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Synthesis of Thioesters from Carboxylic Acids via Acyloxyphosphonium Intermediates with Benzyltriethylammonium Tetrathiomolybdate as the Sulfur Transfer Reagent

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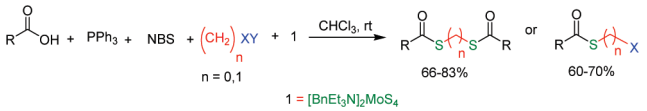
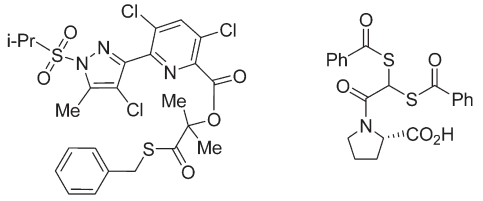


An efficient protocol is reported for the synthesis of thioesters from carboxylic acids with use of acyloxy phosphonium salts as intermediates and benzyltriethylammonium tetrathiomolybdate as the sulfur transfer reagent

Thioesters are important synthetic intermediates in organic synthesis and are used for peptide coupling,[1] acyl transfer,[2] protecting groups for thiols,[3] and also as coupling partners in organometallic reactions.[4] They are also key intermediates in various biological systems[5] and find broad application in medicinal chemistry[6] (Figure 1). From a synthetic perspective thioesters could be readily transformed into a more versatile SH group under mild reaction conditions.[7]

Traditional methods for the formation of thioesters include the direct coupling of a thiol with the parent carboxylic acid and an activating agent,[8] the coupling of a thiol with an acid chloride,[9] or reaction of thiols with an acid anhydride.[10] Other syntheses of thioesters include the coupling of thiocarboxylates with arenediazonium salts[11] and alkyl halides.[12] These methodologies, however, suffer from limitations such as difficulties encountered in handling thiols and thioacids and also the availability of starting materials. However, given the prevalence of the thioester moiety in a wide range of pharmaceutically active compounds it is desirable to find novel procedures that provide an efficient access to such highly useful organic products. In this regard, we envisaged a novel methodology for the synthesis of highly functionalized thioesters from readily available carboxylic acids as starting materials.



i. 2-Pyridinecarboxylic acid ester derivative (a herbicide)

ii. 1-[bis(benzoylthio)acetyl] - L-Proline

FIGURE 1. Structures of pharmacologically important thioesters.

Herein, we present the synthesis of various substituted thioesters directly from carboxylic acids using benzyltriethylammonium tetrathiomolybdate[13] ($[BnEt_3N]_2MoS_4$, **1**) as an efficient sulfur transfer reagent. Aryl carboxylic acids are first activated by using PPh_3 and NBS to form the corresponding acyloxy phosphonium salts,[14] **2**, which then on reaction with reagent (**1**) generate thioaroylate ions *in situ*. These thioaroylates on further reaction with various electrophiles such as alkyl halides/dihalides in the same pot will lead to the corresponding functionalized thioesters (Scheme 1).

While attempting the synthesis of dibenzoyl disulfide, benzoic acid (1 equiv) was treated with PPh_3 (1.1 equiv) and NBS (1.1 equiv) in the presence of benzyltriethylammonium tetrathiomolybdate ($[BnEt_3N]_2MoS_4$, **1**; 1.5 equiv) in CH_2Cl_2 as solvent (28 °C, 2 h); we obtained two interesting products, namely methanedithiol dibenzoate **3a** and

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(3) Christian, F.; Bjorn, S.; Andreas, T. *Eur. J. Org. Chem.* **2007**, *6*, 1013.

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(5) Bjorn, H. T.; Ben, F. L.; Adriaan, M. J. *Chem. Commun.* **2007**, *5*, 489.

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(10) Peterson, M. J.; Marchal, C.; Loughlin, W. A.; Jenkins, I. D.; Healy, P. C.; Almesaker, A. *Tetrahedron* **2006**, *63*, 1395.

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(13) Prabhu, K. R.; Devan, N.; Chandrasekaran, S. *Synlett* **2002**, 1762.

(14) (a) Froyen, P. *Phosphorus, Sulfur Silicon* **1994**, *89*, 57. (b) Froyen, P. *Phosphorus, Sulfur Silicon* **1994**, *91*, 145. (c) Froyen, P. *Synth. Commun.* **1995**, *25*, 959. (d) Sucheta, K.; Reddy, G. S. R.; Ravi, D.; Rama Rao, N. *Tetrahedron Lett.* **1994**, *25*, 4415.

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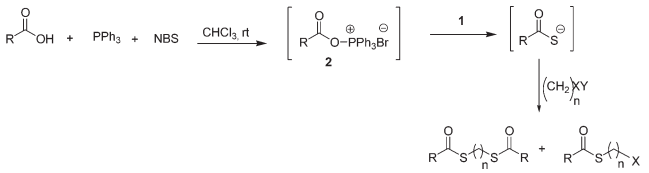
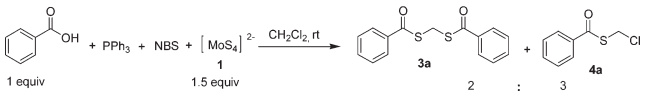
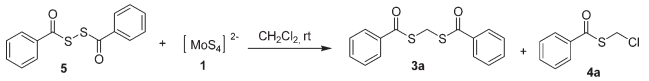
SCHEME 1. General Reaction Scheme



SCHEME 2. Reaction of in Situ Generated Thiobenzoate with Solvent Dichloromethane



SCHEME 3. Reaction of Dibenzoyl Disulfide with Reagent 1



chloromethylbenzoyl sulfide **4a** respectively in 2:3 ratio (Scheme 2). We speculated that thioaroylate ion could be a possible intermediate (formed by the reductive cleavage[13,15] of dibenzoyl disulfide with excess reagent, **1**), which on reaction with the solvent molecule (CH_2Cl_2) leads to **3a** and **4a**.

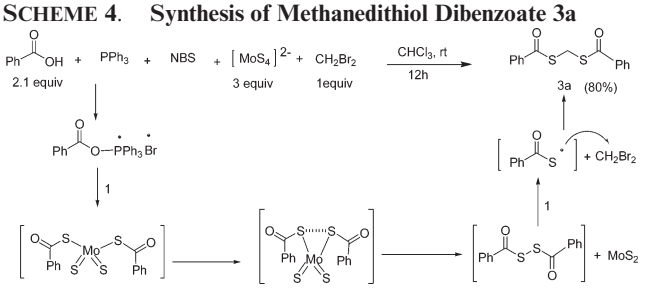
This was further proved by the reaction of **1** with dibenzoyl disulfide[16] (**5**) in CH_2Cl_2 to give the corresponding thioesters **3a** and **4a** thereby indicating the intermediacy of thiobenzoate ion in the above reaction (Scheme 3).

To achieve selectivity in the formation of these thioesters, the solvent was changed to chloroform as it was inert to thioaroylate ion due to the steric crowding around the carbon and various amounts of dihalomethane were added to obtain the corresponding thioesters. Initially we directed our efforts toward optimizing the conditions for the formation of product **3a**. This could be achieved by taking a large excess of acyloxyphosphonium intermediate **2** and reagent **1**. After various trials it was found that the reaction works well with dibromomethane as the electrophilic partner (compared to two other dihalomethanes) and with benzoic acid (2.1 equiv) taken as the standard, PPh_3, NBS, and reagent **1** (3 equiv) to give the corresponding thioester **3a** as the major product in 80% yield (Scheme 4).

The chloromethylaroyl sulfides are known for their fungicidal activity.[17] To achieve selective synthesis of chloromethylbenzoyl sulfide **4a**, bromochloromethane was used instead of dibromomethane in the above reaction (Scheme 5). Selective displacement of bromide by the thiobenzoate ion gave the corresponding thioester **4a** in 63% yield. The results of this study with various carboxylic acids and dihalomethanes are summarized in Table 1.

Subsequently, we attempted the reaction of carboxylic acids, via intermediate **2** with 1,2-dihaloethanes. After some experimentation it was found that reaction of benzoic acid (2.4 equiv), PPh_3, NBS, dibromomethane (1 equiv), and reagent **1** (3 equiv) gave the corresponding thioester,

SCHEME 4. Synthesis of Methanedithiol Dibenzoate 3a



SCHEME 5. Synthesis of Chloromethylbenzoyl Sulfide 4a

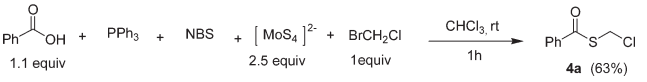
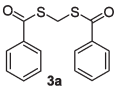
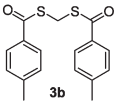
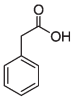
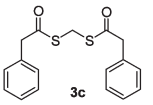
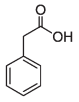
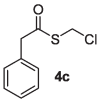
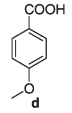
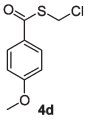
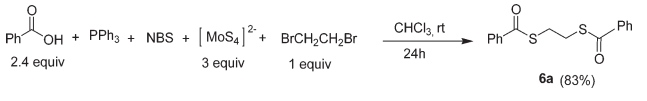


TABLE 1. Synthesis of Methanedithiol Diaroylates and Chloromethylaroyl Sulfides

Entry	Substrate	Dihalomethane	Product	Yield (%)
1		CH_2Br_2		80
2		CH_2Br_2		70
3		CH_2Br_2		66
4		$BrCH_2Cl$		63
5		$BrCH_2Cl$		62
6		$BrCH_2Cl$		70

SCHEME 6. Synthesis of Ethanedithiol Dibenzoate 6a

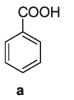
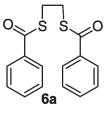
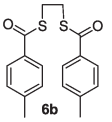
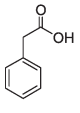
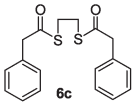
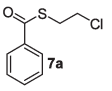
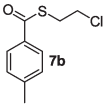
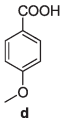
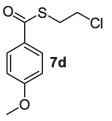


ethanedithiol dibenzoate **6a**, as the major product in 83% yield (Scheme 6).

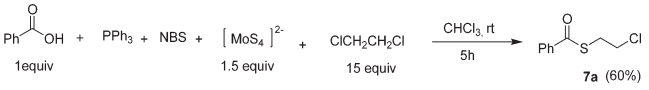
Chlroethylbenzoyl sulfide **7a**, a fungicide, was synthesized by using benzoic acid, PPh_3, NBS, dichloroethane (15 equiv), and reagent **1** (1.5 equiv) in 60% yield (Scheme 7). The synthetic utility of this reaction with different dihaloethanes is exemplified in Table 2.

(15) Pan, W. H.; Harmer, M. A.; Halbert, T. R.; Stiefel, E. I. *J. Am. Chem. Soc.* **1984**, *106*, 459.
(16) Tamami, B.; Kiasat, A. *Synth. Commun.* **1998**, *28*, 1275.
(17) Karl, K.Ernst, P. H. Ger. Offen., 1970, p 12.

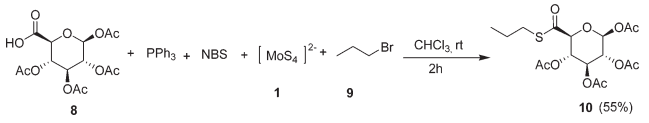
TABLE 2. Synthesis of Ethanedithiol Diaroylates and Chloroethylaroyl Sulfides

Entry	Substrate	Dihaloethane	Product	Yield (%)
1	 a	$BrCH_2CH_2Br$	 6a	83
2	 b	$BrCH_2CH_2Br$	 6b	72
3	 c	$BrCH_2CH_2Br$	 6c	70
4	 a	$ClCH_2CH_2Cl$	 7a	60
5	 b	$ClCH_2CH_2Cl$	 7b	62
6	 d	$ClCH_2CH_2Cl$	 7d	61

SCHEME 7. Synthesis of Chloroethylbenzoyl Sulfide 7a



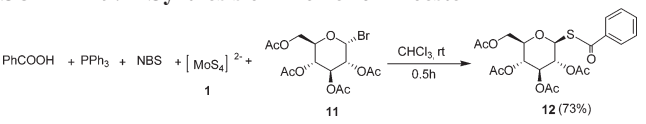
SCHEME 8. Synthesis of Glucuronic Acid Based Thioester 10



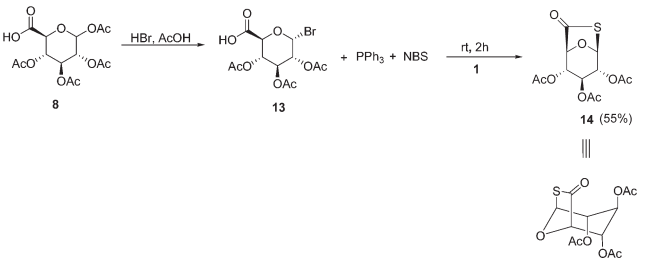
Carbohydrate-based thioesters are important synthetic intermediates in various transformations and also they could be deprotected later to form synthetically more valuable thiols. Therefore, we took 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronic acid[18] **8**, which was synthesized from glucuronic acid by acetylation with acetic anhydride, iodine, and methanol. Carboxylic acid **8** was then treated with PPh_3, NBS, reagent **1**, and 1-bromopropane **9** ($CHCl_3$, 28 °C, 2 h) to afford the corresponding thioester **10** in 55% yield (Scheme 8).

It was of interest to study the reactivity of anomeric bromides to show the generality of the present methodology. Accordingly 2,3,4,5-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **11** was treated with benzoic acid, PPh_3, NBS, and reagent **1** to form the corresponding thioester **12** in 73% yield (Scheme 9).

SCHEME 9. Synthesis of Anomeric Thioester 12



SCHEME 10. Synthesis of Bicyclic Thiolactone 14



To expand the scope of our methodology, an intramolecular version of the reaction was performed on a compound containing both anomeric bromide and carboxylic acid functionality. This was achieved by treating carboxylic acid **8** with HBr/AcOH[19] to form α-D-bromoglucopyranuronic acid **13** (Scheme 10). Compound **13** was then treated with PPh_3, NBS, and reagent **1** to give the corresponding bicyclic thiolactone **14** in 55% yield.

In conclusion, a wide variety of functionalized thioesters have been synthesized from carboxylic acids by using acyloxyphosphonium salts as intermediates and benzyltriethylammonium tetrathiomolybdate **1** as the sulfur transfer reagent.

Experimental Section

General Procedure for the Formation of Methanedithiol Diaroylate 3. To a well-stirred solution of the corresponding carboxylic acid (2.1 mmol), PPh_3 (2.2 mmol), and NBS (2.2 mmol) in $CHCl_3$ (5 mL) (stirred for 10 min) was added benzyltriethylammonium tetrathiomolybdate **1** (3 mmol) followed by dibromomethane (1 mmol). The reaction was complete after 12 h at room temperature (28 °C). Diethyl ether (20 mL) was added to the reaction mixture, which was then filtered through a Celite pad. The residue was again extracted with CH_2Cl_2 (5 mL) followed by extraction with diethyl ether (20 mL) and filtered again through a Celite pad. The combined extract was evaporated and the residue was purified by column chromatography on silica gel to give the corresponding thioester derivative **3**.

Methanedithiol dibenzoate, 3a: white crystalline solid (0.23 g, 80%); mp 113 °C; IR (neat) 1668, 1208, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97−7.94 (m, 4H), 7.61−7.57 (m, 2H), 7.48−7.43 (m, 4H), 4.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 136.2, 133.8, 128.7, 127.3, 28.0, 21.7; HR-MS *m*/*z* calcd for $C_{15}H_{12}O_2S_2Na^+$ [M + Na^+] 311.0176, found 311.0186.

General Procedure for the Formation of Chloromethylaroyl Sulfide 4. To a well-stirred solution of the corresponding carboxylic acid (1.1 mmol), PPh_3 (1.2 mmol), and NBS (1.2 mmol) in $CHCl_3$ (5 mL) (stirred for 10 min) was added benzyltriethylammonium tetrathiomolybdate **1** (2.5 mmol) followed by bromochloromethane (1 mmol). The reaction was complete after 1 h at room temperature (28 °C). Diethyl ether

(18) Malkinson, J. P.; Falconer, R. A.; Toth, I. *J. Org. Chem.* **2000**, *65*, 5249.

(19) Akin, A.; Curran, T. T. *Synth. Commun.* **2005**, *35*, 1649.

(20 mL) was added to the reaction mixture, which was then filtered through a Celite pad. The residue was again extracted with CH_2Cl_2 (5 mL) followed by extraction with diethyl ether (20 mL) and filtered again through a Celite pad. The combined extract was evaporated and the residue was purified by column chromatography on silica gel to give the corresponding thioester derivative **4**.

***S*-Chloromethyl 4-methoxybenzothioate, 4d:** colorless liquid (0.151 g, 70%); IR (neat) 1671, 1601, 1168, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 9.3 Hz, 2H), 6.95 (d, J = 9.3 Hz, 2H), 5.12 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 164.4, 129.9, 128.6, 55.6, 42.1; HR-MS m/z calcd for $C_9H_9ClO_2SNa^+$ [M + Na^+] 238.9909, found 238.9915.

Synthesis of 2,3,4-Tri-*O*-acetyl-*β*-D-glucopyranuronic Acid *ε*-Thiolactone, 14. To a well-stirred mixture of 2,3,4-tri-*O*-acetyl-1-bromo-α-D-glucopyranuronic acid (0.383 g, 1.0 mmol), PPh_3 (0.576 g, 1.1 mmol), and NBS (0.392 g, 1.1 mmol) in $CHCl_3$ (5 mL) was added benzyltriethylammonium tetrathiomolybdate **1** (1.34 g, 2.2 mmol) and stirring was continued for 2 h at room temperature (28 °C). Diethyl ether (20 mL) was added to the reaction mixture, which was then filtered through a Celite pad. The residue was again extracted with CH_2Cl_2 (5 mL) followed by extraction with diethyl ether (20 mL) and filtered again through a Celite pad. The combined extract was evaporated and the residue was purified by column chromatography on silica gel to give the lactone **14** as a colorless liquid (0.175 g, 55%). $[\alpha]^{26}_D$ +6.5 (*c* 0.8, $CHCl_3$); IR (neat) 1747, 1371, 1215, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, J = 1.5 Hz, 1H), 4.95 (m, 1H), 4.91 (d, J = 1.2 Hz, 1H), 4.88 (m, 1H), 4.55 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 169.5, 169.2, 168.5, 84.9, 79.6, 69.5, 68.7, 67.8, 20.8; HR-MS m/z calcd for $C_{12}H_{14}O_8SNa^+$ [M+Na^+] 341.0307, found 341.0308.

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Supporting Information Available: Experimental procedures, full characterization, ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.