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# Thionation with the Reagent Combination of Phosphorus Pentasulfide and Hexamethyldisiloxane

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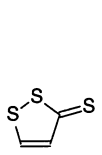
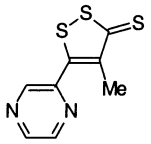
The combination of $P_4S_{10}$ and hexamethyldisiloxane efficiently converts esters, lactones, amides, lactams, and ketones to their corresponding thiono derivatives. In the presence of elemental sulfur, 3-oxoesters are converted to dithiolethiones by this reagent. Yields are comparable to or superior 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.

## Introduction

Organosulfur compounds are valued not only for their rich and varied chemistry, but also for many important biological properties.[1] For a number of years, work in our laboratory has been concerned with the ability of organosulfur compounds to function as chemoprotective agents against a wide variety of carcinogenic and other toxic insults. Of particular interest have been the 3*H*-1,2-dithiole-3-thiones or dithiolethiones, whose parent ring system is shown in structure **1**.



**1**



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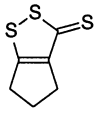
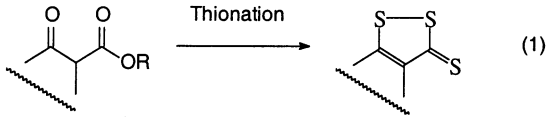


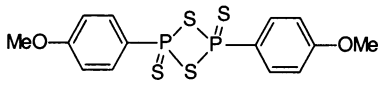
**3**

As a class of compounds, the dithiolethiones appear not only to be active chemoprotective agents,[2] but also to potentiate the activity of certain antitumor agents.[3] One dithiolethione, Oltipraz (**2**), is currently undergoing clinical trials in China as a chemoprotective agent against liver cancer,[4] while another dithiolethione **3** is a candidate drug in the NIH RAPID program, a program designed to speed the development of new chemoprotective agents. As part of our studies, it became necessary to synthesize a large number of dithiolethiones, both in milligram amounts for preliminary biological screening and, in the case of the more active derivatives, in multigram quantities for testing in animals and possibly humans. In the course of this endeavor we were made aware of the fact that existing methods for preparation of the dithiolethiones were often problematical, and a program was mounted to see if better procedures could be found. Three new synthetic routes to the dithiolethiones were developed with ketones as starting materials,[5−7] but these were not particularly well-suited to large-scale production. Attention was next focused on the synthesis of dithiolethiones by thionation of 3-oxoesters (eq 1).




(1)

Thionation, the conversion of the carbonyl group to thiocarbonyl, is a commonly used procedure for the preparation of organosulfur compounds.[8] As for many thionations, the transformation of eq 1, which involves thionation of both the ketone and ester carbonyl groups of the oxoester, can be effected by $P_4S_{10}$, but typically in rather low yield.[9] In recent years Lawesson's reagent (**4**, LR) has displaced $P_4S_{10}$ as the reagent of choice for many thionations.[10] This is indeed the case for the transformation of eq 1, where treatment of 3-oxoesters with the combination of LR and elemental sulfur produces gener-



**4**

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(3) Wang, X.; Doherty, G. P.; Leith, M. K.; Curphey, T. J.; Begleiter, A. *Br. J. Cancer* **1999**, *80*, 1223−1230.

(4) Wang, J.-S.; Shen, X.; He, X.; Zhu, Y.-R.; Zhang, B.-C.; Wang, J.-B.; Qian, G.-S.; Kuang, S.-Y.; Zarba, A.; Egner, P. A.; Jacobson, L. P.; Munoz, A.; Helzlsouer, K. J.; Groopman, J. D.; Kensler, T. W. *J. Natl. Cancer Inst.* **1999**, *91*, 347−354.

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(7) Curphey, T. J.; Libby, A. H. *Tetrahedron Lett.* **2000**, *41*, 6977−6980.

(8) For a review, see: Brillon, D. *Sulfur Rep.* **1992**, *12*, 297−338.

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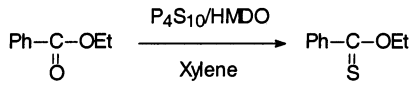
ally excellent yields of dithiolethiones.[11] However, aside from its high cost, LR has the major disadvantage that byproducts derived from the reagent itself cannot, in general, be removed by any extractive procedure and must be separated by column chromatography on silica gel. The high equivalent weight of LR means that relatively large columns must be used, and the procedure becomes unwieldy for any but small-scale reactions or in cases where low molecular weight products may be distilled directly from the reaction mixture.[12] As described below, we have discovered that the addition of hexamethyldisiloxane ($Me_3SiOSiMe_3$, HMDO) to $P_4S_{10}$ dramatically increases its utility as a thionating agent. Yields with the $P_4S_{10}$/HMDO reagent in most cases equal or exceed those obtained with LR, with the additional advantage that a simple extractive or chromatographic workup can be used to remove reagent-derived byproducts. Two preliminary reports on the application of the $P_4S_{10}$/HMDO reagent to preparation of thionoesters, thionolactones, and dithiolethiones have been published.[13,14] We now describe details of this work, along with examples of use of the reagent to prepare thioamides, thiolactams, and thioketones, which demonstrate the wide utility of $P_4S_{10}$/HMDO as a thionating agent.

## Results and Discussion

**Thionation of Esters.** The conversion of esters to thionoesters is among the most difficult of thionations to effect because of the generally low reactivity of the ester carbonyl group toward the usual thionation reagents. For example, while thionation of amides with LR can be achieved by reaction in THF for a relatively short time at room temperature,[15] thionation of esters with this reagent requires prolonged reaction in refluxing toluene or xylene.[16] $P_4S_{10}$ has been used for thionation of esters, but the yields are generally low.[17]

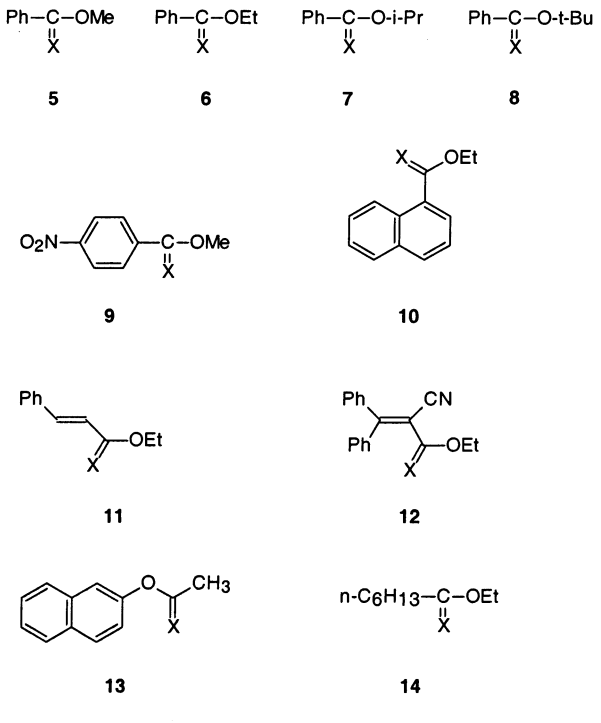
As a test case for the utility of $P_4S_{10}$/HMDO in the thionation of esters, the conversion of ethyl benzoate to the corresponding thionoester in refluxing xylene was chosen (eq 2). The course of the reaction was monitored



(2)

by HPLC, using a photodiode array detector, which allowed both disappearance of starting material and appearance of product to be followed. In selected runs, consumption of HMDO was measured by dilution of the final reaction mixture with xylene, codistillation of HMDO with xylene, and GC quantification of the amount of HMDO present in the distillate. These experiments established that a minimum of 0.2 mol of $P_4S_{10}$ per mol of ester was required to achieve maximum yields of thionoester. Use of more than 0.2 mol of $P_4S_{10}$ per mol of ester, while having little effect on the final yield of thionoester, did reduce the amount of recovered starting material. Consequently, 0.25−0.33 mol of $P_4S_{10}$ per mol of ester was found to give the most satisfactory results. GC analysis showed that 3−4 mol of HMDO per mol of $P_4S_{10}$ were consumed during the course of the reaction. Because some loss of the volatile HMDO is inevitable during the several hours necessary for completion of the reaction in refluxing xylene, use of 5 mol of HMDO per mol of $P_4S_{10}$ was adopted as the standard in subsequent reactions. At a substrate concentration of 0.5−1 mmol/mL in refluxing xylene, the yield of thionoester under the optimum conditions reached a maximum of approximately 80% in 8−13 h, with the resulting solution undergoing little change upon further reaction. In the course of these experiments, it was observed that complete dissolution of the solids occurred shortly before the reaction reached its maximum yield. By allowing a further reaction time of one-third to one-half of that required for the $P_4S_{10}$ to dissolve, one could then be assured of being at or near maximum yield without the necessity of following the reaction by HPLC or TLC.

**CHART 1. Esters and Thionoesters**




**a**: X = O

**b**: X = S

Having established optimum conditions for the conversion of ethyl benzoate to the corresponding thionoester by the $P_4S_{10}$/HMDO reagent combination, thionation by this reagent of the series of esters shown in Chart 1 was examined. In choosing substrates for this study, an effort was made to cover a range of structural types, including aromatic, aliphatic, phenolic, and unsaturated esters. In addition, substrates were chosen whose thionation with LR had been reported to be problematical. For all

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(17) Jones, B. A.; Bradshaw, J. S. *Chem. Rev.* **1984**, *84*, 17−30.

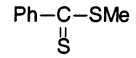
**TABLE 1. Thionation of Esters**[a]

| entry | ester | reagent | time (h)[b] | yield (%) HPLC[c] | yield (%) isolated[d] |
|---|---|---|---|---|---|
| 1[e] | **5a** | $P_4S_{10}$/HMDO | 10 | 92 | 79 |
| 2 | **5a** | LR | 8 | 92 | |
| 3[e] | **5a** | $P_4S_{10}$ | 18 | 67 | |
| 4[e] | **6a** | $P_4S_{10}$/HMDO | 8 | 81 | 73 |
| 5 | **6a** | LR | 8 | 81 | |
| 6[e] | **6a** | $P_4S_{10}$ | 8 | 61 | |
| 7[e] | **7a** | $P_4S_{10}$/HMDO | 8 | 95 | 83 |
| 8 | **7a** | LR | 8 | 92 | |
| 9 | **9a** | $P_4S_{10}$/HMDO | 14 | 28 | 21 |
| 10 | **9a** | LR | 17 | 4 | |
| 11 | **10a** | $P_4S_{10}$/HMDO | 10 | 91 | 87 |
| 12 | **10a** | LR | 12 | 83 | |
| 13[f] | **11a** | $P_4S_{10}$/HMDO | 4 | 75 | 72 |
| 14[f] | **11a** | LR | 6 | 70 | |
| 15[e] | **12a** | $P_4S_{10}$/HMDO | 16 | 51 | 42 |
| 16 | **12a** | LR | 30 | 59 | |
| 17[g] | **13a** | $P_4S_{10}$/HMDO | 17 | 41 | 30 |
| 18[g] | **13a** | LR | 15 | 40 | |
| 19 | **14a** | $P_4S_{10}$/HMDO | 4 | 87 | 75 |
| 20 | **14a** | LR | 8 | 76 | |
| 21 | **14a** | $P_4S_{10}$ | 4 | 35 | |

[a] Reactions were run in refluxing xylene (1 mL per mmol of ester). The amount of $P_4S_{10}$ used was 0.25 mmol per mmol of ester, and the amount of HMDO was 1.67 mmol per mmol of ester. For stoichiometry with respect to LR, see the Experimental Section. [b] Time when the yield of thionation product was judged to have reached a maximum. [c] Yield as determined by HPLC. [d] Yield of isolated and purified material. [e] $P_4S_{10}$ = 0.33 mmol per mmol of ester. [f] Refluxing toluene was used as the reaction solvent. [g] Ethylbenzene was used as the reaction solvent because of interference of xylene with the thionation product in HPLC chromatograms.

substrates, thionation by LR and, in selected cases, by $P_4S_{10}$ alone was also examined with the same HPLC protocol, so that direct comparison of the efficacy of the three reagents might be made. All reactions were run until the yield of thionoester failed to increase or began to decline, so that the reported yields represent the maximum obtainable with the different reagents under the stated conditions. In general, the solvent and stoichiometry chosen for the reactions with LR were those described in the literature.[16,18,19] However, when these conditions appeared to lead to excessively long reaction times and/or low yields, attempts were made to find better conditions, with some limited success. Table 1 summarizes the results of this study.

Comparison among the three benzoates esters, methyl, ethyl, and isopropyl, showed that yields with all three thionation reagents tended to be lower with the ethyl ester (**6a**) than with either the methyl (**5a**) or isopropyl (**7a**) esters (entries 1−8). In the case of thionation of methyl benzoate **5a** with either $P_4S_{10}$/HMDO (entry 1) or LR (entry 2), most of the remaining starting material was converted to the dithioester **15**, identified by comparison of its HPLC retention time and UV spectrum with an authentic sample. Formation of **15** by thionation of methyl benzoate with LR has been previously reported.[20] There was no evidence for formation of similar




**15**

dithioesters from ethyl and isopropyl benzoates. As shown by entries 3 and 6, omitting HMDO gave a significant decrease in yield for the two benzoates examined, although the yields with $P_4S_{10}$ alone were, as has been reported,[21] not particularly low. With *tert*-butyl benzoate **8a** as substrate, reaction with the $P_4S_{10}$/HMDO reagent in refluxing xylene led to rapid disappearance of the starting material and appearance of a plethora of UV-absorbing products, none of which was present in major amount. This reaction was also reported to fail with LR.[18]

The substituted benzoate ester, methyl 4-nitrobenzoate **9a**, was included in the study because its reaction with LR was reported not to give a thionoester.[18] In fact, thionoester **9b** *was* produced by reaction of ester **9a** with LR in refluxing xylene, but the yield after 17 h was only 4% (entry 10), at which point 18% of the starting ester **9a** remained unchanged. In contrast, reaction of **9a** with the $P_4S_{10}$/HMDO reagent under the same conditions gave a 28% chromatographic yield of **9b** in 14 h (entry 9), with 36% unchanged starting material. Although the yield with $P_4S_{10}$/HMDO was not good, workup gave a crude mixture consisting principally of ester **9a** and thionoester **9b**, which was readily separated by flash chromatography. Clearly, for this substrate thionation by $P_4S_{10}$/HMDO rather than LR turned an impractical transformation into a practical, if not particularly efficient, one.

Ethyl 1-naphthoate (**10a**) was included in the study because Lawesson had reported that this ester gave the lowest yield (70%) with LR of the eight aromatic esters he examined, which included methyl, ethyl, and isopropyl benzoates.[16] However, no evidence of a problem with this ester was found, either with LR or with $P_4S_{10}$/HMDO (entries 11 and 12), yields of thionoester **10b** being comparable to those obtained with the benzoate substrates.

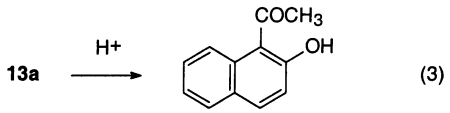
Unsaturated esters were reported to undergo thionation with LR, although not always in good yield,[19,22] so it was of interest to examine the $P_4S_{10}$/HMDO reagent with this class of substrate. Thionation of ethyl cinnamate (**11a**) with $P_4S_{10}$/HMDO was best carried out in refluxing toluene rather than xylene. Although reaction took place rapidly in refluxing xylene, the product thionoester **11b** was not completely stable under these conditions, and the optimum reaction time became more difficult to judge. With toluene as the reaction solvent, the $P_4S_{10}$/HMDO reagent gave **11b** in slightly better yield than that obtained with LR (entry 13 versus entry 14).

A second cinnamate ester **12a** was included in the study because of the report by Lawesson that this ester was very difficult to thionate with LR, giving a 39% yield of thionoester **12b** after refluxing for 12 h in xylene, accompanied by 48% of recovered starting material.[22] As shown in Table 1, entry 16, by prolonging the reaction time to 30 h, the yield with LR was raised to 59%, with

(18) Baxter, S. L.; Bradshaw, J. S. *J. Org. Chem.* **1981**, *46*, 831−832.
(19) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768−770.
(20) Smith, C.; Tunstad, L. M.; Gutierrez, C. G. *Phosphorus Sulfur* **1988**, *37*, 257−260.
(21) Trebaul, C. *Bull. Soc. Chim. Fr.* **1971**, 1102−1103.
(22) Scheibye, S.; Lawesson, S. O.; Roemming, C. *Acta Chem. Scand., Ser. B* **1981**, *B35*, 239−246.

only 11% recovered starting material. Substrate **12a** provided the one example of thionation of an ester where the $P_4S_{10}$/HMDO reagent was inferior to LR, the yield of **12b** with $P_4S_{10}$/HMDO leveling off at 51% after 16 h reflux in xylene (entry 15). Only 8% of the starting ester remained unreacted at this point. At the moment, no explanation for the slightly inferior results obtained with $P_4S_{10}$/HMDO and this ester is in hand.

Like cinnamate **12a**, the phenolic ester **13a** was included as a substrate because its thionation with LR was reported to proceed in both low yield (29%) and conversion, neither of which could be improved by prolonged refluxing in toluene or addition of an excess of LR.[19] In our hands, thionation of ester **13a** with either $P_4S_{10}$/HMDO or LR proved to be highly capricious, the reaction sometimes giving lower yields for no apparent reason. With either reagent, the best yields were obtained with ethylbenzene as solvent, the two reagents giving essentially identical chromatographic yields (entries 17 and 18). Some evidence that the reaction was unusually sensitive to traces of water was obtained, since carefully dried ethylbenzene appeared to give more reproducible results than commercial anhydrous solvent, but the effect was not a consistent one. A possible explanation for these results is that the phenolic ester **13a** undergoes a Fries rearrangement (eq 3) catalyzed by traces of acids in the thionating agents or derived from reaction of these agents with adventitious water. The resulting hydroxy ketone




(3)

**16**

**16** might then be expected to react further with the thionating reagent, undergoing both thionation of the carbonyl group and thiophosphorylation of the hydroxyl group. Indeed, consistent with the latter reaction, the only other UV-absorbing substances formed in major amounts from thionation of **13a** with either $P_4S_{10}$/HMDO or LR were highly polar species which eluted with the solvent front on the reversed-phase HPLC column. Moreover, exposure of authentic ketone **16** to $P_4S_{10}$/HMDO in refluxing xylene converted it within less than 5 min into similar polar species. Since thiophosphorylation of hydroxy ketone **16** would produce a strong acid capable of acting as the acid catalyst in eq 3, production of **16** would become autocatalytic, providing an explanation for the capricious nature observed for the thionations of **13a**.

Ethyl heptanoate **14a**, the one simple aliphatic ester examined, responded well to thionation by the $P_4S_{10}$/HMDO reagent combination, giving a better yield of thionoester **14b** in half the reaction time required with LR (entries 19 and 20). The beneficial effect of adding HMDO to $P_4S_{10}$ (entries 19 and 21) was considerably greater in this case than for the two aromatic esters examined. This may reflect the ability of HMDO to suppress side reactions involving the α-hydrogen atoms of the aliphatic ester.

The most striking feature of the data in Table 1 is the close parallel between yields obtained with the $P_4S_{10}$/HMDO reagent and with LR under optimum conditions. Only in the case of one of the ten substrates examined (**12a**) was the yield with $P_4S_{10}$/HMDO lower than that obtained with LR, and the difference was relatively small. In all other cases, yields with the $P_4S_{10}$/HMDO reagent equaled or exceeded those obtained with LR. As shown in the last column of Table 1, removal of the byproducts derived from the $P_4S_{10}$/HMDO reagent by the simple workup procedures discussed below gave good recovery of purified thionoesters, suggesting that this reagent is the one of choice for the preparation of thionoesters from esters of widely varying structural type.

**CHART 2. Lactones and Thionolactones**

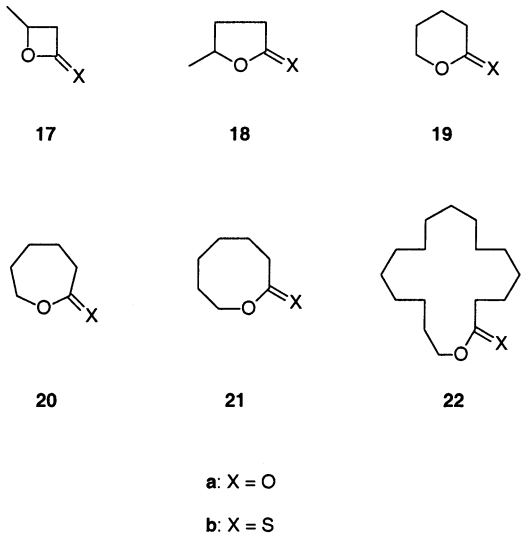



**TABLE 2. Thionation of Lactones**[a]

| entry | lactone | reagent | solvent | time (h)[b] | yield (5) HPLC[c] | yield (5) isolated[d] |
|---|---|---|---|---|---|---|
| 1 | **18a** | $P_4S_{10}$/HMDO | MeCN | 1.5 | 87 | 78 |
| 2 | **18a** | LR | PhMe | 3 | 85 | |
| 3 | **19a** | $P_4S_{10}$/HMDO | MeCN | 0.75 | 82 | 65 |
| 4 | **19a** | LR | MeCN | 4 | 71 | |
| 5 | **20a** | $P_4S_{10}$/HMDO | MeCN | 0.40 | 82 | 77 |
| 6 | **20a** | LR | PhMe | 1 | 73 | |
| 7 | **20a** | $P_4S_{10}$ | MeCN | 0.25 | 31 | |
| 8 | **21a** | $P_4S_{10}$/HMDO | MeCN | 0.50 | 77 | 73 |
| 9 | **21a** | LR | PhMe | 1 | 58 | |
| 10 | **21a** | $P_4S_{10}$ | MeCN | 0.30 | 35 | |
| 11 | **22a** | $P_4S_{10}$/HMDO | xylene | 4 | 87 | 86 |
| 12 | **22a** | LR | xylene | 5 | 84 | |

[a] Reactions were run at reflux in the indicated solvent (1 mL per mmol of ester). The amount of $P_4S_{10}$ used was 0.25 mmol per mmol of ester, and the amount of HMDO was 1.67 mmol per mmol of ester. For stoichiometry with respect to LR, see the Experimental Section. [b] Time when the yield of thionation product was judged to have reached a maximum. [c] Yield as determined by HPLC. [d] Yield of isolated and purified material.

**Thionation of Lactones.** Chart 2 shows the structures of a series of small, medium, and large ring lactones whose thionation with the $P_4S_{10}$/HMDO reagent was examined and compared with LR. $P_4S_{10}$ alone was also examined in a limited number of cases. The results of these studies are summarized in Table 2.

As was expected,[23] the small and medium ring lactones underwent thionation more readily than the acyclic

(23) Scheibye, S.; Kristensen, J.; Lawesson, S. O. *Tetrahedron* **1979**, *35*, 1339−1343.

esters, which meant that a wider choice of reaction solvents was potentially available. In this regard, caprolactone **20a** made a particularly good test case, since its thionation by the $P_4S_{10}$/HMDO reagent was found to be particularly sensitive to choice of reaction solvent. The best conditions for this thionation were found to be acetonitrile at reflux (entry 5). Reaction in refluxing dichloromethane also gave a relatively good yield, but other solvents tried were noticeably less effective. These included 1,2-dichloroethane, chloroform, benzene, toluene, DME, and THF, all at reflux. The poor yields obtained with the aromatic solvents were surprising, given the utility of these solvents in thionation of the acyclic esters. However, the effect seemed to be confined to thionations with caprolactone as substrate and $P_4S_{10}$/HMDO as the thionating reagent. Thus, while thionation of lactones **18a**, **19a**, and **21a** by $P_4S_{10}$/HMDO gave the best yields in acetonitrile as solvent (entries 1, 3, and 8), the yields of **18b** were almost as good when toluene or benzene was used. Further, thionation with LR of both caprolactone and valerolactone **19a** gave very similar yields in toluene and acetonitrile, the results in Table 2 (entries 4 and 6) reflecting only minor differences between the two solvents. The smooth thionation of lactone **21a** by the $P_4S_{10}$/HMDO reagent was especially noteworthy, given the sensitive nature of this substance.[24] Although by no means a definitive study, the conclusion seemed to be that acetonitrile was the most generally useful solvent for the thionation of small and medium ring lactones, with other solvents being equally good in some cases. For the one macrocyclic lactone examined, **22a**, acetonitrile was somewhat inferior to xylene as a reaction solvent with $P_4S_{10}$/HMDO as the thionating reagent (entry 11), but this lactone more nearly resembles the acyclic esters in its reactivity.

Encouraged by these results, an attempt was made to prepare the $\beta$-thionolactone **17b** from lactone **17a** with the $P_4S_{10}$/HMDO reagent, since this preparation fails with LR[25] and because lactones such as **17b** are rare in the literature. For reactions run either at reflux or at room temperature in acetonitrile, no peak in the HPLC chromatograms was found in the region expected for thionolactone **17b** and having the expected UV spectrum. Moreover, $^1$H and $^{13}$C NMR examination of the reaction mixtures failed to show any peaks attributable to thionolactone **17b**. Only unchanged starting material **17a** and a substance identified from its $^1$H NMR spectrum as thioacetamide were present. If the $\beta$-thionolactone **17b** is formed under these conditions, it appears to be too unstable to survive.

For all substrates examined, thionation by the $P_4S_{10}$/HMDO reagent was found to give yields as good as or better than those obtained with LR. Moreover, in the two cases where the issue was examined (entries 7 and 10), addition of HMDO greatly improved the yields obtained when $P_4S_{10}$ was used as the thionation reagent. The thionation of $\delta$-valerolactone **19a** furnished a particularly good example of the utility of the $P_4S_{10}$/HMDO reagent as compared to LR. Lawesson had reported that lactone **19a** failed to give thionolactone **19b** with **4**, although a reagent-derived byproduct indicating that thionation had occurred was isolated.[23] The results in Table 2 (entry 4) show that thionolactone **19b** was, in fact, formed by the reaction of LR with lactone **19a**. However, careful examination by TLC of the reaction mixture showed two overlapping spots, one of which corresponded in $R_f$ to authentic thionolactone **19b** and the other, presumably, to a reagent-derived byproduct. It seems likely that these two substances would be difficult to separate by the usual silica gel column chromatography that is the standard procedure for workup of reactions with LR, and this may explain the failure of Lawesson to isolate thionolactone **19b**. In contrast, as shown in Table 2 (entry 3), the thionolactone **19b** was readily isolated in 65% yield from thionation with $P_4S_{10}$/HMDO. As in the case of the acyclic thionoesters, workup of the $P_4S_{10}$/HMDO reaction mixtures gave the purified thionolactones in good to excellent recovery (last column of Table 2), suggesting that this reagent is the one of choice for the preparation of these derivatives.

**Thionation of 3-Oxoesters.** As stated in the Introduction, the original incentive for development of the $P_4S_{10}$/HMDO reagent was to prepare dithiolethiones by thionation of 3-oxoesters (eq 1). Exploratory experiments with ethyl acetoacetate as substrate indicated that a nearly quantitative yield of dithiolethione could be obtained by refluxing the 3-oxoester with 0.6−0.7 equiv of $P_4S_{10}$, 1 equiv of sulfur, and an excess of HMDO in xylene. Determination by GC of the amount of HMDO present at the end of the reaction showed that slightly less than 4 mol of the disiloxane were consumed per mol of $P_4S_{10}$ taken, an amount very similar to that found for thionation of simple esters. Omission of sulfur from the reaction mixture lowered the yield of dithiolethione to 70%, in agreement with the beneficial effects of sulfur noted for the conversion of 3-oxoesters to dithiolethiones by $P_4S_{10}$ alone[9] and by LR.[11] The details of how sulfur acts to increase the yields in these thionations are not clear. While the overall transformation of 3-oxoester to dithiolethione (eq 1) requires an oxidant, which is most likely the role played by sulfur, it is apparent that $P_4S_{10}$, or some species derived from it, can also perform this function.

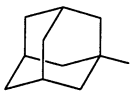
By using in most cases the conditions found to be optimal for ethyl acetoacetate, the utility of the $P_4S_{10}$/HMDO reagent for the conversion of a series of 3-oxoesters to the corresponding dithiolethiones (Scheme 1) was examined and for some substrates compared to LR. The results of these experiments are shown in Table 3. The particular dithiolethiones synthesized were chosen because of interest in their biological activity (**24a**−**d**, **2**, **3**),[26] novelty of structure (**24e**,**f**), or to allow direct comparison with results reported by Lawesson (**24a**,**c**,**h**,**i**).[11] For the $P_4S_{10}$/HMDO reagent, xylene proved to be the most generally useful reaction solvent. Except for the two sterically more demanding examples (Table 3, entries 7 and 9), maximum yields were reached after 1−2 h refluxing in this solvent. Yields of dithiolethiones were excellent for all except the sensitive ferrocenyl derivative **24f** (entry 10) and for Oltipraz **2** (entry 17).

(24) Meyer, W. L.; Taylor, P. W.; Reed, S. A.; Leister, M. C.; Schneider, H. J.; Schmidt, G.; Evans, F. E.; Levine, R. A. *J. Org. Chem.* **1992**, *57*, 291−298.

(25) Shabana, R.; Rasmussen, J. B.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1981**, *90*, 103−104.

(26) Maxuitenko, Y. Y.; Libby, A. H.; Joyner, H. H.; Curphey, T. J.; MacMillan, D. L.; Kensler, T. W.; Roebuck, B. D. *Carcinogenesis* **1998**, *19*, 1609−1615.

**SCHEME 1. Synthesis of Diothiolethiones**


| | R1 | R2 |
|---|---|---|
| a | Me | H |
| b | Et | H |
| c | Ph | H |
| d | t-Bu | H |
| e |  | H |
| f |  | H |
| g | Me | Me |
| h | Me | i-Pr |
| i | -(CH2)4- | |
| j | -(CH2)3- | |
| k |  | Me |

Although the ethyl homologue **24b** was obtained in good yield under standard conditions (entry 3), a small increase in the amounts of $P_4S_{10}$ and sulfur improved this to essentially quantitative (entry 4). Synthesis of **24b** with the $P_4S_{10}$/HMDO reagent was then used as a test case to probe the effect of solvent on this reaction. In addition to xylene, solvents giving 90% or greater chromatographic yield of **24b** in this transformation included ethylbenzene, toluene, diglyme, dioxane, chlorobenzene, and 1,1,2,2-tetrachloroethane. HMDO was somewhat less effective (80% chromatographic yield), while tetrachloroethylene and pyridine gave poor yields (47% and 31% chromatographic yields, respectively). A good yield of **24b** was obtained with diglyme only when all reactants were first mixed at room temperature and then heated. When the usual procedure of adding 3-oxoester **23b** to refluxing $P_4S_{10}$/HMDO was employed, the yield dropped precipitously. The likely explanation for this difference is that $P_4S_{10}$ and diglyme react when heated in the absence of the substrate, but this point was not investigated further.

In general, yields of dithiolethiones with the $P_4S_{10}$/HMDO reagent were greater than those obtained with LR when the latter was used in refluxing toluene, the conditions employed by Lawesson[11] (entries 2, 6, 14, 16, and 18). In the case of the thionation of 4-isopropyl-5-methyl derivative **23h** by LR, use of refluxing xylene (entry 13) rather than toluene (entry 14) as reaction solvent led to some increase in yield, and this change might have been beneficial for thionation of other 3-oxoesters by LR. It should be noted that for the cases in common between this study and that of Lawesson (entries 2, 6, 14, and 16), the yields in Table 3 are not as high as those reported by Lawesson.[11] An explanation for this difference is not in hand, although it might be related to the fact that the reported yields appeared to be based on the weights of crude chromatographic fractions, with no indication of purity.

**TABLE 3. Synthesis of 3*H*-1,2-Dithiole-3-thiones According to Scheme 1[a]**

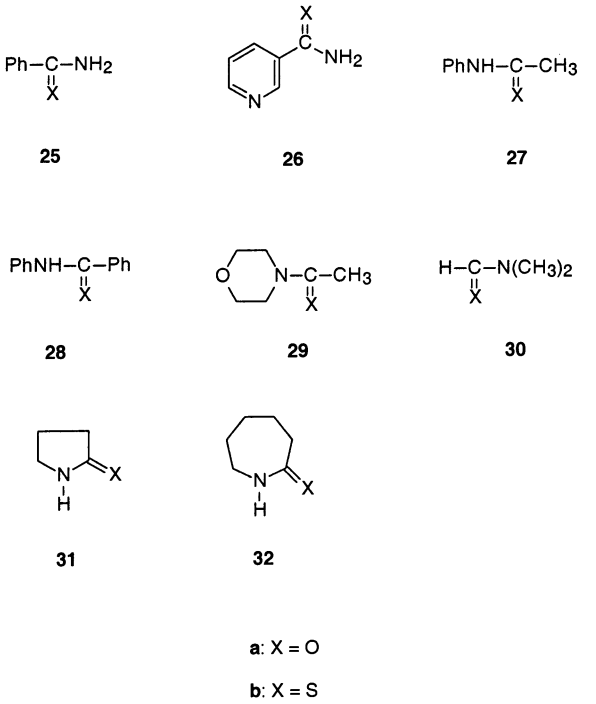
| entry | dithiolethione | reagent | solvent | time (h)[b] | yield (%) HPLC[c] | yield (%) isolated[d] |
|---|---|---|---|---|---|---|
| 1 | **24a** | $P_4S_{10}$/HMDO | xylene | 1 | 98 | 80 |
| 2 | **24a** | LR | PhMe | 5 | 84 | |
| 3 | **24b** | $P_4S_{10}$/HMDO | xylene | 2 | 93 | 74 |
| 4[e] | **24b** | $P_4S_{10}$/HMDO | xylene | 1 | 98 | |
| 5 | **24c** | $P_4S_{10}$/HMDO | xylene | 1 | 83 | 70 |
| 6 | **24c** | LR | PhMe | 3 | 80 | |
| 7 | **24d** | $P_4S_{10}$/HMDO | xylene | 8 | 93 | 83 |
| 8 | **24d** | LR | xylene | 4 | 79 | |
| 9 | **24e** | $P_4S_{10}$/HMDO | xylene | 5 | 78 | 70 |
| 10 | **24f** | $P_4S_{10}$/HMDO | xylene | 0.5 | 45 | 36 |
| 11 | **24g** | $P_4S_{10}$/HMDO | xylene | 2 | 95 | 84 |
| 12 | **24h** | $P_4S_{10}$/HMDO | xylene | 2 | 86 | 72 |
| 13 | **24h** | LR | xylene | 8 | 80 | |
| 14 | **24h** | LR | PhMe | 46 | 72 | |
| 15 | **24i** | $P_4S_{10}$/HMDO | xylene | 1 | 98 | 86 |
| 16 | **24i** | LR | PhMe | 10 | 73 | |
| 17 | **2** | $P_4S_{10}$/HMDO | xylene | 1 | 19 | |
| 18 | **2** | LR | PhMe | 10 | 2.5 | |
| 19 | **3** | $P_4S_{10}$/HMDO | xylene | 2 | 83 | 68 |

[a] For experiments with $P_4S_{10}$, the oxoester was added at reflux to the indicated solvent (2 mL per mmol oxoester) containing the other components. The amounts of the other components, per mmol of oxoester, were $P_4S_{10}$ = 0.6 mmol, HMDO = 3 mmol, and sulfur = 1 mg atom. Experiments with LR used 2.4 mmol per mmol of oxoester and all components were mixed together prior to heating. [b] Time when the yield of the dithiolethione was judged to have reached a maximum. [c] Yield as determined by HPLC. [d] Yield of isolated and purified material. [e] $P_4S_{10}$ = 0.7 mmol and sulfur = 1.2 mg atom per mmol of oxoester.

The preparation of Oltipraz **2** was compared by using $P_4S_{10}$/HMDO and LR as thionation reagents. The yield of Oltipraz with LR was very low (entry 18), while $P_4S_{10}$/HMDO under standard conditions gave a better, but still low yield (entry 17). Because of the need to prepare large quantities of Oltipraz for biological studies, some effort was made to optimize the synthesis of **2** from oxoester **23k**. The best conditions were found to involve addition of **23k** to $P_4S_{10}$ in refluxing xylene over a 1.5-h period. Inclusion of sulfur in the reaction mixture had no effect on the yield of **2**. Under optimum conditions, chromatographic yields of **2** as high as 26% have been obtained.[27] Departing from these conditions, for example by adding oxoester **23k** rapidly to the refluxing reaction mixture, gave yields similar to those obtained with the $P_4S_{10}$/HMDO combination (entry 17). Conversely, slow addition of oxoester **23k** to the $P_4S_{10}$/HMDO reagent only served to lower the yield. Clearly, with the $P_4S_{10}$-based thionation reagents, yields of **2** were sensitive to the precise

(27) Curphey, T. J.; Libby, A. H. Unpublished.

**CHART 3. Amides and Thioamides**




details of how the reaction was conducted. However, it does appear that the preparation of Oltipraz was one of the few examples studied where the yield with $P_4S_{10}$ alone was low and where the addition of HMDO did not give a more effective thionating reagent. It seems likely that this failure is related to the presence of basic nitrogen atoms in oxoester **23k** and may, in turn, be related to the observation, noted above, that pyridine was a poor solvent for thionation by $P_4S_{10}$/HMDO of the simple aliphatic oxoester **23b**. In both cases, the reaction mixtures contained large amounts of insoluble and intractable solids, possibly polymeric, which were not further characterized.

For most of the cases in Table 3, isolation and purification of the dithiolethione from the $P_4S_{10}$/HMDO reaction mixture was easily effected after removal of the phosphorus byproducts by one of the workup procedures discussed below. Only for the adamantyl (**24e**) and ferrocenyl (**24f**) derivatives was flash chromatography necessary to separate the dithiolethione product from unchanged starting material. Thus, the use of the $P_4S_{10}$/HMDO reagent appears to be the method of choice for the preparation of dithiolethiones from 3-oxoesters.

**Thionation of Amides and Lactams.** The amide carbonyl group, cyclic or acyclic, is generally the most easily thionated of the common carbonyl derivatives, and a number of reagents not otherwise useful for thionations give good yields of thioamides from amides.[8,28] To further explore the utility of the $P_4S_{10}$/HMDO reagent, thionation with this reagent of the representative set of amides and lactams shown in Chart 3 was studied and compared with thionation by LR and, in selected cases, by $P_4S_{10}$ alone. The results are shown in Table 4.

Considerably less $P_4S_{10}$ was required for these thionations than for the thionation of esters, with 0.18 mol of

**TABLE 4. Thionation of Amides and Lactams[a]**

| entry | amide | reagent | solvent | temp | time (h)[b] | yield (%) HPLC[c] | yield (%) isolated[d] |
|---|---|---|---|---|---|---|---|
| 1 | **25a** | $P_4S_{10}$/HMDO | $CH_2Cl_2$ | reflux | 0.33 | 88 | 80 |
| 2 | **25a** | LR | $CH_2Cl_2$ | reflux | 1 | 96 | |
| 3 | **25a** | $P_4S_{10}$ | $CH_2Cl_2$ | reflux | 0.33 | 64 | |
| 4 | **26a** | $P_4S_{10}$/HMDO | HMPA | 80 °C | 18 | 82 | 69 |
| 5[e] | **26a** | $P_4S_{10}$/HMDO | HMPA | 110 °C | 6 | 93 | |
| 6 | **26a** | LR | HMPA | 80 °C | 7 | 73 | |
| 7 | **26a** | $P_4S_{10}$ | HMPA | 80 °C | 9 | 60 | |
| 8 | **27a** | $P_4S_{10}$/HMDO | $CH_2Cl_2$ | rt | 4 | 100 | 84 |
| 9 | **27a** | LR | $CH_2Cl_2$ | rt | 9 | 98 | |
| 10 | **27a** | $P_4S_{10}$ | $CH_2Cl_2$ | rt | 4 | 84 | |
| 11 | **28a** | $P_4S_{10}$/HMDO | PhH | reflux | 0.33 | 96 | |
| 12 | **28a** | LR | PhH | reflux | 1 | 96 | |
| 13 | **28a** | $P_4S_{10}$ | PhH | reflux | 0.33 | 98 | |
| 14 | **29a** | $P_4S_{10}$/HMDO | $CHCl_3$ | reflux | 0.75 | 100 | 94 |
| 15 | **29a** | LR | $CH_2Cl_2$ | rt | 6 | 100 | |
| 16 | **29a** | $P_4S_{10}$ | $CHCl_3$ | reflux | 0.75 | 49 | |
| 17 | **30a** | $P_4S_{10}$/HMDO | $CHCl_3$ | reflux | 0.75 | 100 | |
| 18 | **30a** | LR | $CH_2Cl_2$ | rt | 0.5 | 100 | |
| 19 | **30a** | $P_4S_{10}$ | $CHCl_3$ | reflux | 0.75 | 100 | |
| 20 | **31a** | $P_4S_{10}$/HMDO | $CH_2Cl_2$ | rt | 3 | 91 | 83 |
| 21 | **31a** | LR | $CH_2Cl_2$ | rt | 1 | 100 | |
| 22 | **31a** | $P_4S_{10}$ | $CH_2Cl_2$ | rt | 4 | 69 | |
| 23 | **32a** | $P_4S_{10}$/HMDO | $CH_2Cl_2$ | rt | 2 | 100 | 92 |
| 24 | **32a** | LR | $CH_2Cl_2$ | rt | 1 | 100 | |
| 25 | **32a** | $P_4S_{10}$ | $CH_2Cl_2$ | rt | 2 | 87 | |

[a] Reactions were in the indicated solvent (1 mL per mmol of ester). The amount of $P_4S_{10}$ used was 0.183 mmol per mmol of ester, and the amount of HMDO was 1.67 mmol per mmol of ester. For stoichiometry with respect to LR, see the Experimental Section. [b] Time when the yield of thionation product was judged to have reached a maximum. [c] Yield as determined by HPLC. [d] Yield of isolated and purified material. [e] $P_4S_{10}$ was increased to 0.25 mmol per mmol of amide, and water (0.5 mmol per mmol of amide) was added.

$P_4S_{10}$ per mol of amide sufficing. Dichloromethane proved to be the most generally useful solvent for thionations by both $P_4S_{10}$/HMDO and LR, although in some cases reaction in the higher boiling chloroform or benzene gave slightly better yields. Thionation of the sparingly soluble nicotinamide **26a** proceeded best in HMPA as solvent, as originally employed by Lawesson.[29] THF, which has been recommended as a solvent for thionation of amides with LR,[15,30] proved generally less effective than dichloromethane with both $P_4S_{10}$/HMDO and LR as the thionating agent. For two amides, **28a** and **30a**, yields were essentially quantitative with $P_4S_{10}$ alone, and the addition of HMDO offered no particular advantage. For the other amide substrates examined, the combination of $P_4S_{10}$ and HMDO gave yields of thioamide comparable to those obtained with LR.

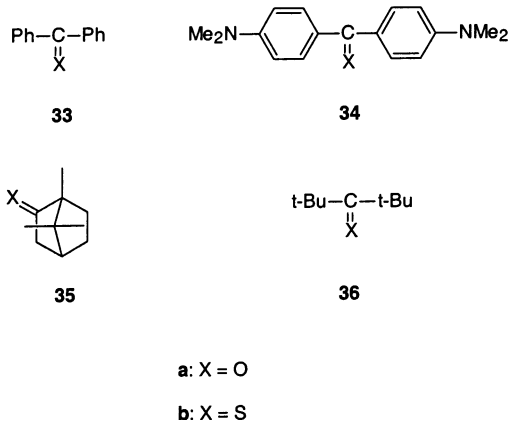
Despite claims to the contrary for LR,[29] reaction of the three thionating agents with the two primary amides, **25a** and **26a**, gave more or less of the corresponding nitrile as byproduct, which was readily detected and quantified by HPLC. The amount of nitrile formed depended on solvent, as well as on the nature and amount of thionating agent. Interestingly, it was found for **26a** that adding water to the $P_4S_{10}$/HMDO reagent reduced the amount of nitrile and increased the yield of thioamide to over 90% (entry 5). The likely explanation

(28) Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N. *Tetrahedron* **1985**, *41*, 2567−2624.

(29) Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229−238.

(30) Xia, M. *Jingxi Huagong* **1999**, *16*, 34−37.

**CHART 4. Ketones and Thioketones**




for this observation is that the reaction between $P_4S_{10}$ and water produces thiophosphoric acids, and it is known that these acids convert nitriles to thioamides.[28] Indeed, HPLC showed that the addition of water did not affect the course of the reaction until most of the starting material had disappeared. At this point, the nitrile byproduct began to decrease in amount and the thioamide to increase in the reaction mixture to which water had been added, but not in the anhydrous reaction. It is possible that a similar effect might operate with LR and with $P_4S_{10}$ alone, but this point was not investigated.

As shown in the last column of Table 4, the thioamides may be readily isolated from the $P_4S_{10}$/HMDO reaction mixtures by the workup procedures described below, a major advantage over the use of LR, which might outweigh the fact that the latter may give somewhat higher yields of thioamide with some substrates.

**Thionation of Ketones.** Because simple thioketones are relatively unstable at room temperature, their preparation by thionation of ketones finds only limited application.[10,31] As a rule, only diaryl thioketones and highly hindered aliphatic thioketones are stable enough to be prepared by this approach. The results of application of the $P_4S_{10}$/HMDO reagent to thionation of four ketones (Chart 4) are shown in Table 5, along with comparisons of thionations of these ketones by LR and $P_4S_{10}$ alone.

Thionation of benzophenone **33a** with the $P_4S_{10}$/HMDO reagent proceeded smoothly in refluxing xylene (entry 1). The chromatographic yield obtained under these conditions was identical to that with LR (entry 2). The beneficial effect of HMDO was evident from the lower yield obtained when the thionation was carried out with $P_4S_{10}$ alone (entry 3). Thionation of the second diaryl ketone examined, Michler's ketone (**34a**), by the $P_4S_{10}$/HMDO reagent proceeded well only when HMPA was used as the solvent (entry 4). The problem seemed to be related to the low solubility of ketone **34a** in most organic solvents, with respect to which the thionation of **34a** resembled that of nicotinamide **26a**. However, this insolubility proved not to be a problem with LR, the thioketone being obtained in good yield in xylene solvent at 110 °C (entry 5). Use of $P_4S_{10}$ alone in HMPA solvent (entry 6) gave essentially the same yield as obtained with $P_4S_{10}$/HMDO. Thus, for this substrate, all three thionating reagents gave the same, nearly quantitative, yield of **34b**, although under somewhat different conditions.

**TABLE 5. Thionation of Ketones[a]**

| | | | | | | yield (%) | |
|---|---|---|---|---|---|---|---|
| entry | ketone | reagent | solvent | temp | time (h)[b] | HPLC[c] | isolated[d] |
| 1 | **33a** | $P_4S_{10}$/HMDO | xylene | reflux | 1.5 | 94 | 93 |
| 2 | **33a** | LR | PhMe | reflux | 0.25 | 94 | |
| 3 | **33a** | $P_4S_{10}$ | PhMe | reflux | 12 | 44 | |
| 4 | **34a** | $P_4S_{10}$/HMDO | HMPA | 110 °C | 0.5 | 97 | |
| 5 | **34a** | LR | xylene | 110 °C | 1.5 | 96 | |
| 6 | **34a** | $P_4S_{10}$ | HMPA | 110 °C | 0.5 | 95 | |
| 7 | **35a** | $P_4S_{10}$/HMDO | PhMe | reflux | 12 | 82 | 54 |
| 8 | **35a** | LR | PhMe | reflux | 7 | 95 | |
| 9 | **35a** | $P_4S_{10}$ | PhMe | reflux | 4 | 50 | |

[a] Reactions were in the indicated solvent (1 mL per mmol of ester). The amount of $P_4S_{10}$ used was 0.183 mmol per mmol of ester, and the amount of HMDO was 1.67 mmol per mmol of ester. For stoichiometry with respect to LR, see the Experimental Section. [b] Time when the yield of thionation product was judged to have reached a maximum. [c] Yield as determined by HPLC. [d] Yield of isolated and purified material.

Thionation of camphor (**35a**) with the $P_4S_{10}$/HMDO combination proceeded smoothly in refluxing toluene (entry 7). Use of xylene gave essentially the same yield in a shorter reaction time, but removal of solvent without excessive loss of the very volatile **35b** posed more of a problem with this solvent than with toluene. For this particular substrate, yield with the $P_4S_{10}$/HMDO reagent was not as high as that obtained with LR under similar conditions (entry 8). The beneficial effect of adding HMDO to thionations by $P_4S_{10}$ was again apparent (entry 9). Finally, an attempt to bring about thionation of the highly hindered di-*tert*-butyl ketone (**36a**) with the $P_4S_{10}$/HMDO combination was not successful. Prolonged refluxing in xylene provided a reaction mixture that was shown by $^1$H NMR to be principally unchanged starting material. The NMR spectrum did show a small singlet at the position reported for authentic thioketone **36b**,[32] but a positive identification of this peak was not made. Thionation of ketone **36a** is also reported to fail with LR.[33]

For the limited number of ketones examined, thionation by $P_4S_{10}$/HMDO did not prove to be superior to LR in terms of chromatographic yield and in the case of Michler's ketone required the use of HMPA as solvent. Nevertheless, the reagent still offered the advantage of convenience in workup, as shown by the good recovery of the air-sensitive **33b** from the thionation mixture (Table 5, entry 1). The lower than usual recovery of thiocamphor **35b** (entry 7) reflected the extremely volatile and soluble nature of this thioketone, which led to unavoidable losses during isolation and purification.

**Workup Procedures.** It had been expected that byproducts from the $P_4S_{10}$/HMDO reagent, presumed to be trimethylsilylated phosphates and thiophosphates, would be readily hydrolyzed to the corresponding acids and thereby rendered water-soluble. In fact, these byproducts proved to be considerably more resistant to hydrolysis than originally expected. With water immiscible

(31) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223−228.

(32) Ohno, A.; Nakamura, K.; Nakazima, Y.; Oka, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2403−2404.

(33) Scheibye, S.; Shabana, R.; Lawesson, S. O.; Roemming, C. *Tetrahedron* **1982**, *38*, 993−1001.

reaction solvents such as xylene, stirring many hours with water was necessary to remove the phosphorus byproducts from the organic phase. However, addition of acetone as cosolvent greatly increased the rate of reaction. Addition of acetone was not necessary for thionations conducted in water-miscible solvents such as acetonitrile or HMPA. To avoid the strongly acidic conditions produced when water alone was used for hydrolysis, the reaction mixtures were buffered with $K_2CO_3$. Under these conditions, removal of phosphorus-containing byproducts from the organic phase was complete within 30 min at 0 °C. The aqueous phase at the end of this time was mildly alkaline (pH 8), but hydrolysis under completely neutral conditions could be effected by using $Na_2HPO_4$ as a buffer. Reaction under these conditions was slower but was essentially complete after 1−2 h of stirring at room temperature. In a number of earlier experiments involving synthesis of dithiolethiones from 3-oxoesters (Table 3), byproducts were removed by stirring the reaction mixture with powdered $K_2CO_3$ and methanol. However, byproduct removal was not always complete under these conditions and, while no difficulty was experienced in subsequent purification of the crude products, the procedure is probably not as generally applicable as those employing aqueous $K_2CO_3$ or $Na_2HPO_4$.

Preliminary experiments suggested that the removal of phosphorus byproducts could also be effected with KF·$2H_2O$ or with KF in the presence of 18-crown-6. Since these processes were slower, required expensive and/or toxic reagents, and seemed to offer no advantage over the use of $K_2CO_3$ or $Na_2HPO_4$ buffers, they were not investigated further. It was also found possible to avoid an aqueous workup completely by passing the total reaction mixture through silica gel, using an eluting solvent of the appropriate strength. Under the proper conditions, the phosphorus-containing byproducts appeared to travel part way down the column and then to undergo sudden reaction. This was signaled by a change in the appearance of part of the gel, the odor of $H_2S$ in the eluate, and irreversible binding of the phosphorus byproducts to the gel. Curiously, attempts to carry out this process in a batch mode by stirring the reaction mixture with silica gel, either dry or wet, were not successful, with no or only a very slow reaction occurring. A plausible explanation for these observations is that the presence in the reaction mixture of the thionation products and of possibly other more polar products prevents adsorption of the silylated phosphate derivatives onto the gel. However, once even partial separation occurs on the column, the silylated phosphates adsorb onto the gel, undergo rapid autocatalyzed hydrolysis accompanied by $H_2S$ formation, and produce the corresponding acids that bind irreversibly to the gel. The amount of gel required for this procedure was small enough that the process is a practical one for workup of even multimillimolar scale reactions.

**Stoichiometry and Mechanism.** The work described above made it clear that in most cases HMDO had a beneficial effect on thionations brought about by $P_4S_{10}$. However, the mechanism by which this effect was exerted was not obvious. At the outset, the possibility was entertained that HMDO reacted directly with $P_4S_{10}$ to produce a new and more effective thionating species, although these two components are known not to react at room temperature.[34] Indeed, control experiments in which mixtures of $P_4S_{10}$, HMDO, and xylene were refluxed under an argon atmosphere and examined periodically by GC showed that the amount of HMDO present slowly decreased. However, the rate of decrease was only slightly larger than that observed in a control containing just HMDO and xylene and was far less than that observed in the presence of a carbonyl substrate. Furthermore, it was often observed that, while thionation reactions in the presence or absence of HMDO proceeded at similar rates, in the presence of HMDO the $P_4S_{10}$ dissolved as the reaction proceeded, whereas in its absence, the $P_4S_{10}$ and/or its byproducts remained undissolved. The sum total of these observations suggested that in thionations by the $P_4S_{10}$/HMDO combination, $P_4S_{10}$ and HMDO did not react directly with each other. Instead, $P_4S_{10}$ first reacted with the carbonyl substrate to produce the thiocarbonyl derivative. As a result of this reaction, $P_4S_{10}$ was converted to species which then reacted with HMDO to give soluble, nonpolar, byproducts, presumed to be trimethylsilylated phosphates or thiophosphates.

In an effort to gain further understanding of this process, an attempt was made to determine the exact stoichiometry of the reaction between a carbonyl substrate, $P_4S_{10}$, and HMDO and to determine the nature of the phosphorus-containing byproducts formed. Although the stoichiometry was known approximately from the experiments whose results were outlined above, such experiments suffered from imprecision due to mechanical loss of HMDO, yields less than 100%, and the tendency of the reaction to become less efficient with respect to $P_4S_{10}$ utilization as it neared completion. Isopropyl benzoate (**7a**) was chosen as the carbonyl substrate for further study because HPLC had shown that thionation of **7a** by $P_4S_{10}$/HMDO proceeded with a mass balance close to 100% during all but the last few percent of conversion to thionoester **7b**. Moreover, the final composition obtained in this reaction did not change even after prolonged heating at the temperature of refluxing xylene. The stoichiometry experiments consisted of heating an excess of ester **7a** in a closed tube with differing amounts of $P_4S_{10}$ and HMDO for a length of time sufficient to guarantee complete reaction of the $P_4S_{10}$. This was determined by doubling the time required for the $P_4S_{10}$ to go into solution. The products of these reactions were then analyzed by HPLC to determine the absolute amounts of ester **7a** and thionoester **7b** present. An aliquot of the reaction mixture was also analyzed by $^1$H NMR to confirm the HPLC results with respect to the ratio of **7a** to **7b** and to determine the relative amounts of unchanged and reacted HMDO. The latter appeared as a complex of peaks near $\delta$ 0.3, a position typical of trimethylsilylated phosphates,[35] and well separated from unchanged HMDO at $\delta$ 0.07. Finally, to gain insight into the number and nature of the phosphorus-containing products of the reaction, the $^{31}$P NMR spectrum of a reaction aliquot was examined. The results of these experiments are summarized in Table 6.

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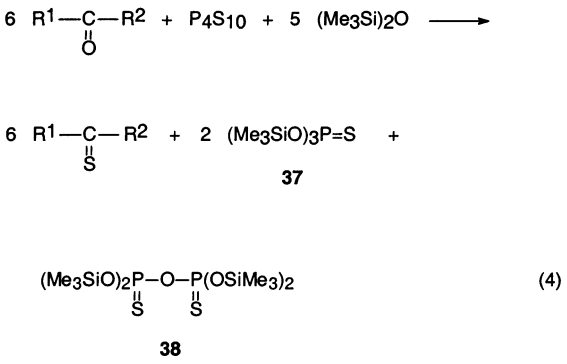
(35) Chojnowski, J.; Cypryk, M.; Fortuniak, W.; Michalski, J. *Synthesis* **1977**, 683−686.

**TABLE 6. Reaction of Isopropyl Benzoate (7a) with $P_4S_{10}$ and HMDO in Xylene at 137 °C**

| entry[a] | ester **7a** (%)[b] | thionoester **7b** (%)[b] | $P_4S_{10}$ taken[c] | HMDO taken[c] | HMDO consumed[c,d] | thionoester/ $P_4S_{10}$[e] | HMDO/ $P_4S_{10}$[f] |
|---|---|---|---|---|---|---|---|
| 1 | 9 | 84 | 0.166 | 0.82 | 0.59 | 5.1 | 3.6 |
| 2 | 41 | 62 | 0.104 | 1.66 | 0.33 | 6.0 | 3.2 |
| 3 | 48 | 57 | 0.103 | 0.66 | 0.27 | 5.5 | 2.6 |
| 4 | 63 | 35 | 0.058 | 1.69 | 0.19 | 6.0 | 3.3 |
| 5[g] | 65 | 32 | 0.061 | 7.95 | 0.27 | 5.3 | 4.4 |

[a] Reaction times: entry 1, 2 h; entries 2−4, 75 min; entry 5, 18 h. The concentration of **7a** was ca. 1 M for all entries. [b] Determined by HPLC analysis. [c] Mol per mol of **7a**. [d] Determined from $^1$H NMR spectra using the ratio of integrals for the TMS phosphates to that of unreacted HMDO. For entry 5, the ratio of integrals for the TMS phosphates to the isopropyl methine hydrogens was used instead because of the very large peak for unchanged HMDO. [e] Mol of thionoester **7b** produced per mol of $P_4S_{10}$ taken. [f] Mol of HMDO consumed per mol of $P_4S_{10}$ taken. [g] Solvent = HMDO.

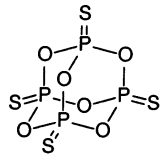
As shown in the penultimate column of Table 6, the mol of thioester **7b** produced per mol of $P_4S_{10}$ taken ranged from 5 to 6, with an apparent upper limit of 6. This suggested that at most 6 out of the 10 sulfur atoms of $P_4S_{10}$ were available for thionation, leaving 4 unreacted, or one per phosphorus atom. The picture with respect to HMDO consumption was less clear, with the observed values (Table 6, last column) ranging from 2.6 to 4.4 mol consumed per mol of $P_4S_{10}$ taken. The $^1$H and $^{31}$P NMR spectra for these reactions were generally complex, with one telling exception. The $^1$H NMR spectrum for the reaction run in pure HMDO as solvent (entry 5) was relatively simple. In the region due to TMS groups, the spectrum showed a large peak for unchanged HMDO, plus two major singlets and several minor peaks. The singlets fell at $\delta$ 0.32 and 0.36, with integrals in the ratio of 1.65 to 1. The $^{31}$P NMR spectrum of an aliquot of this reaction was also relatively simple, consisting primarily of two singlets of approximately equal area at 27 and 33 ppm, plus several minor peaks. These data are most consistent with the products and overall stoichiometry of the thionation reaction shown in eq 4.




(4)

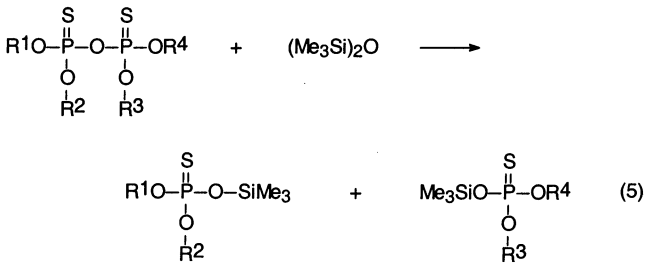
Based on eq 4, the predicted ratio for the TMS groups of monophosphate **37** and diphosphate **38** in the $^1$H NMR spectrum is 1.5 to 1, in good agreement with the observed value. Moreover, eq 4 predicts that the products will show two singlets of equal intensity in the $^{31}$P NMR spectrum, exactly as observed. The peak at 33 ppm in this spectrum is assigned to monophosphate **37** whose resonance is reported to fall at 31 ppm.[36] Diphosphate **38** appears to have been prepared only as an intermediate to the free acid,[37] and its $^{31}$P NMR spectrum was not reported. However, the chemical shift of **38** calculated from that of **37** is predicted to be in the range of 26 to 30 ppm. This calculation is based on the observation that successive replacement of the trimethylsiloxy groups in tris(trimethylsilyl) phosphate (e.g. **37** with oxygen in place of sulfur) by phosphate gives rise to upfield shifts of 3−7 ppm.[38] The observed 6 ppm upfield shift on going from **37** to **38** agrees well with this predication.

The products and stoichiometry indicated by eq 4 may perhaps be best understood by separating the overall change into two *hypothetically* discrete stages: thionation by $P_4S_{10}$ and reaction with HMDO. In the first stage, the six bridging sulfur atoms of $P_4S_{10}$ are exchanged for oxygen, converting 6 molecules of carbonyl to thiocarbonyl, leaving one atom of sulfur per phosphorus atom, and leading to structure **39** (a well-known substance[39]). In the second stage of the reaction, five of the



**39**

six P−O−P units in **39** are cleaved with HMDO in the manner shown in eq 5, and as occurs during reaction of




(5)

the analogous $P_4O_{10}$ with HMDO.[38] If no reorganization of the resulting phosphates is permitted, then the reaction products must still possess 1, and only 1, equiv of P−O−P units. As a result, 1 equiv of diphosphate **38** must be produced, and the remaining two phosphorus atoms of the original $P_4S_{10}$ must then appear as the monophosphate **37**. Of course, it is unlikely, although possible, that the original six bridging sulfur atoms of $P_4S_{10}$ are first exchanged for oxygen to give **39**, which

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then reacts with the 5 equiv of HMDO. It is more likely that these two processes occur concurrently. However, the overall result will be the same, provided that the two processes proceed with 100% efficiency, and that reorganization of the product phosphates does not occur. Such seems to be the case with the reaction of Table 6, entry 5, in which a very large excess of HMDO and an excess of ester substrate were used. Under the more usual conditions for thionation reactions, where neither carbonyl substrate nor HMDO are in large excess, the two processes may proceed with less than 100% efficiency. The result in this case will be that more than the amount of $P_4S_{10}$ dictated by eq 4 (1/6 mol per mol of carbonyl group) will be required to obtain good conversion to thionation product, and less than 5 mol of HMDO per mol of $P_4S_{10}$ may be consumed. Furthermore, reaction under these conditions should result in a more complex mixture than that predicted by eq 4, and concomitantly more complex $^1$H and $^{31}$P NMR spectra. These predictions agree with experiment. For example, the conditions for Table 6, entry 1, more closely approximate those under which thionations are usually conducted. The $^{31}$P NMR spectrum of this reaction showed the predicted complexity, with four major resonances in the 20−40 ppm region, the two largest of which corresponded to **37** and **38**. Several other resonances were also present in this region, but in lesser amounts. The corresponding $^1$H spectrum was similarly complex, showing major peaks from **37** and **38** and a large number of other smaller resonances.

The mechanistic considerations outlined above provide a reasonable, if not detailed, rationalization for the beneficial effect of HMDO on (most) thionations by $P_4S_{10}$. In the absence of HMDO, thionation by $P_4S_{10}$ will of necessity produce highly condensed polythiophosphates of which **39** might be regarded as the extreme example. These species might be expected to be potent electrophiles, in analogy to $P_4O_{10}$, and therefore capable of promoting undesirable side reactions of both the carbonyl and thiocarbonyl derivatives. In fact, as the reaction with $P_4S_{10}$ proceeds in the absence of HMDO, the general reaction environment becomes increasing electrophilic with each successive replacement of sulfur on phosphorus by oxygen. However, in the presence of HMDO, the reaction of eq 5 intervenes, converting highly electrophilic species to innocuous silylated phosphates and thereby raising the yield of the thionation product. The observation that even in the presence of a very large excess of HMDO species **38** survives as an end product suggests that it is principally tri and higher polythiophosphates which are responsible for the yield-lowering side reactions. This is reasonable, since these phosphates should be more electrophilic than the simple diphosphate **38**. Ultimately, the beneficial effect of HMDO on thionations by $P_4S_{10}$ depends on the fact that the disiloxane acts via eq 5 as a scavenger for the P−O−P unit, while displaying much less reactivity toward the P−S−P units present in the active thionating species.

## Conclusions

In this work thionation by the reagent combination of $P_4S_{10}$ and HMDO of nearly 40 carbonyl compounds of diverse structure and reactivity has been examined and compared with thionations of the same substrates by LR and, in some cases, by $P_4S_{10}$ alone. The $P_4S_{10}$/HMDO combination generally gave yields comparable to, or greater than those obtained with LR or with $P_4S_{10}$ alone. In addition, the $P_4S_{10}$/HMDO combination offered the advantage over LR that phosphorus-containing byproducts were readily removed either by mild hydrolysis or by passage through silica gel, facilitating large-scale preparations and avoiding interference in the purification process by reagent-derived byproducts. In view of these advantages, the $P_4S_{10}$/HMDO reagent should find wide applicability as a thionating agent in the preparation of organosulfur compounds.

## Experimental Section

**General.** HPLC chromatography was conducted on a C18 reverse-phase column coupled to a photodiode array detector, with methanol−water mixtures as the mobile phase. GC analysis was on a 0.25 mm i.d. × 30 m fused silica capillary column coated with poly(dimethylsiloxane) and coupled to an FID detector. Silica gel used for chromatography was Merck Grade 9385, 230−400 mesh. Melting points were taken in a stirred oil bath with short-range thermometers and were not corrected. All reactions were conducted in a well-ventilated fume hood under an atmosphere of dry argon that was maintained via a T-tube at the top of a reflux condenser connected to a mineral oil bubbler. Moisture-sensitive reagents (e.g. $P_4S_{10}$ and LR) were weighed and charged into reaction vessels in a glovebag filled with dry air. HMPA and ethylbenzene were dried by distillation from $CaH_2$. All other reaction solvents were either commercially available anhydrous solvents (Aldrich Chemical Co.) or reagent grade solvents allowed to stand several days over 3A molecular sieves prior to use. Xylene refers to the mixture of isomers plus ethylbenzene. Chloroform stabilized with pentenes (Fisher Scientific Co.) was used to avoid reaction of ethanol with $P_4S_{10}$. The sulfur used was precipitated purum grade purchased from Fluka Chemie AG. Use of sublimed sulfur (Aldrich Chemical Co.) gave inferior results. Activated carbon was 50−200 mesh (Fisher Scientific Co.). A technical grade of $\delta$-valerolactone (**19a**) was purified by vacuum distillation and stored under argon at −20 °C prior to use. 2-Oxocanone (**21a**) was prepared as described in the literature[24] and stored under argon at −20 °C prior to use. 3-Ethoxy-1,3-dioxopropylferrocene (**23f**) was prepared from acetylferrocene and diethyl carbonate by a modification of the procedure described in the literature,[40] using KH in place of $KNH_2$ as the base and THF rather then ether−liquid $NH_3$ as the solvent. A practical grade of ethyl 2-isopropylacetoacetate (**23h**) was freed of contaminating enol ether by stirring and refluxing 18 h with 2 vol of water, followed by fractional distillation under reduced pressure. Other carbonyl substrates were used as received. Except for **24e** and **24f**, all the thiocarbonyl products prepared were known compounds, whose identity was confirmed by comparison of physical properties (mp or bp) and NMR spectra with commercially available samples or with literature values. When authentic samples were available, identity was also confirmed by comparison of HPLC retention times and UV spectra and, for liquids, of GC retention times. Purity of distilled liquid products was determined by GC using area percent, and of solids by HPLC using area percent and the MaxPlot feature of the Millennium software package (Waters Corp.) in which each peak in the chromatogram is integrated at the wavelength corresponding to its maximum absorption. Microanalyses were by Atlantic Microlabs, Inc., Norcross GA.

**General Thionation Procedure. Method A.** Carbonyl substrate, $P_4S_{10}$, solvent, HMDO, and sulfur, when used, were

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combined, refluxed, and stirred magnetically. At intervals, an aliquot of the reaction mixture was withdrawn, added to a measured volume of methanol to give a solution at a nominal 1 mM concentration, and analyzed by HPLC. Yields were determined by comparing the area of the product peak to an authentic sample at 1 mM concentration. When the reaction was judged to be complete, the reaction mixture was processed in one of two ways. For runs where the objective was only to obtain yields and not to prepare the thionation product, the reaction mixture was made to a known volume in a volumetric flask. An aliquot of this solution was diluted in methanol to 1 mM nominal concentration and reanalyzed by HPLC to obtain the chromatographic yields reported in the tables. For runs whose objective was the preparation of the thionation product, the reaction mixture was worked up by one of the procedures described below without redetermining the final yield. The reaction times reported in the tables were those at which the yield of product appeared to be no longer increasing. Because of sampling errors (estimated at 2−3%), solvent evaporation, and the subjectivity involved in deciding when yields were no longer increasing, the times in the tables should be regarded as approximate.

**Method B.** For some substrates, particularly the 3-oxoesters, the above procedure was modified by adding the carbonyl compound over a 2−5 min period to the refluxing mixture of the other components. This was done because the vigorous reaction of these substrates with $P_4S_{10}$ can be difficult to control on a large scale if all components are first combined at room temperature and then heated. Comparison of small-scale reactions run both ways showed no significant difference in yield.

**Thionations with $P_4S_{10}$ and LR.** Thionations with $P_4S_{10}$ alone were run identically to those with $P_4S_{10}$/HMDO (general thionation procedure, method A or B), omitting the HMDO. Thionations with LR were conducted as described in the literature, the standard experiment employing 3 mmol of substrate in 3 mL of solvent. For esters and lactones **21a** and **22a**, 3.6 mmol LR was used.[16,41] For other lactones and for all amides and lactams, 1.5 mmol of LR was used.[15,23,29] For ketones, 1.8 mmol of LR was used,[31,33] while for 3-oxoesters, 6 mmol of LR was used.[11] Details of solvent, temperature, and reaction times are to be found in Tables 2, 3, 5, 6, and 7. Reactions were sampled for HPLC analysis as for the general thionation procedures.

**Reaction Workup Procedures. Method A: Aqueous $K_2CO_3$.** The reaction mixture was cooled to 0 °C and aqueous $K_2CO_3$ solution (1.26 mL of 5.3 M/mmol of $P_4S_{10}$ taken) was added. For reaction solvents immiscible with water, a volume of acetone equal to one-half of the reaction solvent was added, while for reaction solvents miscible with water additional water (1 mL/mmol of $P_4S_{10}$ taken) was added to obtain a stirable mixture. The reaction mixture was stirred vigorously for 30 min at 0 °C. Water and an extraction solvent were added, the layers were separated, and the organic phase was washed with dilute $K_2CO_3$ solution, water, and brine. The organic extract was dried over $MgSO_4$ or $Na_2SO_4$ and evaporated, and the crude product was purified as indicated.

**Method B: Methanolic $K_2CO_3$.** A mechanical stirrer was used because of the formation of thick salt suspensions that cannot be adequately stirred magnetically. The reaction mixture was cooled to 0 °C and finely powdered $K_2CO_3$ (0.921 g or 6.67 mmol/mmol of $P_4S_{10}$ taken) was added. Methanol (1.67 mL/mmol of $P_4S_{10}$ taken) was added cautiously dropwise, monitoring gas evolution via the mineral oil bubbler, until a vigorous gas evolution ensued. When this subsided, the remainder of the methanol was added rapidly. The mixture was vigorously stirred at 0 °C until gas evolution had ceased, which generally required 30 to 45 min. Water and an extraction solvent were added, and the mixture then processed as for method A.

**Method C: Aqueous $Na_2HPO_4$.** The reaction mixture was cooled to room temperature and, for reaction solvents immiscible with water, a volume of acetone equal to one-half of the reaction solvent was added. Water (2 mL/mmol of $P_4S_{10}$ taken) and finely powdered $Na_2HPO_4$ (1.14 g or 8 mmol/mmol of $P_4S_{10}$ taken) were added and the mixture was stirred vigorously for 1−2 h. If desired, the progress of the reaction may be followed by $^1$H NMR, monitoring the disappearance of peaks in the $\delta$ 0.3 region due to the TMS thiophosphates. When hydrolysis was complete, water and an extraction solvent were added, and the mixture then processed as for method A.

**Method D: Filtration though Silica Gel.** The reaction mixture was concentrated under reduced pressure to a small volume, dissolved in the appropriate solvent, and passed through a column of silica gel (20 g/mmol of $P_4S_{10}$ taken). The usual flash chromatography setup may be used, or the gel may be supported on a funnel. After evaporation of the eluate, the product was purified further as indicated.

***O*-Methyl Benzenecarbothioic Acid (5b).** The reaction was carried out for 10 h according to the general thionation procedure, method A, with **5a** (3.73 mL, 30 mmol), $P_4S_{10}$ (4.45 g, 10 mmol), HMDO (10.6 mL, 50 mmol), and xylene (30 mL). Workup by the reaction workup procedure, method A, with benzene as the extraction solvent, followed by distillation gave **5b** (3.63 g, 79%) as an orange liquid, bp 62−65 °C/0.25 Torr (lit.[16] bp 110−112 °C/10 Torr). Purity by GC was 99.5%.

**Dihydro-5-methyl-2(3*H*)-furanthione (18b).** The reaction was carried out for 1.5 h according to the general thionation procedure, method A, with **18a** (4.74 mL, 50 mmol), $P_4S_{10}$ (5.56 g, 12.5 mmol), HMDO (17.7 mL, 83 mmol), and acetonitrile (50 mL). Workup by the reaction workup procedure, method A, with ethyl acetate as extraction solvent gave a crude liquid that was dissolved in 2:1 hexane/toluene, filtered through silica gel, and distilled to give **18b** (4.53 g, 78%) as a yellow liquid, bp 39−42 °C/0.02 Torr (lit.[23] bp 125−127 °C/30 Torr). Purity by GC was 99.8%.

**5-Methyl-3*H*-1,2-dithiole-3-thione (24a).** The reaction was carried out for 1 h according to the general thionation procedure, method B, with **23a** (3.19 mL, 25 mmol), $P_4S_{10}$ (6.67 g, 15 mmol), sulfur (0.802 g, 25 mg atom), HMDO (16 mL, 75 mmol), and xylene (50 mL). Workup by the reaction workup procedure, method A, with toluene as extraction solvent gave a dark oil, which was dissolved in toluene, filtered through a column of silica gel (11 g) plus activated carbon (7.4 g), and recrystallized from $CCl_4$ to give **24a** (2.95 g, 80%) as large orange needles, mp 34−35 °C (lit.[48] mp 33 °C). Purity by HPLC was 99.0%.

**Benzenecarbothioamide (25b).** The reaction was carried out for 20 min according to the general thionation procedure, method A, with **25a** (0.363 g, 3 mmol), $P_4S_{10}$ (0.253 g, 0.57 mmol), HMDO (1.06 mL, 5 mmol), and dichloromethane (3 mL). Workup by the reaction workup procedure, method D, with dichloromethane as eluent, followed by recrystallization from benzene/cyclohexane gave **25b** (0.329 g, 80%), mp 117−118 °C (lit.[15] mp 118 °C). HPLC showed no detectable impurities.

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**Diphenylmethanethione (33b).** The thionation reaction was carried out for 80 min according to the general thionation procedure, method A, with **33a** (10.93 g, 60 mmol), $P_4S_{10}$ (4.89 g, 11 mmol), HMDO (21 mL, 100 mmol), and xylene (60 mL). The reaction was worked up by the reaction workup procedure, method C, without adding any additional extraction solvent and maintaining an argon atmosphere throughout. Distillation in a Kugelrohr apparatus gave **33b** (11.2 g, 96%) as a deep-blue air-sensitive solid, bp 84−105 °C (bath temperature)/ 0.03 Torr, mp 53−54 °C (sealed evacuated capillary, lit.[31] mp 52−53 °C). HPLC showed a purity of 98.7%.

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**Supporting Information Available:** Detailed procedures for the synthesis of all compounds whose preparation is not otherwise described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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