Tetrahedron Letters, Vol. 34, No. 23, pp. 3703-3706, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A New Synthesis of 3H-1,2-Dithiole-3-thiones

Thomas J. Curphey* and H. Howard Joyner

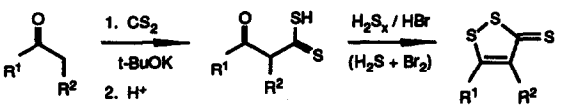
Department of Pathology, Dartmouth Medical School, Hanover, New Hampshire 03755

Abstract: Exposure of 3-oxo dithioic acids to a solution of polysulfanes in liquid hydrogen sulfide gives 3H-1,2-dithiole-3-thiones in yields varying from poor to excellent. The method tolerates the presence of functional groups which are problematical for other methods of synthesis.

A number of compounds having the 3H-1,2-dithiole-3-thione (dithiolethione) ring system **2** display marked biological activity. Oltipraz (**2**, R^1 = pyrazinyl, R^2 = methyl) was originally marketed as an antischistosomal drug, although more effective agents are now available for this purpose.[1] The 5-(4-methoxyphenyl) derivative (**2**, R^1 = 4-methoxyphenyl, R^2 = H) is currently used in Canada and Europe as a choleretic and to stimulate salivary secretion.[2] More recently, the dithiolethiones as a class have been shown to have potent chemoprotective activity against a variety of carcinogens in a number of animal model systems,[3] with the parent compound, 3H-1,2-dithiole-3-thione (**2**, R^1 = R^2 = H), being among the most active of those tested.[4] With a view to its eventual use as a chemoprotective agent in man, oltipraz is currently undergoing Phase I clinical trials in the United States.[5] In addition, a large scale intervention trial of oltipraz as a chemoprotective agent is underway in areas of China and Africa having a high incidence of liver cancer.[6] A very recent development is the finding that oltipraz inhibits replication of the HIV-1 (AIDS) virus.[7] The wide spectrum of biological activity displayed by the dithiolethiones as a class, and the resulting need for preparation of various substituted derivatives, have led us to embark on a program to develop new methods for synthesis of this ring system. We report here efforts which have culminated in a new synthetic method having some advantages over those previously used.

One of the most commonly employed methods for preparation of the dithiolethiones involves thiation of 3-oxo esters.[8] Typically, P_4S_{10}, with or without added elemental sulfur, has been used as the thiating reagent. More recently, Lawesson's reagent in combination with elemental sulfur is claimed to give yields superior to P_4S_{10}.[9] Both reagents require prolonged reaction at elevated temperature and are incompatible with some functional groups such as carboxamido. In addition, the high equivalent weight of Lawesson's reagent and the need to use it in excess leads to a crude product grossly contaminated with byproducts which must be removed by chromatography. Other methods for synthesis of dithiolethiones employed in the past either lack generality, require several steps, or proceed in low overall yield.[8]

In considering new approaches to synthesis of dithiolethiones, we were attracted to the possibility of constructing the dithiolethione ring by the addition of disulfane (H_2S_2), or its equivalent, to a 3-oxo ester, or equivalent. Unfortunately, disulfane is an unstable substance whose preparation and purification require special apparatus.[10] We reasoned that the mixture of polysulfanes, H_2S_X, produced by addition of oxidants to liquid hydrogen sulfide,[11] although consisting principally of polysulfanes with $x > 2$, might serve as an *in situ* source of disulfane via rapid disproportionation of the higher polysulfanes. Indeed, similar procedures have been used for the preparation of 1,2-dithiolium salts from diketones, polysulfanes, and strong acids.[12] In the event, when 3-oxo dithioic acids **1**, readily prepared from ketones and carbon disulfide,[13] were added to a solution of polysulfanes in liquid hydrogen sulfide, the expected dithiolethiones **2** were produced (Eq. 1).[14] The results obtained for a variety of substrates are shown in Table I.[15]



1 **2** (1)

Table I. Preparation of 3H-1,2-Dithiole-3-thiones

			Yields (%)[a]		Melting Point (°C)	
Entry	R^1	R^2	HPLC[b]	Isolated[c]	Observed	Lit
1	CH_3	H	62	42	33-34	33[16]
2	C_6H_5	H	62	52	125-126	125-126[17]
3	$(CH_3)_3C$	H	70	64	69-70	70[18]
4	CH_3	CH_3	29[d]	—	—	—
5	C_6H_5	CH_3	85	71	104-105	103-104[17]
6	Pyrazinyl	CH_3	2	—	—	—
7	$-(CH_2)_4-$		50	35	102-103	102[19]
8	$-(CH_2)_3-$		21	18	121-122	122-123[19]
9[e]	H	CO_2Et	20	15	63-64	—[20]
10[e]	CH_3	CO_2Et	79	68	69-70	68[21]

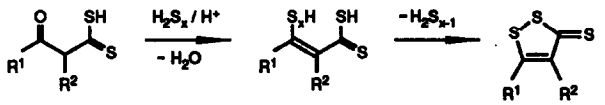
[a]Based on starting ketone. [b]Chromatographic yield determined on a Beckman Ultrasphere ODS column with water-methanol mobile phase. [c]Yield of purified material. [d]A small amount (ca 2%) of isomeric 5-ethyl compound was detected. [e]Reaction with CS_2 carried out under phase transfer conditions.[22]

The polysulfane reaction may be conducted either by adding bromine to liquid hydrogen sulfide, followed by a solution of the 3-oxo dithioic acid in dichloromethane, or, alternatively, by adding bromine to the 3-oxo dithioic acid dissolved in a mixture of liquid hydrogen sulfide and dichloromethane. No consistent difference was noted in the yields obtained by the two procedures. Bromine can be replaced by sulfur monochloride,[11] but

the yields suffer. Even in cases where the yields were only moderate, the crude dithiolethione obtained after workup was remarkably free of byproducts, as compared to similar preparations utilizing P_4S_{10} or Lawesson's reagent. As a rule, simple bulb-to-bulb distillation or filtration through silica gel, followed by recrystallization, gave product of good purity with very little material loss. The method tolerated the presence of an ester group (Entries 9 and 10), in contrast to preparations involving P_4S_{10}, which gave thiono esters as byproducts.[23]

Unfortunately, the preparation of oltipraz (Entry 6) by this procedure was not successful, only a trace of product being detected chromatographically. The reasons for this failure are uncertain. However, we have observed that the yields of dithiolethiones seems to depend markedly on the quality and stability of the intermediate 3-oxo dithioic acids. In the case of oltipraz, the crude 3-oxo dithioic acid precursor gave NMR spectra suggestive of a complex mixture, so it seems likely that the preparation failed at the first stage.

Details of the course of the reaction between the 3-oxo dithioic acid and the polysulfane mixture leading to dithiolethione formation are not clear at this time. The conditions used for this ring closure are similar to those employed to convert 3-oxo esters to *gem*-dithiols and enethiols by reaction with H_2S.[24] It is tempting, therefore, to propose (Eq. 2) that the polysulfane, in an acid-catalyzed reaction, converts the 3-oxo dithioic acid **1** to an enepolysulfide **3**, which then cyclizes to the dithiolethione **2** by an intramolecular thiol-disulfide interchange reaction.



1 **3** **2** (2)

While the use of liquid hydrogen sulfide has obvious drawbacks with regard to toxicity and difficulty of scale-up, we have found the method convenient for the preparation of dithiolethiones on a 1 - 100 mmol scale. Methods which avoid the use of large quantities of hydrogen sulfide are currently under investigation and will be reported in due course.

Acknowledgement: Financial support for this work was provided by the National Cancer Institute (CA39416).

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14. We have found that 3-oxo esters, when treated under the same conditions, give complex mixtures of what appear to be polysulfides formed by addition of the polysulfanes to the ketone carbonyl group. No 3H-1,2-dithiol-3-ones are formed.

15. Representative procedure: To a stirred solution of potassium *tert*-butoxide in THF (27.8 mL of 1.08M, 30 mmol) was added a mixture of propiophenone (1.34 g, 10 mmol) and carbon disulfide (1.52 g, 20 mmol). The resulting orange suspension was stirred for 2 h, cooled in an ice bath, and methanesulfonic acid (2.88 g, 30 mmol) added dropwise. The cooling bath was removed and water (1.62 g, 90 mmol) was added, followed by magnesium sulfate (1 g). After stirring an additional 15 min, the mixture was filtered and the solvent removed under reduced pressure to yield the crude 3-oxo dithioic acid as a red oil. This material was used in the next step without further purification.

    CAUTION: All further operations should be carried out in a well-ventilated fume hood. To liquid hydrogen sulfide (15 mL) cooled in a Dry Ice-acetone bath was added slowly with stirring a solution of the crude 3-oxo dithioic acid in dichloromethane (10 mL). Bromine (1.6 g, 10 mmol) was then added dropwise over a 15 min period. The reaction mixture was stirred for 6 h in the cooling bath, then allowed to warm to room temperature overnight. The reaction mixture was diluted to a total volume of 100 ml with dichloromethane, and a small aliquot was removed for quantitative analysis by HPLC. The amount of dithiolethione present corresponded to an 85% yield, based on propiophenone taken. The remaining methylene chloride solution was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized from carbon tetrachloride to give 4-methyl-5-phenyl-3H-1,2-dithiole-3-thione (1.82 g, 71%) as a crystalline orange solid, mp 104-105°C (lit[17] mp 103-104°C). ^{1}H NMR δ 7.45-7.56 (m, 5 H), 2.20 (s, 3 H). ^{13}C NMR δ 215.6, 167.9, 141.8, 133.3, 130.7, 129.2, 128.6, 16.6.

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(Received in USA 30 March 1993)