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One-pot synthesis of 3*H*-1,2-dithiole-3-thione derivatives from dithiolmalonic esters

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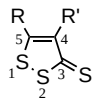
Abstract—The reaction of dithiolmalonic esters with P_2S_5/S_8 in boiling xylene and with 2-mercaptobenzothiazole/ZnO as catalyst produces 5-R (R = alkyl or aryl) thio-3*H*-1,2-dithiole-3-thiones as the major identifiable product. The use of Lawesson's reagent as sulfurizing agent gives even better yields. For instance with R = phenyl the yield rises from 44 to 82%.

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



R, R'= H, alkyl, aryl, etc

1

A wide variety of alkyl and aryl derivatives have been synthesized and a great number of these compounds display biological activity and 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*.[4,5] In addition, recent studies have demonstrated that oltipraz inhibits HIV-1 (AIDS)[6–8] 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.[9–13]

Other derivatives like 4-aryl-5-chloro-3*H*-1,2-dithiole-3-thiones have been found to be fungitoxic[14,15] and they have also been used as insecticides.[16]

Due to their reactivity against metal surfaces, they have been used as protective agents against corrosion from strong mineral acids.[17]

Owing to the great variety of applications reported for this type of compounds, we have undertaken this study in search of simple synthetic routes for new derivatives.

Recently we reported that alkyl esters of malonic acid exposed to a mixture of P_2S_5/S_8 in boiling xylene and in the presence of catalytic amounts of 2-mercaptobenzothiazol (MBT) and ZnO, leads to 5-alkylthio-3*H*-1,2-dithiole-3-thiones as reaction products.[18,19] With that method it is possible to synthesize compounds with primary alkyl groups as substituents, but it fails with secondary and tertiary alkyl groups and with aryl esters. In this paper we report a method of synthesis of compounds **1** starting from dithiol esters. This method is better than those previously published by us and by others because higher yields are obtained and some derivatives which fail to be formed with the other methods could be synthesized.

Dithiolmalonates with different alkyl and aryl groups were formed from malonyl dichloride and the corresponding thiols in anhydrous ether. These compounds were sulfurized, using P_2S_5/S_8 or Lawesson's reagent (*LR*) and 2-mercaptobenzothiazole (MBT) and ZnO in catalytic amount (Eq. (1)). Lawesson's reagent is known as a very selective sulfurizing agent,[20,21] and for the reactions reported here much better yields are obtained with this reagent than with P_2S_5/S_8 (Table 1). The reaction was followed by TLC analysis and it was stopped when no unreacted substrate remained.

Keywords: 1,2-dithiole-3-thione; synthesis; sulfurization; thiolmalonate esters.

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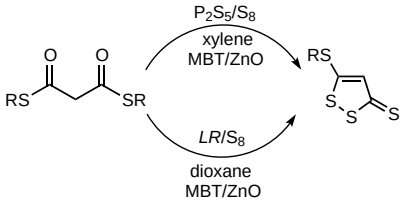
Table 1. Yields and properties of compounds synthesized[a]

Entry	R	Mp (°C)	Yield (%)[b]	Yield (%)[c]	Ref.
1	$CH_3(CH_2)_3$	47–48	61	83	18
2	$CH_3(CH_2)_{11}$	58–59	65	86	(New)[22]
3	C_5H_9	44–45	46	75	(New)[23]
4	C_6H_5	83–84	44	82	(New)[24]
5	$(CH_3)_3C$	47.5–49	17	47	(New)[25]
6	$C_6H_5CH_2$	97–98	41	71	19

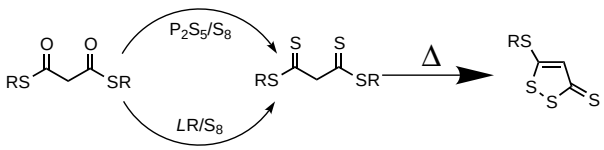
[a] R refers to Eq. (1). The yield correspond to the isolated product after purification as indicated in the text.
[b] With P_2S_5/S_8 as sulfurizing agent.
[c] With *LR*/S_8 as sulfurizing agent.



(1)

It is remarkable that the method is suitable for the synthesis of derivatives of **1** that have phenyl, benzyl, primary, secondary and tertiary alkyl thio groups in the five position. The preparation of this type of derivative is not possible using previously published methods.

Based on literature data, we suggest that the formation of the 5-RS (R = alkyl or aryl) derivatives can be explained in terms of a tetrathiomalonic intermediate, which can be formed as shown in Eq. (2). The transformation of a carbonyl thiolester into a dithiolester is well known.[26] Once the tetrathiomalonic intermediate is formed, it cyclizes in the reaction media to give the 5-alkylthio derivative.[27]



(2)

A typical run is the following: 15.7 mmol of P_2S_5, 9.7 mmol of S_8, 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 N_2 and the corresponding dithiolmalonate (15.7 mmol) dissolved in 40 mL of xylene was added dropwise for 30 min under continuous stirring. The reaction was boiled for an additional 1.5 h. 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 benzene/hexane 50:50 was used as eluent.

For the reactions with Lawesson's reagent, 3.6 mmol of *LR*, 2.5 mmol of S_8, 0.0395 mmol of MBT, 0.0197 mmol of ZnO and 2.02 mmol of the corresponding dithiolmalonate were loaded into a three-necked round-bottomed flask and dioxane (30 mL) was added. The mixture was then boiled under N_2 for 15–18 h with continuous stirring. These reactions are cleaner than those using P_2S_5/S_8 and the purification of the products is easier. It was carried out by column chromatography on silica gel 73–200 mesh eluted with a gradient of hexane/CH_2Cl_2.

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21. Pedersen, B. S.; Lawesson, S. O. *Tetrahedron* **1979**, *35*, 2433.
22. **5-Dodecylthio-3*H*-1,2-dithiole-3-thione**: IR ν_{max}: 2915; 2856; 1508; 1446; 1300; 1267; 1173; 1095; 1034, 906; 796; 715; 654; 545; 512 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 6.94 Hz, 3H); 1.26–1.55 (s and m, 18H); 1.74 (m, 2H); 3.11 (t, 7.3 Hz, 2H); 6.99 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.07; 22.64; 28.59; 28.78; 28.93; 29.21; 29.29; 29.35; 29.46; 29.56; 31.88; 35.90; 135.22; 174.67; 212.75. HRMS: calcd for $C_{15}H_{26}S_4$: 334.09173; found: 334.09169.
23. **5-Cyclopentylthio-3*H*-1,2-dithiole-3-thione**: IR ν_{max}: 3026; 2947; 2914; 1503; 1439; 1268; 1225; 1176; 1031; 906; 830; 649; 550; 505 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.77 (m, 6H); 2.22 (m, 2H); 3.75 (m, 1H); 7.00 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.90; 33.82; 48.59; 135.59; 174.94; 212.70. MS: $M^+=234$; 166 (M^+-68, protonated dithiole thione $C_3H_2S_4^+$); 133 (M^+-101, $C_3HS_3^+$); 101 ($C_3HS_2^+$); 69 ($C_5H_9^+$); 57 ($C_4H_9^+$); 41 ($C_3H_5^+$) HRMS: calcd for $C_8H_{10}S_4$: 233.96654; found: 233.96759.
24. **5-Phenylthio-3*H*-1,2-dithiole-3-thione**: IR ν_{max}: 3058; 1501; 1456; 1274; 1205; 1168; 1034; 965; 901; 817; 744; 680; 650; 543; 485 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 6.96 (s, 1H), 7.42–7.70 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 127.89; 130.12; 131.31; 134.70; 135.05; 175.45; 212.68. MS: $M^+=242$; 177 (M^+-65, loss of S_2H, $C_9H_5S_2^+$); 133 (M^+-109, C_3H_5S); 121 (M^+-121, $C_7H_5S^+$); 101 (M^+-141, loss of $C_6HS_3^+$, $C_3H_5S_2^+$); 77 ($C_6H_5^+$); 69 ($C_3HS_2^+$). HRMS: calcd for $C_9H_6S_4$: 241.93523; found: 241.93474.
25. **5-*tert*-Butylthio-3*H*-1,2-dithiole-3-thione**: IR ν_{max}: 3006; 2960; 1446; 1367; 1286; 1174; 1157; 1034; 906; 805; 655; 550 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 9H); 7.17 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 31.15; 51.56; 144.12; 167.58; 214.91. MS: $M^+=222$; 166 (M^+-56, loss of C_4H_8, $C_3H_2S_4^+$); 101 ($C_3HS_2^+$); 57 ($C_4H_9^+$); 44 (CS^+). HRMS: calcd for $C_7H_{10}S_4$: 221.96690; found: 221.96653.
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