Phosphorus Pentasulfide: A Mild and Versatile Catalyst/Reagent for the Preparation of Dithiocarboxylic Esters
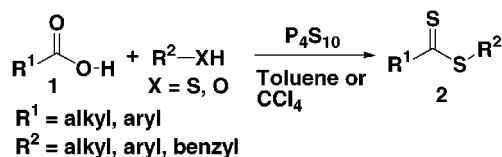
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ABSTRACT

The reaction of carboxylic acids (1) with a variety of thiols or alcohols in the presence of phosphorus pentasulfide (P_4S_{10}) as a catalyst and reagent (20–40 mol %) proceeded effectively to afford the corresponding dithiocarboxylic esters (2) in high yields.

Esters of dithiocarboxylic acids are versatile synthons in organic synthesis,[1] valuable sensitizers in the manufacture of dyes and photographic materials,[2] potent agents in bactericidal, fungicidal, and antitumor activities,[3] and efficient reversible addition−fragmentation chain transfer agents for living radical polymerization.[4] They are generally prepared by the following methods: (i) alkylation of dithio acid salts,[5] prepared by the reaction of carbon disulfide either with organometallic reagents and nucleophile carbanions or with aromatic compounds under Friedel−Crafts conditions, (ii) thiohydrolysis of imidothiolates, prepared from nitrile

or thioamide precursors,[6] (iii) thionation of thioesters using Lawesson's reagents,[7] (iv) oxidative sulfuration of benzyl halides or benzaldehydes with elemental sulfur under alkaline conditions,[8] (v) transesterification of dithioesters with thiols,[9] and (vi) exchange of bis(thiocarbonyl) disulfide with azo compounds.[10] Many of the published procedures suffer from the following disadvantages: expensive or scarcely available reagents, use of strongly basic conditions, use of large excess of reagents often resulting in quite variable yields, and incompatibility of certain reactive functional groups (NO_2, CN, etc.) under Grignard conditions. Phosphorus pentasulfide (P_4S_{10}), a commercially available reagent, has been widely

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employed in organic synthesis for effecting the conversion of carbonyl to thiocarbonyl compounds under a variety of conditions such as use of polar solvents or base catalysts.[11] We became interested in synthesizing benzyldithio esters as chain transfer agents (CTAs) for living radical polymerization of vinyl monomers. In this communication, we wish to provide an efficient and single-step procedure for the preparation of such substituted dithioesters (**2**) when carboxylic acids (**1**) are reacted either with thiols or alcohols in the presence of 20−40 mol % P_4S_{10} (Scheme 1).

Scheme 1
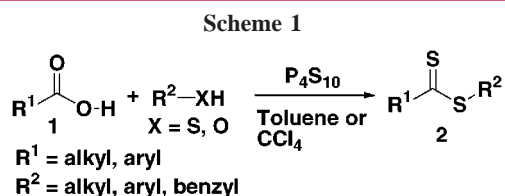
One of the most important features of the methodology is that P_4S_{10} can be used in reduced amounts (20 mol %). By varying the molar proportions of P_4S_{10}, it is possible to establish the nature of the intermediate formed in the reaction from GC-MS. For example, when 4-cyanobenzoic acid was subjected to thiation with benzyl mercaptan in the presence of 15 mol % P_4S_{10}, the corresponding thiocarboxylic S-ester was formed in 86% yield. However, further addition of 5 mol % to this reaction mixture completely transformed thioester to dithioester. The conversion was generally faster in toluene and benzene compared to chlorinated and other solvents. To optimize the reaction parameters, benzoic acid and benzyl mercaptan were subjected to treatment with P_4S_{10} in toluene at various temperatures (Table 1). The reaction

Table 1. Reaction of Benzoic Acid and Benzyl Mercaptan with P_4S_{10}: Effect of Temperature[a]

| | | | product distribution (%)[b] | | | |
no.	temp (°C)	time (h)	benzoic acid	benzyl mercaptan	dithio ester[c]	unknown[d]
1	25	24	19	25	27	48
2	60	12	- -	27	24	49
3	110	1	- -	16	74	10
3	110	3	- -	- -	99	<1

[a] Benzoic acid, benzyl mercaptan, and P_4S_{10} (each 5 mmol), toluene (30 mL). [b] Analyzed by GC-MS with capillary column. [c] (R^1 = Ph, R^2 = Bz). [d] The fragmented peak in GC-MS corresponds to m/z 105 ($PhCO^+$) as base peak with no M^+ ion.

proceeded at room temperature to produce considerable yield (27%) of dithioester. At 60 °C and 110 °C, benzoic acid was completely consumed. However, at 110 °C after 3 h, both benzoic acid and benzyl mercaptan were quantitatively converted to the corresponding dithioester (99%). The unknown in Table 1 may be due to the formation of activated carboxylic acid derivative by P_4S_{10} (see species **A**, in Scheme 2).

Scheme 2

Step 1

Step 2
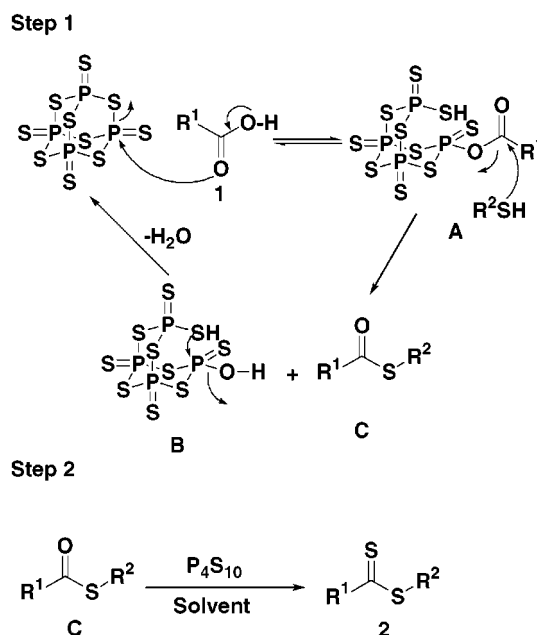
To study the scope and limitation of the reaction, various substituted carboxylic acids and thiols were subjected to treatment with P_4S_{10} in refluxing toluene (Table 2). As

Table 2. Synthesis of Dithioesters (**2**) via Mercaptans[a]

no.	carboxylic acid, R^1	mercaptan R^2	dithioester (%)[b]
1	C_6H_5	benzyl	96
2	$o\text{-}MeC_6H_4$	benzyl	82
3	$p\text{-}MeC_6H_4$	benzyl	91
4	$p\text{-}Me_3CC_6H_4$	benzyl	77
5	$p\text{-}MeOC_6H_4$	benzyl	91[12]
6	$(X)_3\text{-}C_6H_2$[c]	benzyl	76
7	$m\text{-}FC_6H_4$	benzyl	85
8	$p\text{-}FC_6H_4$	benzyl	84
9	$p\text{-}ClC_6H_4$	benzyl	87
10	$p\text{-}BrC_6H_4$	benzyl	91
11	$p\text{-}IC_6H_4$	benzyl	79
12	$p\text{-}CF_3C_6H_4$	benzyl	78
13	$m\text{-}NO_2C_6H_4$	benzyl	67
14	$p\text{-}NO_2C_6H_4$	benzyl	80[13]
15	$p\text{-}CNC_6H_4$	benzyl	75
16	C_6H_5	$n\text{-}C_3H_7$	81
17	C_6H_5	$n\text{-}C_4H_9$	78
18	C_6H_5	$t\text{-}C_4H_9$	45
19	C_6H_5	C_6H_5	55
20	$p\text{-}FC_6H_4$	$o\text{-}MeOC_6H_4$	68
21	C_6H_5	$p\text{-}ClC_6H_4$	66
22	C_6H_5	2-thienyl	91
23	2-thiophene	benzyl	88
24	$n\text{-}C_3H_7$	benzyl	60

[a] Carboxylic acid (5 mmol), mercaptan (5 mmol), and P_4S_{10} (20 mol %), toluene (40 mL), 110 °C, 4 h. [b] Isolated yield after chromatographic purification over neutral alumina. The purified products (minimum purity 95 % after 1 column pass) were characterized by IR, ^1H and ^{13}C NMR, and GC-MS. [c] X = 3,4,5-(MeO)$_3$.

evident from Table 2, the method appears to be quite general as a variety of thiols and carboxylic acids can be employed. The yields of dithioesters were good to excellent. Remarkably, even benzoic acids with electron-withdrawing groups such as CN, NO_2, CF_3, etc., were efficiently transformed to the corresponding dithioesters, which otherwise may be difficult to obtain by the conventional Grignard reaction. Also heteroaryl carboxylic acid reacted smoothly to give the corresponding dithioester in high yield (entry 23). However, substrates such as p-hydroxybenzoic acid, p-acetoxybenzoic acid, and pyridinecarboxylic acid failed to produce the required dithioesters when subjected to similar treatment with P_4S_{10} and benzyl mercaptan possibly due to the formation of highly insoluble polymeric materials.

It was also of interest to replace benzyl mercaptan with benzyl alcohol in the P_4S_{10}-mediated reaction with carboxylic acids (Table 3). As seen in Table 3, the thiation reaction

Table 3. Synthesis of Dithioesters (**2**) via Alcohols[a]

no.	carboxylic acid, R^1	alcohol, R^2	solvent	temp (°C)	dithio ester(%)[b]
1	C_6H_5	benzyl	benzene	80	70
2	C_6H_5	benzyl	chlorobenzene	110	52
3	C_6H_5	benzyl	toluene	110	30[c]
4	C_6H_5	benzyl	$ClCH_2CH_2Cl$	80	71
5	C_6H_5	tert-butyl	CCl_4	70	70
6	C_6H_5	1-phenethyl	CCl_4	70	75
7	p-$MeOC_6H_4$	benzyl	$ClCH_2CH_2Cl$	80	61
8	p-FC_6H_4	benzyl	benzene	80	72
9	p-$NO_2C_6H_4$	benzyl	benzene	80	66

[a] Carboxylic acid, alcohol, and P_4S_{10} (each 5 mmol), 8 h. [b] Isolated yield after chromatographic purification over neutral alumina. [c] The major product (52%) is a mixture of o- and p-benzyltoluenes (Friedel−Crafts alkylated products).

proceeded to give dithioesters in high yields. A novel feature of this system is the unexpected reactivity shown by the tertiary as well as secondary alcohols affording good yields of the corresponding dithioesters without undergoing dehydration. Chlorinated solvents seemed to work well for this system whereas aromatic hydrocarbon solvents such as toluene undergo Friedel−Crafts benzylation to afford benzyltoluenes (52%).

The probable mechanism for the formation of dithioester is believed to take place in two steps as shown in Scheme 2. In step 1, P_4S_{10} activates carboxylic acid through its electrophilic phosphorus center to give an active species **A**. The evidence in favor of formation of such species can be deduced from the GC-MS analysis of the reaction mixture, in which the complete conversion of carboxylic acids and the simultaneous formation of active species **A** (R^1CO^+, base peak in MS) can be seen when the reactions were done at lower temperatures (cf. unknown in Table 1). The nucleophilic attack of thiols with the species **A** generates the species

B and thiocarboxylic S-ester, **C**. Such condensation reactions with the use of phosphorus reagents are well established in the literature.[14] It is also possible that both the species **A** and **B** are in equilibrium (at different time intervals of the reaction mixture, appearance and disappearance of thiol can be seen in GC-MS). The formation of the intermediate thiocarboxylic S-ester, **C** was confirmed from GC-MS analysis and by isolating and characterizing it (IR, ^{1}H, and ^{13}C NMR) when 15 mol % of P_4S_{10} was employed. However, further addition of 5 mol % of P_4S_{10} transformed the species **C** completely to the corresponding dithioester **2**. It is also quite likely that **B** might undergo dehydration to regenerate P_4S_{10}. In step 2, the intermediate **C** undergoes thiation of carbonyl group with P_4S_{10} readily to yield dithioesters (**2**). In the case of alcohols, we believe that they are at first converted to the corresponding thiols on reaction with P_4S_{10} before they could react with activated species **A**. Otherwise, thiocarboxylic O-esters would be formed which are difficult to convert to dithioesters under the reaction conditions. It is further confirmed from our observation that when methyl 4-methoxybenzoate was subjected to thiation reaction with P_4S_{10}, only the C=O of the ester group was converted to C=S (thiocarboxylic O-ester) in agreement with literature.[15]

In summary, we have conducted an alcohol thiation, condensation, and carbonyl thiation in one pot and in the appropriate order to obtain high to moderate yields of the desired dithioesters. The reagents are inexpensive and readily available, yields are generally high, and the method avoids the use of basic conditions or higher temperature required by many previously reported procedures. Alcohols can also be employed instead of thiols to react with carboxylic acids

(11) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; J. Wiley & Sons: New York, 1995; Vol. 6, p 4138.

(12) **Benzyl 4-methoxydithiobenzoate**: In a typical experiment, a mixture of 4-methoxybenzoic acid (1.52 g, 10 mmol), benzyl mercaptan (1.24 g, 10 mmol), and phosphorus pentasulfide (0.88 g, 20 mol %) in toluene (40 mL) was refluxed for 10 h. A dark red color was developed immediately after heating. The reaction was monitored by GC-MS. After the reaction was completed, it was cooled to room temperature and the product purified by column chromatography packed with neutral alumina, eluting with toluene. Removal of the solvent by distillation gave the red-colored oil, benzyl 4-methoxydithiobenzoate (2.49 g, 91%). IR (neat): ν 3028, 2837, 1595, 1501, 1453, 1417, 1309, 1243, 1170, 1045, 886 cm^{-1}; ^{1}H NMR: (500 MHz, CDCl$_3$): δ 3.85 (s, 3H), 4.70 (s, 2H), 6.92 (d, J = 8.0 Hz, 2H), 7.30−7.50 (m, 5H), 8.25 (d, J = 8.0 Hz, 2H); ^{13}C NMR: (125 MHz, CDCl$_3$): δ 42.3, 55.8, 113.9, 128.0, 128.9, 129.0, 129.5, 129.7, 136.0, 138.1, 164.0, 225.1 (C=S); MS (m/z % rel intensity): 274 (M$^+$, 25), 241(15), 183 (10), 152 (12), 151 (100), 136 (10), 108 (10), 91 (35), 77 (10) and 65 (10).

(13) **Benzyl 4-nitrodithiobenzoate**: In a typical experiment, a mixture of 4-nitrobenzoic acid (1.67 g, 10 mmol), benzyl alcohol (1.08 g, 10 mmol), and phosphorus pentasulfide (1.78 g, 40 mol %) in benzene (40 mL) was refluxed for 12 h. A dark red color was developed immediately after heating. The reaction was monitored by GC-MS. After the reaction was complete, it was cooled to room temperature and the product purified by column chromatography packed with neutral alumina eluting with toluene. Removal of the solvent by distillation gave the red-colored oil, benzyl 4-nitro-dithiobenzoate (2.31 g, 80%). IR (neat): ν 3060, 3027, 2920, 1665, 1600, 1522, 1493, 1452, 1403, 1343, 1243, 1199, 1109, 1057, 1028, 1012, 916, 890, 844, 764, 697 cm^{-1}; ^{1}H NMR: (500 MHz, CDCl$_3$): δ 4.62 (s, 2H), 7.25−7.4 (m, 5H), 8.05 (d, J = 7.2 Hz, 2H), 8.2 (d, J = 7.2 Hz, 2H); ^{13}C NMR: (125 MHz, CDCl$_3$): δ 43.0, 123.8, 128.0, 128.4, 128.9, 129.0, 129.1, 129.6, 129.7, 134.4, 149.0, 149.8, 224.6 (C=S); MS (m/z % rel intensity): 289 (M$^+$, 12), 120(15), 108 (10), 91(100), 69 (12), 65 (25), and 45 (22).

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(15) Trebaul, P. C. *Bull. Soc. Chim. Fr.* **1971**, 1102.

in the presence of P_4S_{10} thereby producing dithioesters in moderate yields.

Supporting Information Available: Experimental procedures and spectral data for other dithiocarboxylic esters.

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OL006407Q