this compound did not behave in a manner similar to anthraquinone or to **7a**. When thionation was attempted with Lawesson's reagent under the conditions used for anthraquinone or with Davy reagent methyl under the conditions used for **7a**, neither the corresponding polydisulfide nor the monothione was obtained. For both reagents, reaction occurred to give complex mixtures of yellow compounds. We also treated the thionation reaction product under conditions of reductive methylation. If dithione were present, then the dithiolate anion could be obtained and trapped as the dithiomethyl compound **11**. This also proved to be unsuccessful, and attempts at reductive methylation led largely to water-soluble material.



11

The cyclic voltammograms of the thiophene annelated quinones and their sulfur analogues were determined in methylene chloride solution containing 0.1 M tetrabutylammonium hexafluorophosphate. The quinone **7a** showed two reversible reduction waves at −0.938 and −2.441 V. Monothione **7b** showed a reversible wave at −1.277 and an irreversible peak at 1.508V. The dithioquinone **7c** showed two quasireversible reduction peaks at −1.645 and −2.171 V.[9]

In conclusion, the first dithioanthraquinone analogue has been isolated, albeit in low yield, and has been characterized fully. The stability may well be due to a combination of steric and electronic factors. Further experiments will be necessary to be enlightened on this aspect.

Acknowledgment. We thank the National Science Foundation for a grant (CHE 99-10177) in support of this work. Y.J. thanks the University of the West Indies for a generous leave of absence. J.B. and M.G. were recipients of REU (NSF) fellowships (Summer 1999). We also thank Dr. James Parakka (Calmec Corporation) for advice on the determination of CVs.

Supporting Information Available: Proton and carbon NMR and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034419G

---

(7) MacDowell, D. W. H. *J. Org. Chem.* **1972**, *37*, 1712.

(8) Cook, M.; Jafari-Fini, A. *Tetrahedron* **2000**, *56*, 4085.

(9) CVs were determined using a Pt W.E., a Pt counter electrode, and a standard calomel electrode. The concentration of the substrates was 0.1−0.2mM and the sweep rate was 200 mV/s. The CV of an isomeric 2,3-b annelated dithioquinone was reported by: Büschel, M.; Stadler, C.; Lambert, C.; Beck M.; Daub, J. *J. Electroanal. Chem.* **2000**, *484*, 24.