Tetrahedron Letters, Vol.31, No.15, pp 2121-2124, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

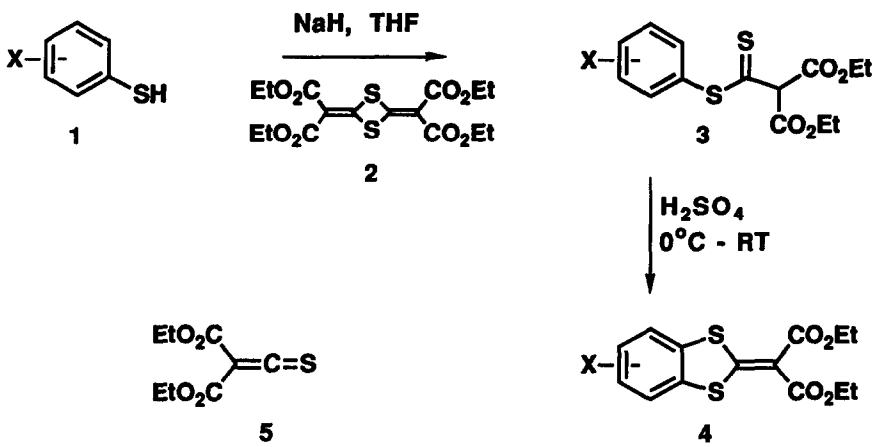
CYCLIZATION OF AROMATIC DITHIOIC ESTERS: SYNTHESIS OF 1,3-BENZODITHIOLES

Clinton M. Yeung and Larry L. Klein*
Anti-infective Division, 47-N, Abbott Laboratories, Abbott Park, IL 60064-3500

Abstract: The two step synthesis of 1,3-benzodithiol-2-ylidene compounds such as 4 is described starting from various aromatic thiols **1**.

During synthetic studies carried out for a related project, we uncovered a novel and convenient method for the preparation of 1,3-benzodithiole analogs such as **4**. Due to their interesting electronic properties,[1] these compounds have seen use as organic electrophotographic materials and as models for organic ferromagnetism. In addition, several reduced analogs have exhibited antimicrobial activity.[2]

Previously, 1,3-benzodithioles of this type have been prepared starting with relatively inaccessible aromatic *o*-dithiols[3a] or via nucleophilic displacement of *ortho*-substituted leaving groups in substrates such as 1,2-dihalo, or *o*-nitro-haloaromatics.[3b,4] In contrast, our approach utilizes the aromatic thiol **1** as our starting material, and constructs the dithiole ring system via a two-step procedure. The first step of this process involves a nucleophilic attack of the thiol **1** upon bis-(2,4-dicarboethoxymethylene)-1,3-dithietane **2**.[5] The stable dithioester **3** is then treated with sulfuric acid to produce the 2-ylidene-1,3-benzodithiole derivative in what is formally an electrophilic thiolation.



The tetraester reagent **2** was first prepared in 1888 and is a member of the family of compounds known as the "desaurins".[6] Although the reactions of these dithietanes with nucle-

ophiles have been well documented,[7] only one report of a thiol addition reaction has appeared.[7a] We have found these addition reactions to proceed smoothly if the conjugate salt of the thiol is used.[8] It is believed that the initial addition to **2** occurs at the dithietane carbon so as to eliminate the bis-(carboethoxy)-thioketene **5**, which can subsequently react with another equivalent of thiol **1**. In this way, **2** serves as a stable dimeric source of the thioketene. The resultant dithioesters can be chromatographically purified prior to the cyclization or carried on directly to the final products. In either case, by simply stirring these esters in concentrated sulfuric acid at 0°C to room temperature, the rapid aromatic thiolation occurs to give **4**.[9]

Table I. Formation of Dithioester 3 and Benzodithiole 4

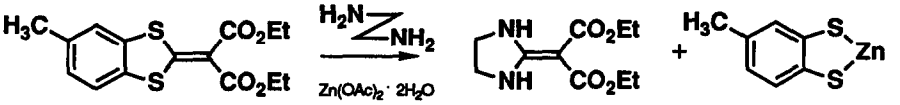
entry	Thiol **1**	yield **3** (%)	yield of **4**(%)[g]	mp of **4**(°C)
a	C_6H_5SH	81%[a]	76%	120
b	2-napthalenethiol	72%[a]	38%[c]	147
c	*p*-MeC_6H_4SH	93%[a]	79%	130
d	2,4-$(Me)_2C_6H_4SH$	92%[a]	60%	125
e	2,5-$(Me)_2C_6H_4SH$	78%[a]	74%	175
f	*p*-FC_6H_4SH	84%[a]	73%	156
g	*o*-ClC_6H_4SH	57%[b]	75%	157
h	*m*-BrC_6H_4SH	74%[b]	82%[d]	125-138[f]
i	3,4-$(Cl)_2C_6H_4SH$	52%[b]	71%[d]	166-179[f]
j	*m*-$(MeO)C_6H_4SH$	61%[b]	36%[e]	135
k	*p*-$(MeO)C_6H_4SH$	85%[b]	15%	same as 10

[a] Toluene was used as solvent. [b] Tetrahydrofuran was used as solvent. [c] Only cyclization onto the napthalene 1 position was observed. [d] An equal mixture of two isomers produced. [e] Only cyclization *para* to the methoxy group was observed. [f] Melting point of 1:1 mixture. [g] All compounds gave satisfactory combustion analyses.

Since this cyclitive process must involve an oxidation we suspect that the sulfuric acid serves as the oxidant. When **3a** was heated with polyphosphoric acid or concentrated hydrochloric acid, **4a** was not produced and in the latter case, only starting material was recovered. Using the standard conditions, there seemed to be little or no effect on the rate or yield of reaction through variation of thiol ring substituents. For example, the 4-fluoro- and 4-methyl-benzenethioester intermediates were cyclized to their corresponding benzodithiole products in equally facile fashion. In cases where regioisomers are possible, the results varied.

Equal mixtures of both isomers were seen in two cases (entries **h, i**) and only one isomer in the others (entries **b, j**).

In order to obtain structural information and to increase the general usefulness of this process, we reacted the monomethyl analog **6** with ethylenediamine in ethanol and obtained 4-(bis-(carboethoxy)methylene)-imidazolidine (**7**) in good yield. When zinc acetate was added to this same reaction, we could also isolate the insoluble zinc salt of the *o*-dithiol **8** in 91% yield. These salts have been known to serve as convenient and stable forms of the readily oxidized dithiols. Since release of the dithiol from these zinc salts can be accomplished using either acid or base,[10] this procedure formally establishes a three step method for the preparation of aromatic 1,2-dithiols from thiols.



6 7 8

In summary we have described here a expeditious synthetic route to 1,3-benzodithioles starting from aromatic thiols.

References

(1) Jap. patent: JP 63/225382 A2 [15 Dec 1986]; CA110(17): 154285y; Jap. patent: JP 63/150274 A2 [15 Dec 1986]; CA110(6): 48378w; Jap. patent: JP 60/170842 A2 [15 Feb 1984]; CA104(12): 99433u; Garito, A.F.; Heeger, A.J. *Acc. Chem. Res.*, **1974**, *7*, 218.

(2) Mazza, M.; Pavanetto, F.; Montanari, L.; Modena, T. *Il. Farmaco - Ed. Sc.*, **1980**, *35*, 1015; for 1,3-oxathioles: Fiedler, H.; Zinner, H. *Arch. Pharm. (Weinheim)*, **1958**, *291*, 330, 480, 493.

(3) (a)Mizuno, M.; Cava, M.P. *J. Org. Chem.* **1978**, *43*, 416. (b) Yokoyama, M. *J. Org. Chem.*, **1970**, *35*, 283; D'Amico, J.J.; Ruminski, P.G.; Suba, L.A.; Freeman, J.J.; Dahl, W.E. *Phos. and Sul.* **1985**, *21*, 307.

(4) A review of the synthetic approaches to 1,3-dithioles: Gotthardt, H. *Comp. Het. Chem.* **1984**, *6(4B)*, 813. Another approach has been via reaction of dithiocarboxylic acid dianions through a Michael-type addition to the corresponding β-carbons of *p*-benzoquinones. In this case, mixtures of multi-substituted 4,7-dioxygenated quinones often resulted due to unreacted quinone acting as a reoxidizing agent: Harris, R.L.N.; Oswald, L.T. *Aust. J. Chem.* **1974**, *27*, 1309; Klemm, K.; Geiger, B. *Justus Liebigs Ann. Chem.*, **1969**, *726*, 103.

(5) Raasch, M.S. *J. Org. Chem.* **1970**, *35*, 3470; Bergreen, H. *Ber.* **1888**, *21*, 337.

(6) General review of 1,3-dithietanes: Dittmer, D.C.; Sedergran, T.C. *The Chem. Het. Cpds.*, **1985**, *42(Pt.3)*, 431; Mayer, R.; Krober, H. *Z. Chem.* **1975**, *15*, 91.

(7) (a) This work involved diketo-dithietanes and few details were available: Schroth,W.; Uhlig, H.-F.; Bahn, H.; Hildebrandt, A.; Schmiedl, D. *Z. Chem.* **1974**, *14*, 186; (b) General

reactions of desaurins with nucleophiles: *nitrogen* - Peseke, K. *Tetrahedron* **1976**, *32*, 483; Peseke, K. *Z. Chem.* **1981**, *21*, 102; Peseke, K. *Z. Chem.* **1975**, *15*, 19; *carbon* - Peseke, K.; Quincoces, J. *Z. Chem.* **1981**, *21*, 406.

(8) When phenol was used as nucleophile in place of thiophenol, the adduct corresponding to **3** was isolated and cyclized to the 1,3-benzooxathiole in modest yield. Using aniline in this reaction sequence yielded adduct but the cyclization reaction led to a complex mixture of products.

(9) A typical procedure is as follows: Using toluene as solvent (see Table) - To a suspension of NaH (60% wt) (11 mmol) in toluene (20 mL) at room temperature was added the appropriate thiophenol (10 mmol) followed by **2** (5.5 mmol). The resulting slurry was heated at 90°C for 0.5 hours and refluxed for 2.5 hours. The cooled mixture was quenched with 1M HCl (6 mL) and partitioned between sat. NaCl solution and chloroform. The organic layer was evaporated and the oily residue was purified by column chromatography on silica gel (25 g) using chloroform as the eluent. When tetrahydrofuran (THF) was used as solvent the addition of thiophenol was carried out at 0°C and after 0.5 hours, **2** was added and the ice bath removed. The mixture was stirred at room temperature for 6 hours and heated to 45°C for one hour, before workup as above.

Cyclization: The diester above (0.3 g) was added to conc. sulfuric acid (6 g) at 0°C. After 10 minutes the ice bath was removed and the mixture was stirred at room temperature for 3-6 hours, and the disappearance of starting material was monitored via TLC. The reaction was quenched with ice water and sat. NaCl solution. After stirring for 0.5 hours the suspension was extracted with chloroform. The resulting solid obtained after solvent evaporation was chromatographed on silica gel (20 g) using chloroform as the eluant and recrystallized from ethanol. Elemental analyses for **4** have been collected and all C,H values are within range of the calculated values (see Supplementary Information).

(10) Clark, R.E.D. *Analyst*, **1957**, *82*, 182.

(Received in USA 12 January 1990)