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EFFICIENT CONVERSION OF CARBOXYLIC ACIDS INTO THIOL ESTERS

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A facile and direct preparation of thiol esters from carboxylic acids and thiols using diphenyl 2-oxo-3-oxazolinylphosphonate in the presence of triethylamine is described.

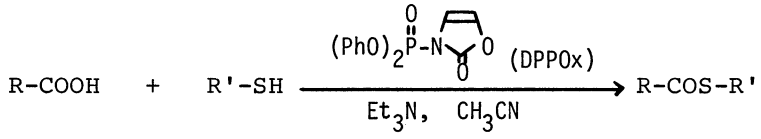
Recently, diphenyl 2-oxo-3-oxazolinylphosphonate [DPPOx][1] was introduced as a versatile reagent for carboxyl-activation, which was successfully applied to a facile preparation of peptides[1] and β-lactams[2] as well as 3-acyl-2-oxazolones[3] as chemo- and regio-selective N-acylating agents or the activated amides of synthetic utility. This reagent has now been found to be quite suitable to the direct conversion of a wide variety of carboxylic acids into thiol esters under mild conditions. Thiol esters are known to be active acylating agents in biological reactions[4] and have been used in the efficient preparation of macrocyclic lactones[5] and peptides.[6]

This transformation was performed by treatment of the acetonitrile solutions of carboxylic acids and thiols with DPPOx in the presence of triethylamine at room temperature. As indicated in Table I, the reaction proceeded smoothly under mild conditions generally in excellent yields. Sterically hindered carboxylic acids such as pivalic acid or diphenylacetic acid reacted well with primary thiols, while treatment with tertiary thiol resulted in the formation of thiol esters in lower, but still moderate, yields.

This particular process can provide the successful conversion of 12-hydroxystearic acid to the thiol ester with hydroxyl group unaffected and the formation of optically pure thiol esters from optically active N-protected α-amino acids.

A typical example is given as follows. To a solution of 12-hydroxystearic acid (1.0 g, 3.3 mmol), DPPOx (1.06 g, 3.3 mmol), and benzenethiol (0.43 g, 3.9 mmol) in acetonitrile (10 ml) was added triethylamine (1.01 g, 10 mmol) and the mixture was stirred at room temperature for 1 hr. Removal of the solvent below

Table I. Preparation of thiol Esters[a]



Acid	Thiol	Time(hr)	Yield(%)
CH_3COOH	$PhCH_2SH$	3	96
CH_3COOH	PhSH	1	91
PhCOOH	PhSH	1	94
PhCOOH	n-BuSH	1	91
PhCOOH	t-BuSH	20	83[b]
$Ph_2CHCOOH$	n-BuSH	2	89
$Ph_2CHCOOH$	t-BuSH	20	68[c]
$(CH_3)_3CCOOH$	$PhCH_2SH$	2	87
$CH_3(CH_2)_5CH(OH)(CH_2)_{10}COOH$	PhSH	1	93
$(CH_3)_2CHCH_2CH(NH\text{-}Boc)COOH$	EtSH	4[d]	86[e]

a) The reactions were performed at room temperature under conditions as described for the typical example given in the text and the thiol esters were fully characterized by spectral (NMR, Mass and IR) and elemental analyses. b) In addition to the thiol ester, 3-benzoyl-2-oxazolone was isolated in 8% yield. c) In addition, 3-diphenylacetyl-2-oxazolone was isolated in 22% yield. d) At 0°. e) $[\alpha]_D$ -39.8°(c=2, $CHCl_3$) [lit., $[\alpha]_D$ -39.6°] [S. Yamada et al., J. Org. Chem., 39, 3302 (1974)].

20° followed by a short column chromatography on silica gel with methylene chloride gave S-phenyl 12-hydroxythiostearate (1.21 g, 92.6%, mp 56°) as colorless crystals. Less amounts of triethylamine (6.6 mmol, 2 eq) was also sufficient for this conversion (88% yield).

The present procedure for a direct preparation of thiol esters from free carboxylic acids and thiols is advantageous with regards to the selective nature, the mildness of conditions, and the easy work-up for the isolation, though several methods and reagents[7] have recently become available for such conversions.

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