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A superior procedure for the conversion of 3-oxoesters to 3*H*-1,2-dithiole-3-thiones

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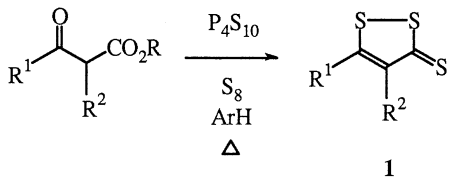
Abstract

The combination of P_4S_{10}, sulfur, and hexamethyldisiloxane converts 3-oxoesters to 3*H*-1,2-dithiole-3-thiones in yields generally superior to those obtained with Lawesson's reagent and without the need for chromatography to remove large amounts of phosphorous-containing byproducts.

Keywords: dithioles; sulfur compounds; sulfur heterocycles; keto acids and derivatives.

The dithiolethiones (3*H*-1,2-dithiole-3-thiones, **1**) are a class of chemoprotective agents which display marked activity against a variety of animal models of cancer.[1] One representative of this class of heterocyclic sulfur compounds (Oltipraz **1**, R^1 = pyrazinyl, R^2 = methyl) is currently undergoing human trials in an area of China having a high incidence of liver cancer.[2] Unfortunately, the existing methods for synthesis of this ring system leave much to be desired,[3] especially for the preparation of the large quantities of material needed for biological testing. We have attempted to develop new procedures for synthesis of the dithiolethione ring system with some success,[4–6] but there still remains a need for methods that can be adapted to large-scale synthesis. This communication reports the discovery of such a method.

Of the usual procedures for synthesis of the dithiolethiones one of the most general and widely used is the reaction of a 3-oxoester with P_4S_{10} and sulfur (Eq. 1), generally conducted in boiling toluene or xylene.[7,8]



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However, even in highly favorable cases the yields are seldom above 50% and are typically in the range of 0–20%.[7] A potential solution to this problem was published by Lawesson some time ago, who found that by replacing P_4S_{10} in Eq. (1) with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent), yields of dithiolethiones could be made nearly quantitative.[9] Unfortunately, the high equivalent weight of Lawesson's reagent and the need to use 2 full moles of the reagent per mole of 3-oxoester means that the dithiolethione comprises only a small percentage by weight of the crude reaction mixture. Because the reagent-derived byproducts cannot be removed by any extractive procedure, the total reaction mixture must be subjected to chromatography to isolate the dithiolethione, and the method becomes impractical for large scale preparations.

A simple solution to these difficulties has now been discovered. Addition of hexamethyldisiloxane (HMDO) to the P_4S_{10}–sulfur mixture of Eq. (1) both greatly increases the yield of dithiolethione **1** and greatly simplifies workup of the reaction mixture.[10] Using the production of 5-methyl-3*H*-1,2-dithiole-3-thione (**1**, $R^1 = Me$, $R^2 = H$) from ethyl acetoacetate as a model, it was found that 0.6 moles of P_4S_{10} per mole of 3-oxoester was optimum. Addition of elemental sulfur up to 1 g atom per mole of 3-oxoester had a beneficial effect on yield, as had been found for Lawesson's reagent[9] and for P_4S_{10} alone,[7] but more than this had no effect. By direct GC analysis of the reaction mixture it was established that 2–2.5 moles of HMDO per mole of 3-oxoester were consumed. Xylene was found to be the most commonly useful solvent, although

Table 1
Preparation of 3*H*-1,2-dithiole-3-thiones from 3-oxoesters, P_4S_{10}, sulfur and HMDO[a]

Entry	R^1	R^2	Time[b] (h)	Yields (%)		
				HPLC[c]	Isolated[d]	LR[e]
1	Me	H	1	98	80	84
2	Et	H	2	98	74	
3	Ph	H	1	83	70	80
4	*t*-Bu	H	8	93	83	79
5[f]	1-Adamantyl	H	5	78	70	
6[g]	Ferrocenyl	H	0.5	45	36	
7	Me	Me	2	95	87	
8	Me	*i*-Pr	2	86	72	80
9	$-(CH_2)_4-$		1	98	86	73
10	$-(CH_2)_3-$		2	83	71	
11	Pyrazinyl	Me	1	19	–	2.5

[a] See text for conditions.

[b] Reaction time in refluxing xylene.

[c] Yield determined by HPLC using the external standards method.

[d] Yield of distilled or recrystallized material. Physical properties (boiling point or melting point) were in good agreement with literature values.

[e] Maximum HPLC yield obtained with Lawesson's reagent.

[f] New substance: mp 141–142°C; ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 6H), 2.00 (s, 6H), 2.13 (s, 3H), 7.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.73, 36.28, 40.91, 43.99, 136.03, 189.47, 215.86. Anal. calcd for $C_{13}H_{16}S_3$: C, 58.16; H, 6.01; S, 35.83. Found: C, 58.27; H, 6.10; S, 35.70.

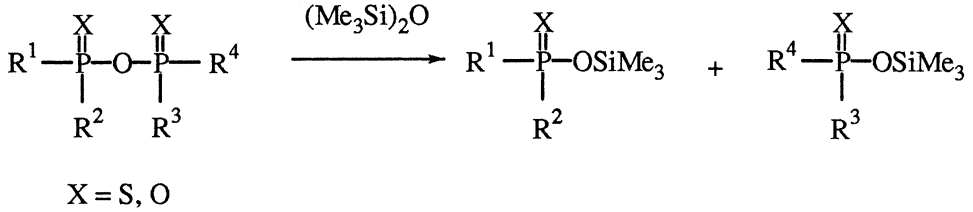
[g] New substance: mp 157–159°C; ^{1}H NMR ($CDCl_3$) δ 4.24 (s, 5H), 4.61 (t, $J = 2$ Hz, 2H), 4.73 (t, $J = 2$ Hz, 2H), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 68.96, 71.41, 72.47, 75.11, 133.79, 176.96, 214.05. Anal. calcd for $C_{13}H_{10}FeS_3$: C, 49.06; H, 3.17; S, 30.22. Found: C, 48.99; H, 3.28; S, 30.38.

the reaction has been successfully run in toluene, ethyl benzene, chlorobenzene, HMDO, dioxane, and 1,1,2,2-tetrachloroethane. The optimum procedure involved refluxing a xylene solution of the 3-oxoester with 0.6 moles of P_4S_{10}, 1 g atom of sulfur, and 3 moles of HMDO per mole of 3-oxoester until HPLC analysis showed the reaction to be over. Results obtained with representative 3-oxoesters are shown in Table 1.

In all but two cases (entries 6 and 11) the chromatographic yields were quite high. Some evidence of a steric effect was apparent, with dithiolethiones having bulky alkyl groups (entries 4 and 5) requiring significantly longer reaction times. Except for entries 5 and 6, isolation of the pure dithiolethiones did not require chromatography. The phosphorus-containing byproducts formed during the reaction were easily removed during workup, most expeditiously by exposure to aqueous K_2CO_3, which hydrolyzed them to water soluble derivatives. After removing small amounts of dark colored polar materials by filtration through a short plug of silica gel plus activated carbon, the final product was then readily purified by distillation, sublimation, and/or recrystallization.

A direct comparison of this new procedure for dithiolethione synthesis with that using Lawesson's reagent was made for six 3-oxoester substrates (entries 1, 3, 4, 8, 9, and 11). In all the cases examined, chromatographic yields using Lawesson's reagent (last column of Table 1) were inferior to those obtained with the P_4S_{10}–HMDO combination.[11] The one case for which the P_4S_{10}–HMDO method proved ineffective was in the synthesis of Oltipraz (entry 11). Although the P_4S_{10}–HMDO combination did give a better yield than Lawesson's reagent, the yield obtained was not significantly different from that obtained with P_4S_{10} alone.[12]

With regard to the way in which HMDO acts to increase the yield of dithiolethione, GC examination established that P_4S_{10} and HMDO, with or without sulfur, do not react in the absence of the 3-oxoester, ruling out prior modification of P_4S_{10} by HMDO as an explanation. Instead, it is proposed (Eq. 2) that pyrophosphate intermediates formed during the course of the thionation reaction are responsible for yield-lowering side reactions and that HMDO converts these pyrophosphates to innocuous trimethylsilylated derivatives.[13]



(2)

Alternatively, and in addition, the trimethylsilyl thiophosphates which result from this scavenging reaction may themselves be active thionating agents,[14] and may thus play a role in modifying the reactivity of the P_4S_{10}.

In conclusion, the combination of P_4S_{10}, sulfur, and HMDO is highly effective in converting 3-oxoesters to dithiolethiones **1**. An investigation of the beneficial effects of HMDO on other thionation reactions of P_4S_{10} is currently underway, the results of which will be reported in due course.

Acknowledgements

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