

One-pot synthesis of 5-alkylthio-3H-1,2-dithiole-3-thiones

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Abstract: Dialkyl malonate esters reacted with P_2S_5/S_8 in boiling xylene and with 2-mercaptobenzothiazole / ZnO as catalyst to yield 5-alkylthio-3H-1,2-dithiole-3-thiones as major products.

Compounds derived from 3H-1,2-dithiole-3-thione are pseudoaromatic heterocycles known from many years. A great variety of alkyl and aryl derivatives have been synthesized and many of them find use in several areas. Oltipraz,[®] (4-methyl-5-pyrazinyl-3H-1,2-dithiole-3-thione) has activity against the *Schistosoma mansoni* and has been long used.¹ It was also shown recently that it inhibits the replication of HIV viruses.² Other derivatives have been shown to have activity against many pathogenic agents.³ Another suggested use for this type of compound is in the protection of surfaces from acid corrosion, since they react readily with metal surfaces.⁴ Compounds such as 5-alkylthio- and 4-tert-butyl-5-neopentyl-3H-1,2-dithiole-3-thione are used as engine oil additives⁵.

The best known method for the synthesis of this type of compound involves the reaction of β -ketoesters with mixtures of P_2S_5/S_8 . Considering that diethyl malonate has the β -dicarbonyl groups required for the reaction, we used it as substrate. Surprisingly, the product obtained was not the 5-ethoxy-substituted compound but the 5-thioethoxy compound **1**. Compounds **1** with R = ethyl, butyl or octyl, as well as that with R = ethyl and R' = benzyl were obtained in fair to modest yield (see Table), but no effort have been made so far to optimize the method. Alternative methods of synthesis of compounds **1** involve several steps using costly reagents and result in low overall yields,⁶ or the heterocycle has to be pre-formed.^{5a}

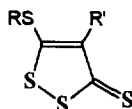
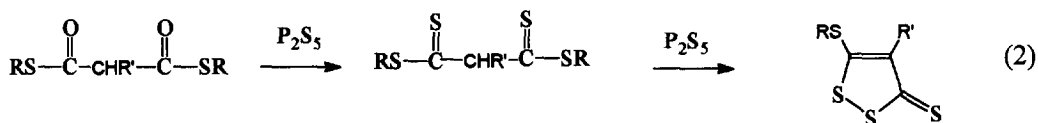
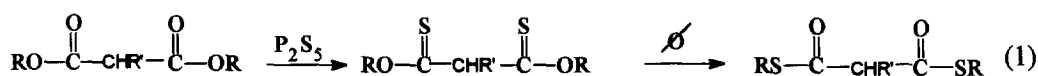


Table: Summary of 1 derivatives synthesized

Reac.	R	R'	mp	% yield	Ref.
1	CH ₃ -CH ₂ -	H	67-68 °C	31	6
2	CH ₃ -(CH ₂) ₃ -	H	47-48 °C	32	New ⁷
3	CH ₃ -(CH ₂) ₇ -	H	51-52 °C	28	New ⁸
4	CH ₃ -CH ₂ -	C ₆ H ₅ -CH ₂ -	97-98 °C	12	New ⁹

The derivatives with different alkyl groups were formed from the corresponding malonate diesters. Dibutyl and dioctyl ester were synthesized by transesterification¹⁰ using ethyl malonate in the presence of an excess of the corresponding alcohol. The ethanol formed was distilled off during the reaction; the yield was more than 90 % in every case, and the NMR and IR spectra were in agreement with literature values. Diethyl 2- benzylmalonate was obtained by alkylation of the diethyl malonate enolate.¹¹

Based on literature data, we suggest that a likely mechanism for the formation of compounds 1 could be as described in eqs 1 and 2: first the carbonyl groups of the ester are exchanged by S¹² which, under the reaction condition, rearrange to thioester¹³ which exchange again their carbonyl oxygens to thiocarbonyls, and finally cyclize to give 1. Experimental work is in progress to check this hypothesis. We did not find in the literature an explanation regarding the function of the catalysts (mercaptbenzothiazol and ZnO)



A typical reaction is as follows: P₂S₅ (3.485 g; 15.7 mmole), S₈ (2.512 g; 0.0785 atom g) 2-mercaptbenzothiazol (MBT) (5.3 mg; 0.032 mmole) and ZnO (1.3 mg; 0.036 mmole) were placed in a three necked round bottomed flask and xylene (40 mL) was added. The mixture was boiled under N₂ stream and ethyl malonate (2.512 g; 15.7 mmole) dissolved in xylene (25 mL) was added dropwise for about 30 min and then the boiling was kept for 1.5 hours. The reaction

mixture changed its color from light yellow to dark brown. The reaction mixture was filtered and the solvent was evaporated. The crude solid residue was purified by column chromatography on silica gel (70-230 mesh) using benzene-hexane (50:50 v/v) as eluent to give 5-ethylthio-3H-1,2-dithiole-3-thione (0.944 g; 31 %) mp 67-68 °C (lit.⁶ 68-68.5°C), IR(KBr): 3050, 2970, 2920, 1455, 1315, 1174, 1040, 910, 658 and 554 cm⁻¹ (lit.⁶ 3050, 2965, 2925, 2854, 1450, 1317, 1174, 1053, 911 cm⁻¹); NMR ¹H (CDCl₃): δ 1.46 ppm (t, 7.4 Hz., 3H), 3.15 ppm (c, 7.4 Hz, 2H) and 7.00 ppm (s, 1H). [lit.⁶ δ 1.47 (t, 7.4 Hz., 3H), 3.15 (c, 7.4 Hz, 2H) and 7.00 (s, 1H)]. NMR ¹³C (CDCl₃): 14.03, 30.09, 135.22, 174.35 and 212.77 ppm (lit.⁶ 13.98, 30.04, 135.09, 174.37 and 212.63 ppm). MS: M⁺ 194, 165 (M⁺ - 29, loss of CH₃-CH₂⁺), 161 (M⁺-33, loss of SH⁺), 130 (M⁺-64, loss of S₂⁺), 129 (M⁺-65, loss of S₂H⁺); UV-visible: (isooctane) λ_{max} 422 nm (log ε 3.86), 319 nm (log ε 4.11), 255 nm (log ε 3.92), 243 nm (log ε 3.84, shoulder).

It should be noted that the same reaction in the absence of ZnO and MBT yield about half the amount of products. Similar results were observed by Voronkov et. al.¹⁴ for related reactions.

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7. 5-Butylthio-3H-1,2-dithiole-3-thione: mp 47-48 °C; IR(KBr): 2963, 2925, 2854, 1445, 1287, 1173, 1032,

- 912, 657 y 552 cm^{-1} ; NMR ^1H (CDCl_3): δ 0.96 ppm (t, 7.26 Hz, 3H), 1.48 ppm (sex, 7.62 Hz, 2H), 1.77 ppm (q, 7.34 Hz, 2H), 3.12 ppm (t, 7.26 Hz, 2H) y 7.01 ppm (s, 1H); NMR ^{13}C (CDCl_3): 13.46, 21.81, 30.74, 35.55, 135.09, 174.99 y 212.59 ppm; MS: M^+ 222; 180 (M^+-42 , loss of C_3H_5^+), 166 (M^+-56 , $\text{C}_3\text{H}_2\text{S}_4$), 165 (M^+-57 , loss of C_4H_5^+), 157 (M^+-65 , loss of S_2H^+), 57 (M^+-165 , C_4H_5^+); UV-visible: (isooctane) λ_{max} 422 nm (log ϵ 3.82), 320 nm (log ϵ 4.15), and 254 nm (log ϵ 3.89), 243 nm (log ϵ 3.81, shoulder). HRMS: M^+ Calculated: 221.96654, Found 221.96655.
8. 5-Octylthio-3H-1,2-dithiole-3-thione: mp 51-52 $^\circ\text{C}$; IR(KBr): 3046, 2962, 2929, 2851, 1455, 1294, 1175, 1043, 911, 660 and 554 cm^{-1} ; NMR ^1H (CDCl_3): δ 0.86 ppm (t, 6.39 Hz, 3H), 1.2-1.5 ppm (s y m 10 H), 1.79 ppm (q, 7 Hz, 2H), 3.13 ppm (t, 7.1 Hz, 2H) y 7.04 ppm (s, 1H); NMR ^{13}C (CDCl_3): 14.04, 22.57, 28.60, 28.80, 28.90, 29.01, 31.67, 35.92, 135.24, 174.80 y 212.73 ppm; MS: M^+ 278; 245 (M^+-33 , loss of SH), 235 (M^+-43 , loss C_3H_5^+), 213 (M^+-65 , loss of S_2H^+), 166 (M^+-112 , loss of $\text{C}_3\text{H}_2\text{S}_4^+$); UV-visible: (isooctano) λ_{max} 422 nm (log ϵ 3.84), 320 nm (log ϵ 4.19), 254 nm (log ϵ 3.90), 242 (log ϵ 3.81, shoulder). HRMS: M^+ Calculated: 278.02914, Found 278.02927.
9. 5-Ethylthio-4-benzyl-3H-1,2-dithiole-3-thione: mp 97-98 $^\circ\text{C}$; IR(KBr): 3069, 3025, 2973, 2913, 1443, 1310, 1183, 1073, 917, 877, 688, 560 y 514 cm^{-1} . NMR ^1H (CDCl_3): δ 1.46 ppm (t, 7.4 Hz, 3H), 3.20 ppm (c, 7.4 Hz, 2H), 4.10 ppm (s, 2H) y 7.15-7.35 ppm (m, 5H), NMR ^{13}C (CDCl_3): 14.19, 28.54, 35.51, 126.49, 128.27, 128.60, 137.19, 143.11, 171.10 y 210.99 ppm.; MS: M^+ 284; 251 (M^+-33 , loss of SH^+), 223 (M^+-61 , loss of $\text{C}_2\text{H}_5\text{S}^+$), 91 (M^+-193 , $\text{C}_6\text{H}_5\text{-CH}_2^+$); 77 (M^+-207 , C_6H_5^+); UV-visible (isooctano): λ_{max} 427nm (log ϵ 3.88), 324 nm (log ϵ 4.12), 253 nm (log ϵ 3.88, shoulder), 240 nm (log ϵ 3.93), 209 nm (log ϵ 4.12). HRMS: M^+ Calculado: 283.98219, Found: 283.98263
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