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A Solid Supported Synthesis of Thiol Esters

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Abstract: A variety of thiol esters was conveniently prepared from thiols and carboxylic acids using ethyl 3-(dimethylamino)propyl carbodiimide (EDAC) on a solid support in good to high yield for primary and aryl thiol esters with lower yields for secondary and tertiary thiol esters. Copyright © 1996 Elsevier Science Ltd

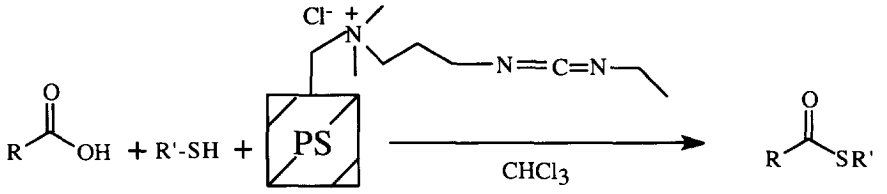
Thiol esters constitute a group of natural products,[1] among which are derivatives of Coenzyme A with their critical role in biochemical transformations.[2] Thiol esters also play an important role in the development of thiol drugs, they protect the unstable thiol moiety, increase the activity of the drug, mask the undesired odor and taste of the native thiol.[3]

Organic compounds with the thiol ester group can be subjected to a wide range of synthetic transformations.[4] They have been used as intermediates in the synthesis of ketones, via organocuprates,[5] Grignard reagents[6] or silylacetylenes.[7] The reduction of thiol esters to aldehydes can be accomplished with a variety of reducing agents such as diisobutylaluminum hydride (DIBAL),[8] lithium[9] or triethylsilane.[10] Also, they can be transformed to the hydroxymethyl moiety with sodium borohydride[11] or other strong reducing agents.[12] Macrolactonization through thiol esters was accomplished in the preparation of a variety of natural products as detailed in the literature.[13,14] Recently, application of this functional group has expanded into total synthesis of proteins by chemical ligation of benzyl thiol esters,[15] use as an acyl donor in the resolution of secondary alcohols catalyzed by lipase,[16] solid phase peptide synthesis,[17] and as cephalosporin derivatives which have been tested as elastase inhibitors.[18] Enolates of 2-pyridyl thiol esters have been used as substrates in the synthesis of β-lactams[19] and diastereoselective aldol condensations,[20] while the thiophenyl and pentafluorothiophenyl[21] derived thiol esters have been used as coupling reagents in the synthesis of amides.

Preparations of thiol esters involve either the direct coupling of a thiol with the parent carboxylic acid and an activating agent,[5,22] the coupling of a heavy metal thiolate with an acid chloride[5,23] or metal thiolate coupled with an acid anhydride.[5,24] Other syntheses of thiol esters include: use of triphenylphosphine with a disulfide and carboxylic acid,[25] coupling of arenediazonium salts with thiocarboxylates[26] and use of triphenylphosphine with a carboxylic acid and thiophenol.[27]

In this paper we describe a new and convenient synthesis of thiol esters which has all the advantages of solid support chemistry,[28] mild reaction conditions and the absence of toxic or corrosive reagents such as heavy metal thiolates or phenyl dichlorophosphate. It represents our continuing effort on the development of new methods needed in bioconjugation.[29]

Thus, a variety of thiols were coupled with carboxylic acids in the presence of polymer supported ethyl (dimethylaminopropyl)carbodiimide[30] (EDAC) to form thiol esters according to Scheme 1 using the experimental procedure described below. In general, the desired thiol ester products were isolated in good to high yield (not optimized) and very pure as indicated by mass spectroscopy and ^{1}H NMR with confirmation by analytical high-performance liquid chromatography (HPLC).



Scheme 1. Convenient Solid Supported Synthesis of Thiol esters

The coupling of thiophenols with a slight stoichiometric excess of carboxylic acid (1.15 equivalents) proceeds faster than for benzylic thiols as shown by production of the phenyl vs benzyl thiol ester of *N*-CBZ-β-alanine (entry 1 vs. entry 3). Longer reaction time for the formation of benzyl thiol esters afforded a moderate increase in yield, as exemplified with *N*-Carbobenzyloxy(CBZ)-β-alanine as the substrate (16 hours, 77% vs. 3 days, 89%). This rate difference is in agreement with the previous observations of Grunwell and Forest[22c] using a soluble carbodiimide in ether. Moderate increases in yield were also noted by the use of excess (3 equivalents) carboxylic acid (for example, the benzyl thiol ester of *N*-CBZ-β-alanine was produced in 95% yield using three equivalents of acid). Therefore, if the carboxylic acid is readily available, use of an excess of carboxylic acid will maximize the conversion of thiol to produce pure thiol ester in high yield.

The more sterically hindered secondary and tertiary alkyl thiols (isopropyl and *tert*-butyl) formed only minor amounts of the desired products using the thiol as the limiting reagent. However, a large excess (ten equivalents) of these volatile thiols and longer reaction times afforded the satisfactory yields of pure products shown for entries 6 and 7. In such cases, purification of product is simple since the remaining thiol can easily be removed *in vacuo*.

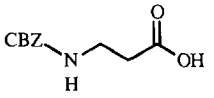
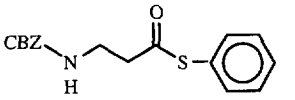
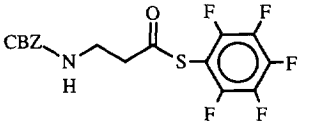
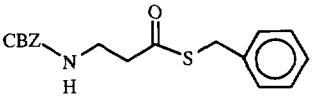
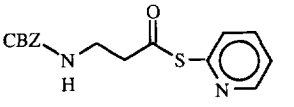
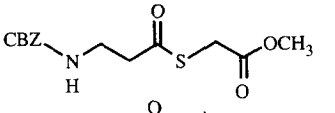
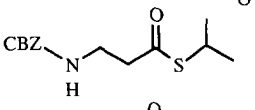
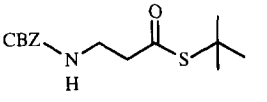
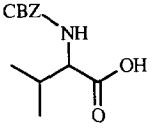
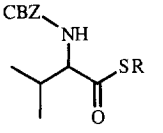
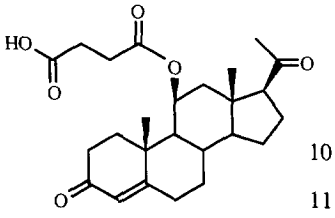
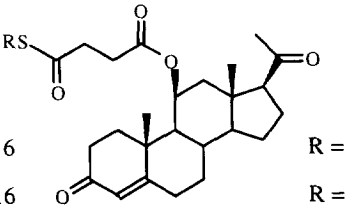
Our method can be extended to the preparation of various α-amino thiol esters as exemplified by entries 8,9. Steroidal thiol esters (entries 10,11) represent desirable intermediates for bioconjugation.

In conclusion, we have presented a new and convenient synthesis of thiol esters. The use of solid supported EDAC to mediate such coupling afforded pure products which could be separated by simple filtration and removal of solvents. Expensive thiols can be quantitatively transformed to pure thiol esters in the presence of excess carboxylic acid while volatile thiols can be used in excess to maximize the yield of the reaction. We are currently exploring expansion of this concept to biological systems and will communicate these results in a separate report.

Procedure for Thiol ester Synthesis

Chloroform (3.5 mL) was added to 600 mg polymer supported EDAC[30] and stirred for 5 min to swell the polymer. A solution of carboxylic acid (0.115 mmol)/1.0 mL chloroform was added to the suspension of swollen polymer, stirred for 5 min and added the liquid thiol (0.10 mmol neat) or a solution of solid thiol (0.10 mmol) in 0.5 mL chloroform. The resulting reaction mixture was stirred until the thiol was consumed and no further production of the desired thiol ester was observed by HPLC, filtered through a 0.5 cm. pad of Celite® and removal of solvents *in vacuo* afforded the desired thiol ester. All thiol esters gave satisfactory ^{1}H NMR, mass spectra and were >98% pure as analyzed by analytical HPLC.

Table 1. Preparation of Thiol esters Using Solid Supported EDAC[a]

Carboxylic Acid	Entry	Thiol	Time (hours)[b]	Thiol ester Product		Yield
 (CBZ = Carbobenzyloxy)	1	PhSH	16			86
	2	Pentafluoro-phenyl-SH	16			74
	3	Benzyl-SH	16			77
	4	2-Mercapto Pyridine	16			86[c]
	5	Methyl Thioglycolate	16			82
	6	Isopropyl-SH	72			63[d]
	7	*tert*-Butyl-SH	72			34[d]
 N-CBZ-L-Valine	8	PhSH	16		R = Ph	85
	9	Benzyl-SH	16		R = BnS	76
	10	PhSH	16		R = Ph	75
	11	Benzyl-SH	16		R = BnS	64

[a] Synthesis performed as described using 1.00:1.15 ratio thiol:carboxylic acid unless otherwise indicated.

[b] Reaction time was determined by monitoring the disappearance of starting thiol and no further production of thiol ester by HPLC [Waters analytical column (μporasil), λ=254nm, 1.0 mL/min, eluent=EtOAc/hexane].

[c] The 2-mercaptopyridine was added 1 hour after the carboxylic acid was introduced to the suspension of solid supported EDAC.

[d] Ten equivalents of thiol was used.

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