Synthesis of Thiol Esters by Carboxylic Trichlorobenzoic Anhydrides

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Synopsis. Thiocarboxylic S-esters were obtained rapidly and in high yields by treating the mixed anhydrides prepared from 2,4,6-trichlorobenzoyl chloride and carboxylic acid, with various types of thiols in the presence of 4-dimethylaminopyridine.

Because of the distinctive properties of thiocarboxylic S-esters as activated esters in synthetic as well as biological reactions, considerable attention has recently been called to the mild and facile preparation of these compounds.[1] Recently we have shown that the combination of carboxylic 2,4,6-trichlorobenzoic anhydrides (**2**) and 4-dimethylaminopyridine[2] are very useful for the preparation of esters from alcohols as well as for macrocyclic lactonizations.[3] Now we wish to describe the synthesis of thiol esters using the same mixed anhydrides.

When the solutions prepared by mixing 2,4,6-trichlorobenzoyl chloride (**1**),[4] carboxylic acid and triethylamine in dichloromethane, were treated with thiols under the presence of 4-dimethylaminopyridine, the corresponding thiol esters were obtained in good yields. The reaction proceeded rapidly, and was usually completed within 30 min at room temperature. The results are summarized in Table 1.

$$\mathrm{R^1COOH} + \underset{\mathbf{1}}{\mathrm{2,4,6\text{-}Cl_3C_6H_2COCl}} \xrightarrow{\mathrm{Et_3N}} \underset{\mathbf{2}}{\mathrm{2,4,6\text{-}Cl_3C_6H_2COOCOR^1}}$$

$$\mathbf{2} + \mathrm{R^2SH} \xrightarrow[\mathrm{CH_2Cl_2}]{\text{4-dimethylaminopyridine}} \mathrm{R^1COSR^2}$$

As can be seen from these results, aliphatic, aromatic or heterocyclic thiol esters could be smoothly prepared. The sterically crowded thiol esters such as *S-t*-butyl 2,2-dimethylpropanethioate (entry 3, Table 1) were also prepared in good yields. Methyl hydrogen meso-2,4-dimethylglutarate was converted into the corresponding 2-methyl-2-propanethiol ester without any detectable epimerization (GLPC, entry 7).

When dimethylaminopyridine was replaced by pyridine or triethylamine, the reaction became very slow and, for example, only 3—4% of *S-t*-butyl 2-methylpentanethioate was formed after 1 h (*cf.* entry 2). Though the aromatic hydrocarbons such as benzene or toluene, were the best solvent for the esterification by the same reagents,[3] dichloromethane was the most effective solvent in the present thiol esterification. Acetonitrile or DMF was much less satisfactory.

The possibility of nucleophilic attack on the undesired carboxyl site is inherent to the mixed anhydride method. For example, when carboxylic pivalic anhydrides which have been sometimes used in peptide[5] or ketone synthesis,[6] were treated with 2-methyl-2-propanethiol or benzenethiol in the presence of 4-dimethylaminopyridine under the similar conditions, both the carboxyl sites were attacked as shown in Eqs. 1, 2, and 3. In the present method, however, thiol attacked exclusively on the desired carboxyl carbon except for one case where sterically crowded pivalic acid was converted into its benzenethiol ester (entry 5, Table 1).[7]

$$\begin{array}{l} \mathrm{C_6H_5COOCOC(CH_3)_3} \\ + \\ \mathrm{HSC(CH_3)_3} \end{array} \xrightarrow[\text{rt, 10 h}]{\text{DMAP (1 eq)}} \begin{array}{ll} \mathrm{C_6H_5COSC(CH_3)_3} & 60\% \\ + & \\ \mathrm{(CH_3)_3CCOSC(CH_3)_3} & 15\% \end{array} \quad \text{(GLPC)} \qquad (1)$$

$$\begin{array}{l} \mathrm{CH_3(CH_2)_2COOCOC(CH_3)_3} \\ + \\ \mathrm{HSC_6H_5} \end{array} \xrightarrow[\text{rt, 10 min}]{\text{DMAP (1 eq)}} \begin{array}{ll} \mathrm{CH_3(CH_2)_2COSC_6H_5} & 48\% \\ + & \\ \mathrm{(CH_3)_3CCOSC_6H_5} & 43\% \end{array} \quad (^1\text{H-NMR}) \qquad (2)$$

$$\begin{array}{l} \mathrm{(CH_3)_2CHCOOCOC(CH_3)_3} \\ + \\ \mathrm{HSC_6H_5} \end{array} \xrightarrow[\text{rt, 10 min}]{\text{DMAP (1 eq)}} \begin{array}{ll} \mathrm{(CH_3)_2CHCOSC_6H_5} & 48\% \\ + & \\ \mathrm{(CH_3)_3CCOSC_6H_5} & 38\% \end{array} \quad (^1\text{H-NMR}) \qquad (3)$$

The use of symmetrical anhydrides[8] or mixed anhydrides with phosphoric acid derivatives[9] has been reported for the synthesis of thiol esters. The main advantage of the present method is the rapidness and the mildness of the reaction, high yields, and the wide applicability.

Experimental

The preparation of *S-t*-butyl 2-methylpentanethioate (entry 2, Table 1) is described below as a typical example of the present thiol esterifications.

2,4,6-Trichlorobenzoyl chloride (80 μl, 0.5 mmol) was added to a stirred mixture of 2-methylpentanoic acid (63 μl, 0.5 mmol), triethylamine (70 μl, 0.5 mmol), and dichloromethane (0.8 ml). After 1 h, the reaction mixture was filtered through a dry celite column. To the filtrate were added 2-methyl-2-propanethiol (56.4 μl, 0.5 mmol) and 4-dimethylaminopyridine (61 mg, 0.5 mmol) and the mixture was stirred at room temperature. GLPC analysis showed the quantitative formation of the thiol ester after 30 min. The reaction mixture was diluted with ether, washed successively with 5% aqueous phosphoric acid, a saturated sodium hydrogencarbonate solution, and brine, dried with sodium sulfate, and distilled at 80 °C/15 mmHg[10] (bath temperature) giving *S-t*-butyl 2-methylpentanethioate in 86.3% yield.

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Table 1. Reaction conditions and yields of thiol esters[a]

	Acid (0.5 mmol) R^1 in R^1COOH	Thiol (0.5 mmol) R^2 in R^2SH	DMAP[b] (mmol)	Time (min)	Yield(%)[c] R^1COSR^2
1	$CH_3(CH_2)_2$	C_2H_5	0.5	4	96 (82)[d]
2	$CH_3CH_2CH_2\underset{\vert}{C}HCH_3$	$(CH_3)_3C$	0.5	30	98 (86)[e]
3	$(CH_3)_3C$	$(CH_3)_3C$	0.5	120	96
4	$(CH_3)_2CH$	C_6H_5	0.5	4	87 (78)[f]
5	$(CH_3)_3C$	C_6H_5	0.5	5	60[g]
6	C_6H_{11} (cyclohexyl)	C_5H_4N[h]	0.5	10	(84)
7	$CH_3O_2CCH(CH_3)CH_2\underset{\vert}{C}HCH_3$[i]	$(CH_3)_3C$	0.5	10	96 (80)[j]
8	C_6H_5	$(CH_3)_3C$	0.5	3	93 (81)
9	$C_6H_5CH{=}CH$	$(CH_3)_2CH$	0.5	3	93 (81)[k]

a) All reactions were carried out in dichloromethane at room temperature. b) 4-Dimethylaminopyridine. c) The yields were determined by GLPC. Isolated yields were given in parentheses. d) A new compound: Bp 150 °C (bath temp). Found: C, 54.32; H, 9.17%. Calcd for $C_6H_{12}OS$: C, 54.50; H, 9.15%. ^{1}H-NMR (δ); 1.25 (t, 3H, J=7.0 Hz), 2.53(t, 2H, J=7.4 Hz). e) Bp 100 °C (10 mmHg, bath temp). Found: C, 63.48; H, 10.56%. Calcd for $C_{10}H_{20}OS$: C, 63.71; H, 10.70%. ^{1}H-NMR; 1.46(s, 9H), 2.50(m, 1H). f) Bp 140 °C (9 mmHg, bath temp). Found: C, 66.34; H, 6.68%. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71%. ^{1}H-NMR; 1.26 (d, 6H, J=6.8 Hz), 7.38 (s, 5H). g) *S*-Phenyl 2,4,6-trichlorothiobenzoate [mp 119 °C, Found: C, 49.05; H, 2.29%. Calcd for $C_{13}H_7Cl_3OS$: C, 49.16; H, 2.22%. ^{1}H-NMR; 7.33(m, 2H), 7.49(m, 5H)] was also formed in 18% yield. h) 2-Pyridinethiol. i) Methyl hydrogen meso-2,4-dimethylglutarate. j) Found: C, 58.21; H, 8.92%. Calcd for $C_{13}H_{22}O_3S$: C, 58.50; H, 9.00%. ^{1}H-NMR; 1.46 (s, 9H), 3.68(s, 3H). k) Bp 180 °C (11 mmHg, bath temp). Found: C, 69.66; H, 6.86%. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84%. ^{1}H-NMR; 1.35(d, 6H, J=6.7 Hz), 6.67(d, 1H, J=16.1 Hz), 7.61(d, 1H, J=16.1 Hz).

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7) The thiol esterification of pivalic acid with benzenethiol by the present method is peculiar in that the reaction with triethylamine or morphorine in place of dimethylaminopyridine gives a quite similar result as that with dimethylaminopyridine in rate, yield, and product distribution. This indicates that the reaction presumably involves the direct attack of thiolate ion formed by the bases, on the mixed anhydride. Benzenethiol is much more acidic than the aliphatic thiols.

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10) 1 mmHg=133.322 Pa.