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First Rational Synthesis of the Thiothiono Analogue of an Unsymmetrically Substituted Phthalic Anhydride

Christopher F. Morrison and D. Jean Burnell*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

jburnell@mun.ca

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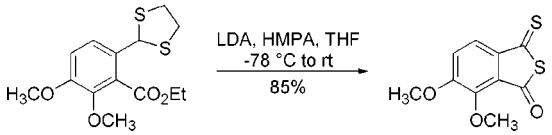
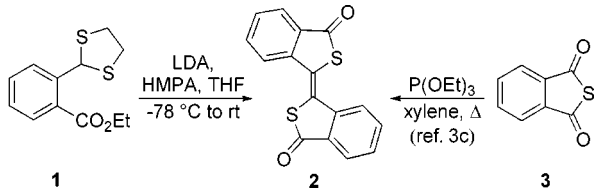
ABSTRACT



Treatment of the dithiolane derivative of an α-carboxyethyl benzaldehyde with LDA at −78 °C smoothly produced the thiothionophthalic anhydride. The mechanism is proposed to involve loss of ethene and attack of an intermediate dithiocarboxylate onto the ester. Heating the thiothionophthalic anhydride gave the 3,3′-bithiophthalide.

Ozaki et al.[1] introduced the dithiolane-bearing benzoate **1** as a reagent for cyclization to a benzocyclohexyl system via a Michael and Claisen process. We were interested in using more complex analogues of **1** for the synthesis of antibiotics. Accordingly, we repeated the work of Ozaki et al., and our results were entirely consistent with theirs. However, we noticed that the anion derived from **1** was relatively short-lived and, in the absence of a Michael acceptor, the 3,3′-bithiophthalide **2** was obtained in 83% yield (Scheme 1).[2]

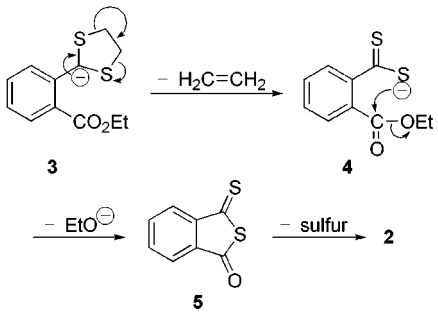
Scheme 1



Compound **2** has been known for over 100 years as the product of reductive dimerization of thiophthalic anhydride **3**.[3]

In our instance it seemed very unlikely that **2** was derived from **3**. Our rationale for the production of **2** is presented in Scheme 2. Fragmentation of the dithiolane, with loss of ethene, would give the thiocarboxylate **4**, and cyclization would then lead to thiothionophthalic anhydride **5**. Cava and co-workers[4] found that **5** is not stable. It loses sulfur readily to give **2**.

Scheme 2



There are very few examples of analogues of anhydrides in which more than one oxygen is replaced by sulfur. These

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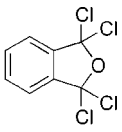
structurally interesting compounds were not reported until the early 1980's.[5] The simple phthalate **5** was synthesized only once. To prepare **5**, Cava[4] began with phthalic anhydride. Treatment with PCl_5 afforded 1,1,3,3-tetrachloro-1,3-dihydroisobenzofuran **6**. Its reaction with 1,1-dimethylethanethiol in trifluoroacetic acid gave, after rearrangement, **5**. The same procedure was used to obtain the dimethoxy compound **7** from the symmetrical 4,5-dimethoxyphthalic anhydride, but this procedure cannot be expected to provide only one thiothionoanhydride from an unsymmetrically substituted phthalate.



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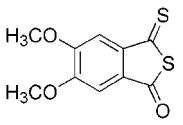

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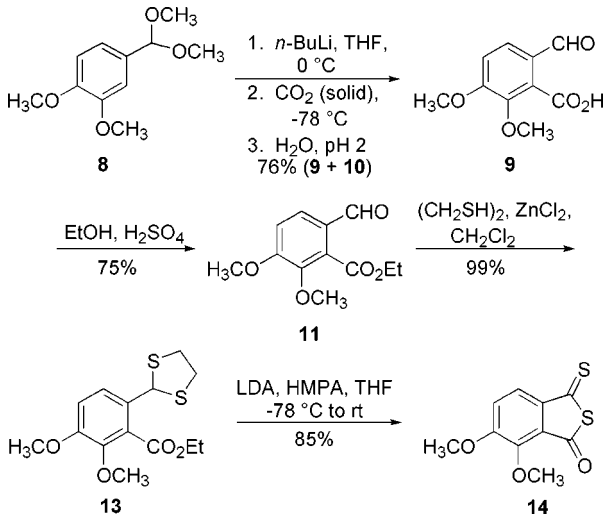
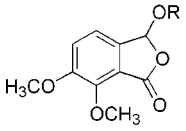
We exploited the process outlined in Scheme 2 to effect the first synthesis of a thiothionophthalic anhydride corresponding to an unsymmetrically substituted phthalate (Scheme 3). Directed orthometalation of the acetal **8**, derived from

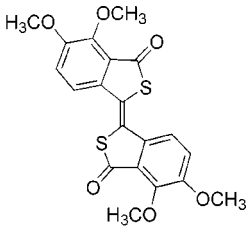
Scheme 3



3,4-dimethoxybenzaldehyde, provided the desired aldehydo-acid **9**.[6] In solution, this compound was in equilibrium with a cyclized form **10**. Esterification of the mixture of **9** and **10** gave mainly **11**, but this was accompanied by 22% of the cyclized form **12**. Thioacetalization of **11**, catalyzed by $ZnCl_2$, provided **13** in good overall yield. LDA was added to a solution of **13** (containing 0.83 equiv of HMPA) at −78 °C. The mixture was allowed to attain room temperature, and following aqueous workup and chromatography, the only product was the dimethoxythiothionophthalic anhydride **14**[7] in a yield of 85%.



10 R = H
12 R = Et



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It had been noted that **7** is less prone to reductive dimerization than is **5**.[4] Similarly **14** proved to be stable over an extended period at room temperature. Nevertheless, when molten **14** was heated above 110 °C, dimeric compound **15** rapidly resolidified.[8] The ^{1}H NMR spectrum of **15** was extremely similar to that of **14**, but the melting point of **15** was above 310 °C. Also, the molecular ions were the base peaks in the mass spectra of **14** and **15**.

In summary, fragmentation of the anion of the dithiolane derivative of an α-carboxyethyl benzaldehyde leads to the efficient production of a rare functional group variant, the thiothionoanhydride.

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(1) Ozaki, Y.; Imaizumi, K.; Okamura, K.; Morozumi, M.; Hosoya, A.; Kim, S.-W. *Chem. Pharm. Bull.* **1996**, *44*, 1785.

(2) In this reaction 0.8 equiv of HMPA was used. It was interesting that **2** was not produced when the amount of HMPA was raised to 3.2 equiv.

(3) (a) Gabriel, S.; Leupold, E. *Chem. Ber.* **1898**, *31*, 2646. (b) Toland, W. G.; Campbell, R. W. *J. Org. Chem.* **1963**, *28*, 3124. (c) Markgraf, J. H.; Heller, C. I.; Avery, N. L., III. *J. Org. Chem.* **1970**, *35*, 1588.

(4) Orange solid, mp >310 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (2H, d, J = 8.5 Hz), 7.20 (2H, d, J = 8.5 Hz), 4.02 (3H, s), 4.00 (3H, s); MS *m/z* (rel intensity) 418 (13, $M^+ + 2$), 416 (100, M^+), 401 (14), 242 (17), 200 (35), 183 (38), 170 (51), 143 (45), 130 (29), 41 (34), 28 (76).

(5) Raasch, M. S.; Huang, N.-Z.; Lakshmikantham, M. V.; Cava, M. P. *J. Org. Chem.* **1988**, *53*, 891.

(6) (a) Kato, S.; Sugino, K.; Matsuzawa, Y.; Katada, T.; Noda, I.; Mizuta, M.; Goto, M.; Ishida, M. *Liebigs Ann. Chem.* **1981**, 1798. (b) Kato, S.; Shibahashi, H.; Katada, T.; Takagi, T.; Noda, I.; Mizuta, M.; Goto, M. *Liebigs Ann. Chem.* **1982**, 1229. (c) Lakshmikantham, M. V.; Carroll, P.; Furst, G.; Levinson, M. I.; Cava, M. P. *J. Am. Chem. Soc.* **1984**, *106*, 6084.

(7) Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* **1977**, *51*, 4921.

(8) Green-brown needles, mp 101−104 °C: IR (Nujol) 1713, 1568, 1265, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3/CD_3COCD_3$, 500 MHz) δ 7.92/7.88 (1H, d, J = 8.8 Hz), 7.19/7.50 (1H, d, J = 8.8 Hz), 4.02/4.06 (3H, s), 4.00/3.96 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 220.1 (0), 190.4 (0), 161.2 (0), 146.9 (0), 138.5 (0), 125.9 (0), 120.9 (1), 118.8 (1), 62.1 (3), 57.6 (3); MS *m/z* (rel intensity) 242 (10, $M^+ + 2$), 240 (100, M^+), 225 (5), 207 (66), 179 (20), 121 (21), 120 (36), 106 (24), 104 (16), 94 (15), 93 (18), 78 (27), 69 (23).