Pergamon

Tetrahedron Letters 43 (2002) 371–373

TETRAHEDRON
LETTERS

Thionation of esters and lactones with the reagent combination of phosphorus pentasulfide and hexamethyldisiloxane

Thomas J. Curphey

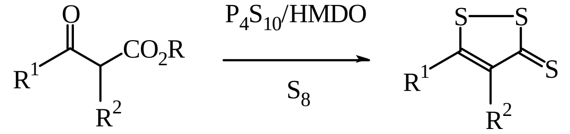
Department of Pathology, Dartmouth Medical School, Hanover, NH 03755, USA

Received 8 June 2001; accepted 29 October 2001

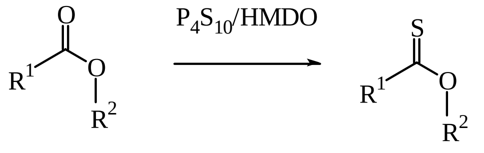
Abstract—The combination of P_4S_{10} and hexamethyldisiloxane converts esters and lactones to thionoesters and thionolactones in yields comparable to or superior to those obtained with Lawesson's reagent. The method has the advantage that reagent-derived byproducts may be removed by a simple hydrolytic workup or by filtration through silica gel, rather than by chromatography, as required for Lawesson's reagent. © 2002 Elsevier Science Ltd. All rights reserved.

Thionoesters and related thionolactones, R^1CSOR^2, are versatile intermediates for organic synthesis.[1] For example, they may be transformed into ethers, $R^1CH_2OR^2$, by reduction with Raney nickel[2,3] or tin hydrides[4,5] and into difluoroethers, $R^1CF_2OR^2$, by treatment with DAST.[6] Reaction of thionolactones with organometallic agents, R^3M, leads to tetrahedral intermediates which may be trapped with methyl iodide and then reduced stereoselectively to alkylated cyclic ethers, $R^1R^3CHOR^2$, a sequence which has proven valuable in the preparation of complex polyether natural products.[7,8] Of the possible precursors to thionoesters, the corresponding esters are highly attractive starting materials, being readily available commercially or by a variety of synthetic methods. Unfortunately, the ester carbonyl group is one of the most difficult of the common carbonyl derivatives to thionate. For example, the apparently straight-forward synthesis of thionoesters from esters using P_4S_{10} suffers from generally low yields.[1] The discovery by Lawesson[9,10] that replacing P_4S_{10} with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent, LR) gives greatly improved yields of thionoesters and lactones has potentially made these derivatives much more accessible and attractive as synthetic intermediates. However, the high equivalent weight of LR and the need to use a full mol of the reagent per mol of ester[9] means that the thionoester often comprises only a small percent 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, and the method becomes impractical (and expensive) for large scale preparations. Moreover, chromatographic separation of the desired product from LR byproducts may, in some cases, be difficult or impossible (vide infra). As a result of these drawbacks to their preparation, the chemistry of the thionoesters and lactones may not have received the attention it deserves. We now report a solution to this problem that makes these useful derivatives available cheaply and in any quantity desired.

Recently, we reported that in the preparation of 3*H*-1,2-dithiole-3-thiones by treatment of 3-oxoesters with LR and sulfur, replacing LR by the combination of P_4S_{10} and hexamethyldisiloxane (HMDO) gave comparable or better yields (Eq. (1)).[11] Moreover, with the P_4S_{10}/HMDO combination, the phosphorus-containing byproducts could be removed by a mild hydrolytic workup. Although it was not clear at what stage the ester carbonyl group was converted into the thiono grouping present in the final product of Eq. (1), it was nevertheless of interest to investigate whether simple esters and lactones could be transformed to their thiono derivatives by the action of P_4S_{10} and HMDO, as shown in Eq. (2). This has indeed been found to be the case, and we now report the results of such an investigation.



(1)



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Keywords: thioesters; thiocarbonyl compounds; thiophosphates; silicon and compounds.

PII: S0040-4039(01)02144-X

Using the production of ethyl thionobenzoate from ethyl benzoate as a model reaction, it was found that the combination of P_4S_{10} and HMDO in refluxing xylenes produced the corresponding thionoester in good yield, as determined by HPLC analysis of the reaction mixture. A series of experiments established that 0.25–0.33 mol of P_4S_{10} per mol of ester were required in order to obtain maximum yields of the thionoester and that approximately 1 mol of HMDO was consumed in the process. Using standard conditions of 0.25–0.33 mol of P_4S_{10} and 1.7 mol of HMDO per mol of ester, thionation of a series of esters and lactones was examined and compared with thionation by LR under similar conditions. The carbonyl substrates were chosen to reflect a variety of structural types: aromatic esters, aliphatic esters, phenolic esters, and unsaturated esters, as well as small ring, medium ring and macrocyclic lactones. Also included were substrates whose thionation by LR was reported to be problematical. The results of these experiments are shown in Table 1.

As shown in Table 1, chromatographic yields of thionoesters and lactones using the combination of P_4S_{10} and HMDO were equal to or greater than those obtained with LR for 13 out of the 14 cases examined. In only one case (entry 9), was a slightly lower yield obtained with the P_4S_{10}/HMDO combination. The results for methyl 4-nitrobenzoate (entry 7) are of particular interest because this ester was reported not to give any thionoester with LR.[2] As indicated in Table 1, thionoester product can in fact be detected by HPLC from the reaction with LR, but the amount is too small to be useful. In contrast, reaction with P_4S_{10}/HMDO gave a better, albeit low, yield and allowed the thionoester to be readily isolated by silica gel chromatography. The difference observed between P_4S_{10}/HMDO and LR in this case may reflect the somewhat greater electrophilicity of the former reagent.

For simple esters and for the one macrocyclic lactone examined (entry 14), reflux in xylenes as solvent proved to be the most generally useful reaction conditions. However, the much greater reactivity of the small and medium ring lactones (entries 10–13) permitted a wider range of solvents and conditions to be employed, of which acetonitrile at reflux proved to be especially effective. Using this solvent, it was even possible to convert caprolactone to the corresponding thionolactone at *room temperature*, the reaction with the P_4S_{10}/HMDO reagent reaching a 65% chromatographic yield in 8 h and a maximum yield of 70% in 20 h. In contrast, the corresponding reaction with LR required 1 h in refluxing toluene to reach a similar maximum yield (entry 12). Thionation of δ-valerolactone (entry 11) provided another telling example of the utility of the P_4S_{10}/HMDO reagent as compared to LR. Although Lawesson reported that this lactone failed to give the thiono derivative with his reagent,[10] δ-valerolactone does, in fact, undergo thionation by LR in refluxing toluene (entry 11). However, examination of the resulting reaction mixture by TLC showed comparable amounts of the thionolactone and of a reagent-derived byproduct whose spots exhibited nearly identical R_f values. Separation of these two components by column chromatography, as in the standard LR procedure,

Table 1. Thionation of esters and lactones $R^1CO_2R^2$ by P_4S_{10}/HMDO and Lawesson's reagent (LR)[a]

Entry	R^1	R^2	Solvent[b]	Chromatographic yields[c] (%)		Isolated yields[d] (%)
				P_4S_{10}/HMDO	LR	
1	Ph	Et	A, A	81	81	73
2	Ph	Me	A, A	92	92	79
3	Ph	*i*-Pr	A, A	95	92	83
4	*n*-Hexyl	Et	A, A	87	76	75
5	Me	2-Naphthyl	B, B[e]	41	40	30
6	1-Naphthyl	Et	A, A	91	83	87
7	4-Nitrophenyl	Me	A, A	28	4	21
8	PhCH=CH-	Et	C, C	75	70	72
9	$Ph_2C=C(CN)$-	Et	A, A	51	59	42
10	$-CH(CH_3)CH_2CH_2-$		D, C	87	85	78
11	$-(CH_2)_4-$		D, C	82	69	65
12	$-(CH_2)_5-$		D, C	82	73	77
13	$-(CH_2)_6-$		D, C	77	58	62
14	$-(CH_2)_{15}-$		A, A	87	84	86

[a] Standard reaction conditions for determination of chromatographic yields: 3 mmol ester, 0.75 mmol P_4S_{10} or 3.6 mmol LR, 5 mmol HMDO (if used), and 3 mL dry solvent were refluxed under argon until HPLC showed the yield of thionoester to have reached a maximum. This required between 45 min and 30 h. For entries 1, 2, 3, and 9, the amount of P_4S_{10} was increased to 1 mmol, which gave slightly improved yields.

[b] The first letter is the reaction solvent used for the P_4S_{10}/HMDO reagent and the second letter is the reaction solvent used for LR: A = xylenes, B = ethyl benzene, C = toluene, D = acetonitrile.

[c] Maximum yield reached, as determined by HPLC using the external standards method.

[d] Yield of distilled or recrystallized material obtained using the P_4S_{10}/HMDO reagent. These experiments were carried out on a 3–50 mmol scale. Physical properties, ^1H and ^{13}C NMR spectra of the isolated thionoesters were in good agreement with literature values. Purities, as determined by GC or HPLC, were greater than 97% in all cases.

[e] Ethyl benzene was used as the reaction solvent because of overlap between xylenes and the thionoester product in HPLC chromatograms.

would have been highly problematical. In fact, Lawesson did report isolation of a reagent byproduct from his reaction.[10] In contrast to these difficulties, the thionolactone from δ-valerolactone was readily prepared and isolated in 65% yield using the P_4S_{10}/HMDO reagent (entry 11) by a procedure which could be scaled up to any desired size.

As expected from previous work with the P_4S_{10}/HMDO reagent,[11] mild alkaline hydrolysis of the P_4S_{10}/HMDO reaction mixtures gave a crude product, substantially free of phosphorus–sulfur byproducts, which was readily purified further by distillation or crystallization.[12] Only for entries 7 and 9 was it necessary to purify the crude product by extensive silica gel chromatography, mainly to effect separation of unchanged ester from the thionoester product. On a small scale, the phosphorus–sulfur byproducts from the P_4S_{10}/HMDO reagent may be removed by passage of the total reaction mixture through a short silica gel column to which these byproducts bind irreversibly.

In previous work[11] we have postulated that the beneficial effect of HMDO on thionations by P_4S_{10} is due to scavenging of yield-lowering intermediates formed during the course of the reaction, and it seems likely that a similar effect operates here. It is also worth noting that the conversion of esters to their thiono derivatives by the P_4S_{10}/HMDO reagent (Eq. (2)) requires more vigorous conditions, in the form of considerably longer reaction times, than the corresponding conversion of 3-oxoesters to 3*H*-1,2-dithiole-3-thiones (Eq. (1)). This observation argues in favor of participation in Eq. (1) of the ketone carbonyl group either in thionation of the ester group or in closure of the five-membered ring, or both, a point which is currently under investigation.

In conclusion, the combination of P_4S_{10} and HMDO converts esters and lactones to thionoesters and thionolactones in yields comparable to or superior to those obtained with LR, with the added advantage that reagent-derived byproducts may be readily removed by a mild hydrolytic workup or by filtration through silica gel. Although LR has heretofore been a universally employed thionation agent,[13] the advantages of the P_4S_{10}/HMDO combination with respect to yield, cost, and ease of workup should make it the reagent of choice for the thionation of esters and lactones. Application of this new thionation procedure to other types of substrates and attempts to understand its mechanism are in progress and will be reported in due course.

Acknowledgements

Financial support for this work was provided by the National Science Foundation (CHE-9904454).

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12. Representative procedure: CAUTION. The reaction and workup should be conducted in a good fume hood. A mixture of isopropyl benzoate (8.13 mL, 50 mmol), P_4S_{10} (7.40 g, 16.7 mmol), HMDO (17.7 mL, 83.3 mmol), and xylenes (50 mL, dried over 3 Å molecular sieves) was mechanically stirred and refluxed under argon for 8 h. The reaction mixture was cooled in an ice-bath and treated with an aqueous K_2CO_3 solution (21 mL of 5.3 M, 111 mmol). Acetone (25 mL) was added and the mixture was stirred vigorously for 30 min in an ice-bath. Water and benzene were then added, the layers separated, and the aqueous phase was extracted with benzene. The combined organic phase was washed with a dilute K_2CO_3 solution, water, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and distillation of the residue through a short Vigreaux column gave 7.46 g (83%) of isopropyl thionobenzoate, bp 54–61°C/0.01 mm: ^{1}H NMR ($CDCl_3$) δ 1.52 (d, $J=6.6$ Hz, 6H), 5.94 (heptuplet, $J=6.6$ Hz, 1H), 7.41 (m, 2H), 7.55 (m, 1H), 8.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.32, 75.60, 128.05, 128.85, 132.59, 139.00, 210.68. Analysis by gas chromatography showed 98.3% purity, with 1.5% of the starting ester as the major impurity.
13. An online search of the *Chemical Abstracts* database for the phrase 'Lawesson's reagent' produced over 700 references.