

Synthesis of 5-(alkylthio or arylthio)-3*H*-1,2-dithiol-3-one derivatives

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Dedicated to Prof. Joan Bosch on the occasion of his 60th Birthday

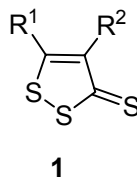
Abstract

5-(*R,S*)-3*H*-1,2-dithiol-3-one derivatives with R=butyl, ethyl, phenyl, cyclopentyl, octyl, p-chlorophenyl, p-bromophenyl and p-methoxyphenyl were prepared in moderate to good yield from the reaction of the corresponding 5-(*R,S*)-3*H*-1,2-dithiol-3-thione with Hg(CH₃COO)₂ in glacial acetic acid.

Keywords: 3*H*-1,2-Dithiol-3-one, 3*H*-1,2-dithiol-3-thione, synthesis

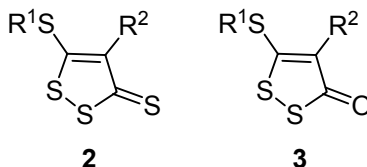
Introduction

The heterocyclic pseudoaromatic compounds 3*H*-1,2-dithiole-3-thiones **1** have been known for several years.¹



A wide variety of alkyl and aryl derivatives have been synthesized and a great number of these compounds display biological activity and have industrial applications. For instance, Oltipraz (4-methyl-5-pyrazinyl-3*H*-1,2-dithiole-3-thione) was originally used as an antischistosomal agent due to its remarkable activity against *Schistosoma mansoni*.² In addition, studies have demonstrated that Oltipraz inhibits HIV-1 (AIDS)³ virus replication by irreversibly binding to the viral reverse transcriptase enzyme. This compound has also shown

chemoprotective activity against a great variety of carcinogens and investigations are in progress to determine its probable use as a chemoprotective agent.⁴⁻⁶ Other derivatives like 4-aryl-5-chloro-3*H*-1,2-dithiole-3-thiones have proven to be fungitoxic⁷ and they have also been used as insecticides.⁸ We reported that several derivatives of **2** have interesting activity as antimycotic agents⁹ and that their solubility increases in the presence of β -cyclodextrin.¹⁰ Besides, it has been claimed¹¹ that the antifungicidal activity of derivatives **1** increases when the thiocarbonyl group is replaced by a carbonyl group.



We therefore undertook a study in order to develop a method to synthesize **3** and the results are presented here.

Results and Discussion

Several methods have been used to exchange the sulfur by oxygen in 3*H*-1,2-dithiol-3-thione derivatives **1**. Some examples include treatment with KMnO_4 in acidic acetone,¹² or the reaction with Cl_2/CCl_4 and then with water.¹³ More recently Torroba has reported that $\text{EtO}_2\text{C-CNO}^-$ in THF gives excellent yields of the oxidation products in compounds that have the same nucleus as **1**.¹⁴ The presence of an extra sulfur atom in compound **2** limits the use of oxidants because the alkyl or arylthio function can be easily oxidized to sulfoxide.¹⁵ The most frequently used method utilizes mercury acetate in acetic acid as reagent.¹⁶ We show here that derivatives **2a-i** can be converted into the corresponding **3** in moderate to good yields using these reagents (see Table 1). Although no other product could be isolated and the substrate was completely consumed, the low yield probably results from ring opening reactions giving rise to an untreatable mixture of products.

Attempts to do the reaction using KMnO_4 in acidic acetone gave only decomposition products while Cl_2/CCl_4 led to about 5% yield of the expected product starting from compound **2a**. It was reported that treatment with $\text{Bi}(\text{NO}_3)_3$ gave good results in the transformation of thioamides into amides¹⁷ but this methodology applied to **2a** yielded only 30% of **3a**.

Table 1. Yield of compounds **3a-i** obtained

2	R ¹	R ²	3 % ^a
a	butyl	H	70
b	ethyl	Cl	43
c	phenyl	H	26
d	ethyl	H	30
e	cyclopentyl	H	57
f	octyl	H	54
g	p-chlorophenyl	H	18
h	p-bromophenyl	H	21
i	p-methoxyphenyl	H	43

^a Isolated yield

Experimental Section

General Procedures. ¹H and ¹³C NMR were recorded on a Bruker 200MHz instrument using TMS as an internal standard. Chemical shifts are reported in δ (ppm). IR spectra were recorded on a Nicolet 5SXC spectrometer using KBr pellets. Reagents used were obtained from commercial suppliers or synthesized as indicated below. The high resolution mass spectrometry analyses were carried out in the University of California, Riverside.

General synthetic procedures

Synthesis of compounds 2. The compounds **2** were prepared according to the method described in the literature.¹⁸ A typical run is the following: 15.7 mmol of P₂S₅, 9.7 mmol of S₈, 0.032 mmol of 2-mercaptobenzothiazole (MBT) and 0.016 mmol of ZnO were loaded into a three-necked round bottomed flask and xylene (40 mL) was added. The mixture was then boiled under N₂ and the corresponding dithiolmalonate (15.7 mmol), dissolved in 40 mL of xylene, was added dropwise for 30 minutes under continuous stirring. The reaction was boiled for an additional 1.5 hour. The color changed from light yellow to dark reddish brown. Then, the crude reaction mixture was filtered and the solvent evaporated. The dried extract was purified by column chromatography over silica gel 70-230 mesh and CH₂Cl₂/hexane 50:50 was used as eluent.

Synthesis of compounds 3. 1 mmole of **2** dissolved in 30 mL of acetone, freshly distilled over KMnO₄, was loaded into a dry three-necked round bottomed flask under a N₂ atmosphere and the solution warmed to 50°C. Afterwards 2 mmoles of (CH₃COO)₂Hg dissolved in 2 mL of glacial acetic acid were slowly added and the solution was stirred additionally for 30 min. A saturated solution of NaHCO₃ was added to stop the reaction and after filtering it, it was extracted with CHCl₃. The product was purified by column chromatography on silica gel eluted with solvents of

increasing polarity from hexane to hexane/CH₂Cl₂ 50% v/v. Compounds **3b**, **3h** and **3i** were crystalline solids and were purified further by recrystallization in hexane (**3b** and **3i**) or CHCl₃ (**3h**).

Compound characterization

Most of the compounds are obtained as a yellow or orange oil with strong and unpleasant odor. Compound **3b**, **3h** and **3i** are crystalline solids (**3b** and **3h** yellow and **3i** orange). A typical UV-Vis spectrum is shown in Figure 1 where the spectrum of **2** is also shown for comparison.

5-Butylthio-3H-1,2-dithiol-3-one (3a). ¹³C NMR (50 MHz, CDCl₃): 13.42; 21.77; 30.86; 34.57; 116.46; 171.03; 192.09. ¹H NMR (CDCl₃): 0.89 (t, 6.94 Hz, 3H); 1.47 (m, 2H); 1.72 (m, 2H); 3.08 (t, 7.3Hz, 2H); 6.37(s, 1H). IR cm⁻¹(KBr): 617.2; 794.9; 939.7; 1110.8; 1229.3; 1512.2; 1636.6; 2868.0; 2927.2; 2960,1; 3078.6. HRMS calculated for C₇H₁₀OS₃ 205.9894, found 205.9896.

4-Chloro-5-ethylthio-3H-1,2-dithiol-3-one (3b). ¹³C NMR (50 MHz, CDCl₃): 14.27; 26.23; 116.76; 161.76; 184.11. ¹H NMR (CDCl₃): 1.49 (t, 7.66 Hz, 3H); 3.20 (c, 7.66 Hz, 2H). IR cm⁻¹ (KBr): 663.3; 801.5; 841.0; 979.2; 1183.2; 1492.5; 1643.9; 2927.2; 2979.9. HRMS calculated for C₅H₅ClOS₃ 211.9191, found 211.9189. mp 98.4–99.3 °C (lit¹⁹ 104°C)

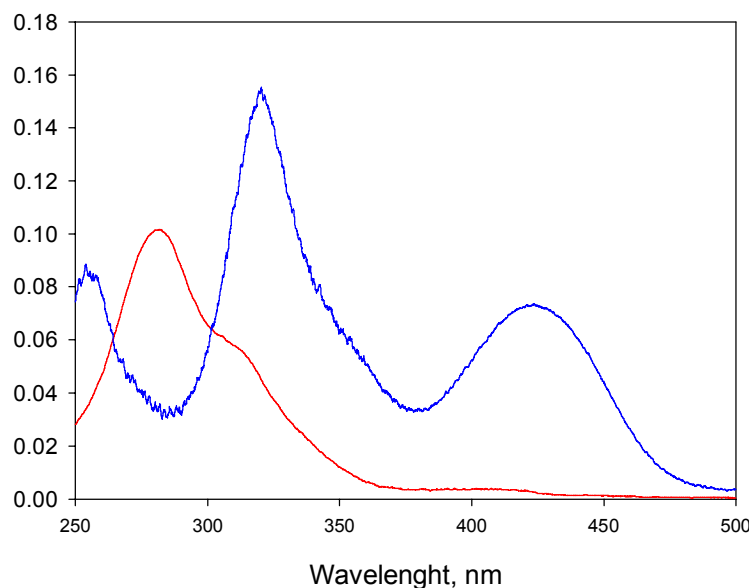


Figure 1. Uv-vis spectrum of 5-butylthio-3H-1,2-dithiol-3-ona (—) and 5-butylthio-3H-1,2-dithiol-3-thione (—) 1.2×10^{-5} M in hexane.

5-Phenylthio-3H-1,2-dithiol-3-one (3c). ¹³C NMR (50 MHz, CDCl₃): 116.22, 126.97, 129.96, 131.25, 135.67, 171.79, 191.90. ¹H NMR (CDCl₃): 6.39 (s, 1H); 7.47-7.62 (m, 5H). IR cm⁻¹ (KBr): 620.8, 691.2, 753.3, 807.1, 947.8, 1026.4, 1121.6, 1237.4, 1444.3, 1477.5, 1506.7, 1643.0, 1670.0, 2363.0, 3050.0. HRMS calculated for C₉H₆OS₃ 225.9581, found 225.9589.

5-Ethylthio-3*H*-1,2-dithiol-3-one (3d). ^{13}C NMR (50 MHz, CDCl_3): 14.01, 29.05, 116.48, 170.65, 192.03. ^1H NMR (CDCl_3): 1.44 (t, 7.32 Hz, 3H), 3.13 (C, 7.32 Hz, 2H), 6.40 (s, 1H). IR cm^{-1} (KBr): 613.2, 799.4, 934.8, 1108.3, 1379.1, 1506.0, 1654.1, 2360.8, 1915.1, 2970.2. HRMS calculated for $\text{C}_5\text{H}_6\text{OS}_3$ 177.9581 found 177.9584.

5-Cyclopentylthio-3*H*-1,2-dithiol-3-one (3e). ^{13}C NMR (50 MHz, CDCl_3): 24.77, 33.66, 47.54; 116.70, 171.17, 192.03. ^1H NMR (CDCl_3): 1.72 (m), 2.17 (m), 3.75 (m), 6.37(s). IR cm^{-1} (KBr): 611.4, 790.5, 930.6, 1105.8, 1226.4, 1448.3, 1506.7, 1646.8, 1658.5, 2861.2, 2954.6, 3075.3. HRMS calculated for $\text{C}_8\text{H}_{10}\text{OS}_3$ 217.9894 found 217.9890.

5-Octylthio-3*H*-1,2-dithiol-3-one (3f). ^{13}C NMR (50 MHz, CDCl_3): 13.96, 22.50, 28.51, 28.81, 28.92, 31.59, 34.71, 34.85, 116.30, 170.57, 191.92. ^1H NMR: 0.86 (t, 3H), 1.26 (m, 10H), 1.72 (m, 2H), 3.07(t, 7.68Hz, 2H), 6.37(s, 1H). IR cm^{-1} (KBr): 494.7, 619.2, 724.3, 790.5, 938.4, 113.6, 1226.4, 1382.1, 1452.2, 1506.7, 1670.2, 2366.9, 2853.4, 2923.5, 2958.5, 3059.7. HRMS calculated for $\text{C}_{11}\text{H}_{18}\text{OS}_3$ 262.0520 found 262.0523.

5-(4-Chlorophenylthio)-3*H*-1,2-dithiol-3-one (3g). ^{13}C NMR (50 MHz, CDCl_3): 116.81, 125.51, 130.34, 136.91, 138.10, 170.71, 191.84. ^1H NMR (CDCl_3): 6.42 (s, 1H), 7.43-7.60 (dd, 4H). IR cm^{-1} (KBr): 615.3, 755.5, 802.2, 825.5, 950.1, 1020.1, 1090.2, 1113.6, 1230.3, 1269.3, 1393.8, 1475.5, 1506.7, 1576.7, 1646.8, 1666.3, 2359.1, 2767.8, 2849.6, 2923.5, 3071.4. HRMS calculated for $\text{C}_9\text{H}_5\text{ClOS}_3$ 259.9191 found 259.9195.

5-(4-Bromophenylthio)-3*H*-1,2-dithiol-3-one (3h). ^{13}C NMR (50 MHz, CDCl_3): 117.02, 126.40, 132.23, 133.38, 137.05, 170.47, 191.93. ^1H NMR (CDCl_3): 6.43 (s, 1H), 7.56 (m, 4H). IR cm^{-1} (KBr): 532.4, 605.5, 728.8, 798.2, 815.7, 1006.4, 1068.7, 1111.5, 1384.0, 1465.7, 1504.6, 1559.1, 1651.5, 1660.5, 2851.4, 2925.3. mp 56.9 – 57.9 °C

5-(4-Metoxyphenylthio)-3*H*-1,2-dithiol-3-one (3i). ^{13}C NMR (50 MHz, CDCl_3): 55.55, 115.25, 115.60, 117.08, 137.97, 162.33, 173.79, 192.25. ^1H NMR (CDCl_3): 3.87 (s, 3H), 6.39 (s, 1H), 6.98 (m, 2H), 7.57 (m, 2H). IR cm^{-1} (KBr): 530.8, 606.5, 794.1, 830.3, 948.8, 1021.2, 1106.8, 1169.3, 1248.3, 1291.1, 1409.2, 1457.1, 1491.9, 1584.0, 1650.5, 1660.1, 2834.7, 2930.1, 3068.35. mp 60.9–61.9 °C. HRMS calculated for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}_3$ 255,9686 found 255,9681.

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