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A New and Efficient Method for the Preparation of *S*-Phenyl Carbothioates via Mixed Anhydrides Using Active Titanium(IV) Salts

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In the presence of a catalytic amount of titanium(IV) salt, various *S*-phenyl carbothioates are prepared in excellent yields by the reaction of nearly equimolar amounts of silyl derivatives of carboxylic acids and benzenethiols with *p*-trifluoromethylbenzoic anhydride.

Recently, a considerable attention has been paid to the preparation of activated carboxylic acid derivatives such as thiol esters because of their high reactivities toward various nucleophiles, and a wide availability was shown in organic synthesis.1) Concerning the preparation of thiol esters, the condensation reaction between carboxylic acid halides and thiols under basic or acidic condition is conventionally employed.2) The chemoselective preparation of various thiol esters via mixed anhydrides under basic conditions using 2,4,6-trichlorobenzoyl chloride as a bulky acid moiety reported by Yamaguchi *et al.* is also known as an efficient method.3) Since the yield and chemoselectivity of the desired thiol ester from pivalic acid and benzenethiol were low in the above procedure, it was desired to develop a facile and efficient method applicable to various substrates under mild conditions.

In the previous paper, we have shown that mixed anhydrides are smoothly generated in situ from silyl derivatives of various aliphatic carboxylic acids and *p*-trifluoromethylbenzoic anhydride by the promotion of a catalytic amount of Lewis acid such as $Sn(OTf)_2$ and a titanium(IV) salt generated from 1 mol of $TiCl_4$ and 2 mol of AgOTf.4) The anhydrides are in turn efficiently converted into the corresponding carboxylic esters on treatment with trimethylsilyl ethers of alcohols under the reaction conditions.

Now, we would like to report a useful method for the preparation of *S*-phenyl carbothioates from nearly equimolar amounts of silyl derivatives of carboxylic acids and benzenethiols by using a titanium(IV) salt as a catalyst.

First, 10 mol% of $Sn(OTf)_2$, which gave good results in the previous esterification,4) was used as a catalyst for the reaction of silyl derivatives of pivalic acid and benzenethiol, and the corresponding thiol esters *S*-phenyl 2,2-dimethylpropanethioate **1** and *S*-phenyl *p*-trifluoromethylthiobenzoate **2** were obtained together indicating unsatisfactory chemoselectivity (see Table 1, Entry 1). Then, our effort was focused on improving the chemoselectivity and several catalysts were examined by taking the reaction of silyl derivatives of pivalic acid and benzenethiol as a model. It was found that the chemoselectivity was improved when the titanium(IV) salt generated in situ from 1 mol of $TiCl_4$ and 2 mol of AgOTf was used as a catalyst (Entry 6). This result was different from that obtained by using $TiCl_2(OTf)_2$ separately prepared from $TiCl_4$ and trifluoromethanesulfonic acid (Entry 3).[5] Since 2 mol of AgCl was formed (quantitatively) by mixing 1 mol of $TiCl_4$ and 2 mol of AgOTf in dichloromethane, the difference in the chemoselectivities might depend on coexisted AgCl. This was further supported from that the addition of 20 mol% of AgCl to the suspention of 10 mol% of $TiCl_2(OTf)_2$ in the present reaction increased the chemoselectivity (Entry 4).

Next, the titanium(IV) salts were further examined by taking the reaction of silyl derivatives of acetic acid and *p*-methoxybenzenethiol as a model. It was shown that the chemoselectivity was improved by using the titanium(IV) salt generated from 10 mol% of $TiCl_4$ and 30 mol% of AgOTf compared with that obtained when 10 mol% of $TiCl_4$ and 20 mol% of AgOTf were used (Entry 6,7). Since 2 mol of AgCl was formed even when 1 mol of $TiCl_4$ was treated with more than 2 mol of AgOTf in dichloromethane, this result might be also explained by considering the effect of silver salts such as AgCl and AgOTf. When 20 mol% of AgOTf was added to the suspention of 10 mol% of $Sn(OTf)_2$ in dichloromethane, the chemoselectivity of the reaction was improved (Entry 2). Furthermore, experimental results by changing the molar ratio of $TiCl_4$ and AgOTf proved our above mentioned hypothesis (Entry 3,6-8).

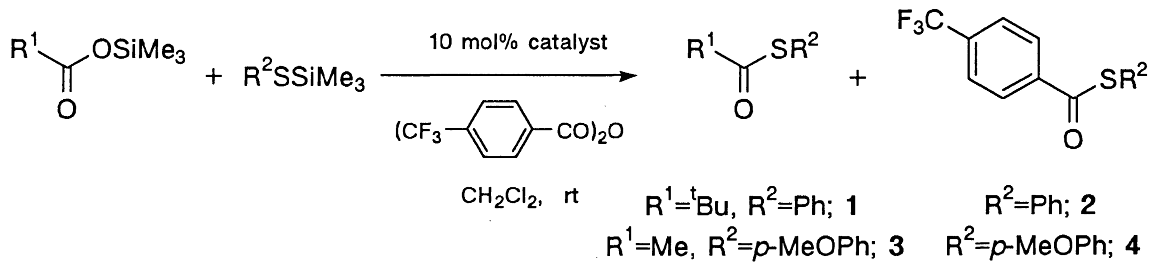

Table 1. Effect of Catalysts

Entry	Catalyst	Yield / %	Ratio of **1** / **2** [a)]	Yield / %	Ratio of **3** / **4** [a)]
1	10 mol% $Sn(OTf)_2$	92	84 / 16	93	73 / 27
2	10 mol% $Sn(OTf)_2$ + 20 mol% AgOTf	78	96 / 4	81	91 / 9
3	10 mol% $TiCl_2(OTf)_2$ [b)]	88	99 / 1	93	99 / 1
4	10 mol% $TiCl_2(OTf)_2$ + 20 mol% AgCl	93	>200 / 1	92	99 / 1
5	10 mol% $TiCl_4$ + 10 mol% AgOTf	83	99 / 1	91	94 / 6
6	10 mol% $TiCl_4$ + 20 mol% AgOTf	89	>200 / 1	94	99 / 1
7	10 mol% $TiCl_4$ + 30 mol% AgOTf	88	>200 / 1	95	>200 / 1
8	10 mol% $TiCl_4$ + 40 mol% AgOTf	86	>200 / 1	93	>200 / 1

a) Determined by ^1H-NMR. b) Prepared according to the procedure reported by Ref. 5.

Thus, several carboxylic acids including pivalic acid are successfully employed in the present experiment to form the desired *S*-phenyl carbothioates in high yields with perfect chemoselectivity (Table 2). In every case, the reaction proceeds smoothly at room temperature in dichloromethane to give the corresponding *S*-phenyl carbothioates in excellent yields starting from nearly equimolar amounts of silyl derivatives of carboxylic acids and benzenethiols.

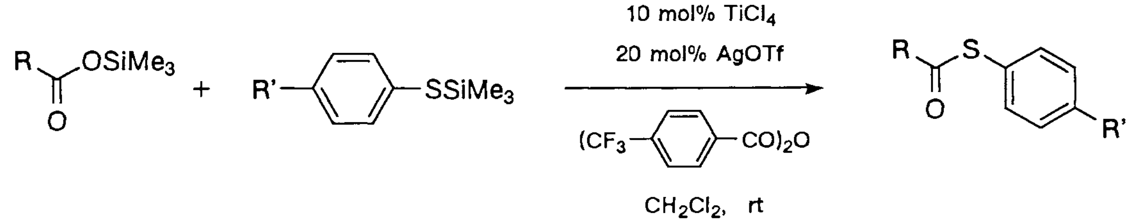

Table 2. Synthesis of *S*-Phenyl Carbothioates

R	Yield / %[a]		
	(R' = H)	(R' = OMe)	(R' = Cl)
Me	84	95[b)]	93
^{i}Pr	94	96[c)]	94
^{i}Bu	99	98	94
^{t}Bu	89	94	97
$Ph(CH_2)_2$	99	95	96

a) Isolated yield. No by-product was obtained at all.

b) Ten mol% of $TiCl_4$ and 30 mol% of AgOTf were used as a catalyst.
(When 10 mol% of $TiCl_4$ and 20 mol% of AgOTf were used, *S*-(*p*-methoxyphenyl) *p*-trifluoromethylphenylmethanethioate was also formed in 0.9 % yield.)

c) Ten mol% of $TiCl_4$ and 30 mol% of AgOTf were used as a catalyst.
(When 10 mol% of $TiCl_4$ and 20 mol% of AgOTf were used, *S*-(*p*-methoxyphenyl) *p*-trifluoromethylphenylmethanethioate was also formed in 0.6 % yield.)

A typical experimental procedure is described for the reaction of 3-methylbutyric acid trimethylsilyl ester and phenyl trimethylsilyl sulfide in the presence of a catalytic amount of titanium(IV) chloride - silver triflate ($TiCl_4$-AgOTf); to a suspension of AgOTf (0.034 mmol) and $TiCl_4$ (0.017 mmol) in dichloromethane (2.0 ml), a solution of *p*-trifluoromethylbenzoic anhydride (0.19 mmol) and 3-methylbutyric acid trimethylsilyl ester (0.19 mmol) in dichloromethane (1.0 ml) and a solution of phenyl trimethylsilyl sulfide (0.17 mmol) in dichloromethane (1.0 ml) were successively added. The reaction mixture was stirred for 6 h at rt, and then quenched with aq. sat. $NaHCO_3$. After usual work up, the crude product was purified by preparative TLC on silica gel to afford *S*-phenyl 3-methylbutanethioate (99% yield) with excellent chemoselectivity (>200/1).

In addition, it is noted that, in a similar manner, several substituted and unsubstituted phenyl carboxylates were obtained in high yields with perfect chemoselectivity from nearly equimolar amounts of silyl derivatives of carboxylic acids and the corresponding subsutituted and unsubstituted phenols as shown in Table 3.

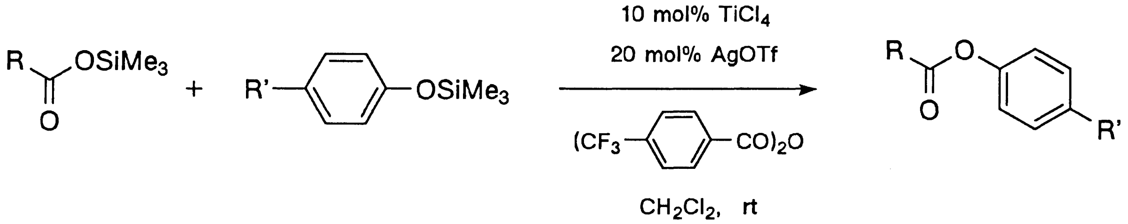

Table 3. Synthesis of Phenyl Carboxylates

R	Yield / %[a)]			
	(R' = H)	(R' = OMe)	(R' = Cl)	(R' = NO_2)
^{i}Pr	77	95	93	86
$Ph(CH_2)_2$	99	91	94	80

a) Isolated yield. No by-product was obtained at all.

Further investigations to examine the precise structure of titanium(IV) salts as well as to develop other useful synthetic reactions by using this efficient catalyst are now in progress.

References

1) S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem., Int. Ed. Engl.*, **16**, 585 (1977).

2) Basic condition: Y. Watanabe, S. Shoda, and T. Mukaiyama, *Chem. Lett.*, **1976**, 741; Acidic condition: S. Ahmad and J. Iqbal, *Tetrahedron Lett.*, **27**, 3791 (1986), and references cited therein.

3) Y. Kawanami, Y. Dainobu, J. Inanaga, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **54**, 943 (1981).

4) T. Mukaiyama, I. Shiina, and M. Miyashita, *Chem. Lett.*, **1992**, 625.

5) M. Schmeißer, P. Sartori, and B. Lippsmeier, *Chem. Ber.*, **103**, 868 (1970); Y. Tanabe, *Bull. Chem. Soc. Jpn.*, **62**, 1917 (1989).

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