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Aminolysis of Triphenylantimony Dicarboxylates and Its Application to Catalytic Amidation

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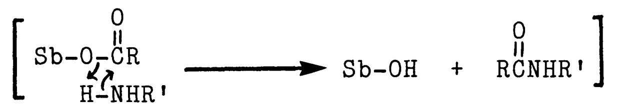
Triphenylantimony dicarboxylates ($Ph_3Sb(O_2CR)_2$, where R=Me, CF_3, Ph and CH_2NH-Z) readily reacted with amines ($R'NH_2$, where R'=*n*-C_6H_{13}, *s*-Bu, C_6H_{11}, and Ph) to afford corresponding amides and triphenylstibine oxide in fairly good yields. The amidation of RCO_2H with $R'NH_2$ was also catalyzed by the orgnoantimony compounds.

Although organometallic carboxylates generally possess bidentate or ionic carboxylate groups,$^{1)}$ organoantimony carboxylates, especially triphenylantimony diacetate $Ph_3Sb(OAc)_2$, have a monodentate and ester-type Sb-OC(O) linkage.$^{2)}$ Consequently, we would expect that the organoantimony carboxylates could be employed as active esters available for the amide syntheses. In addition, there was a considerable merit that triphenylantimony dicarboxylates should be recycled as shown in Scheme 1.$^{3)}$ Similarly, we have recently reported that triphenylstibine oxide catalyzed the intramolecular condensation of carbamic acid groups with amino or hydroxyl moieties.$^{4)}$

$$Ph_3Sb(O_2CR)_2 + 2\ R'NH_2 \longrightarrow 2\ RCONHR' + Ph_3Sb(OH)_2 + H_2O$$



$$\left[Sb{-}O{-}\overset{O}{\overset{\|}{C}}R \;\; H{-}NHR' \longrightarrow Sb{-}OH + R\overset{O}{\overset{\|}{C}}NHR' \right]$$

$$Ph_3Sb(OH)_2 \longrightarrow Ph_3SbO + H_2O$$

$$Ph_3SbO + 2RCO_2H \xrightarrow{-H_2O} Ph_3Sb(O_2CR)_2$$

Scheme 1.

Thus, $Ph_3Sb(OAc)_2{}^{5)}$ was heated with stirring at 50 °C in ten folds excess quantities of *N*-*n*-hexylamine for 10 h. During the course of the reaction, Ph_3SbO precipitated and was finally recovered by filtration quantitatively. The filtrate was analyzed by GLC (OV-1/Uniport KS, 150 °C, N_2) and then chromatographed on silica gel (Wako Gel C-200, eluted by hexane then chloroform). *N*-*n*-Hexylacetamide was isolated in 87% yield (GLC yield was also estimated as 90% with an internal standard method). Reactions of triphenylantimony diacetate or other dicarboxylates with several amines were also carried out and the results are summarized in Table 1.

Table 1. Aminolysis of organoantimony carboxylates with amines at 50 °C[a)]

Organoantimony carboxylates	Amines	t/h	Yields of amides/%[b)]
$Ph_3Sb(OAc)_2$	*n*-$HexNH_2$ [c)]	10	90
	$PhCH_2NH_2$	5	97
	s-$BuNH_2$	5	93
	cyclo-$HexNH_2$ [c)]	10	79
	t-$BuNH_2$	15	10
	$PhNH_2$	40 [d)]	84
$Ph_3Sb(O_2CCF_3)_2$	*n*-$HexNH_2$ [c)]	0.5	36
		24	40
$Ph_3Sb(OBz)_2$ [e)]		24	20
		22 [f)]	97
$Ph_3Sb(OGly\text{-}Z)_2$ [g)]		5	82 [h)]
$Ph_4Sb(OAc)$		24	16
$Sb(OAc)_3$		24	15
$Bu_3Sn(OAc)$		24 [i)]	tr
$Bu_2Sn(OAc)_2$		24 [i)]	tr

a) Typical conditions; antimony carboxylates, 1 mmol, amine 20 mmol.
b) GLC yields. c) Hex denotes hexyl. d) 85 °C. e) Bz denotes PhCO. f) 130 °C. g) OGly-Z means *N*-benzyloxycarbonylglycinate.
h) Isolated yield. i) 80 °C.

The aminolysis of $Ph_3Sb(OAc)_2$ with alkylamines gave corresponding acetamides in good yields for 5-10 h even at 50 °C, however, *tert*-butylacetamide was obtained in a low yield even for 15 h. Aniline could be employed in the aminolysis only at higher temperatures (above 85 °C). While, triphenylantimony bis(trifluoroacetate) and dibenzoate were found to be less reactive than the acetate, and only the first carboxylate group seemed to be available for the aminolysis in these reactions. Besides, benzamide could be obtained in good yields at 130 °C. Further, it is very interesting that an amino acid ester, triphenylantimony bis(*N*-benzyloxycarbonylglycinate)[6)] was found to be reactive even at 50 °C. Now, we are encouraged to extend the use of this aminolysis process to the peptide synthesis.

Typical time-yields curves in the reaction of $Ph_3Sb(OAc)_2$ with *n*-hexylamine at 50, 40, and 37.5 °C are presented in Fig. 1. In the initial periods of the reaction, increases of the yields of the acetamide were very fast. The mode of the reaction then altered into slow one and the yields ascended linearly with time after one of two acetate groups in $Ph_3Sb(OAc)_2$ was consumed. A new absorption band at 1600-1580 cm^{-1} besides that of $Ph_3Sb(OAc)_2$ at 1633 cm^{-1} appeared and increased its intensity with the aminolysis in the precipitates from the reaction mixture. Consequently, we tentatively induced that a half ester (1) was formed by the initial aminolysis and that the overall aminolysis proceeded *via.* a stepwise path as shown in Scheme 2. Since the linkage of Sb-OAc in 1 possessed some bidentate character as in the stibonium acetate[10)] and tetrasubstituted antimony acetates,[7)] the reactivity of 1 should be low as described below. Incidentally, the apparent activation energies for two aminolysis steps were estimated to be 64 and 101 kJ mol^{-1}, respectively.

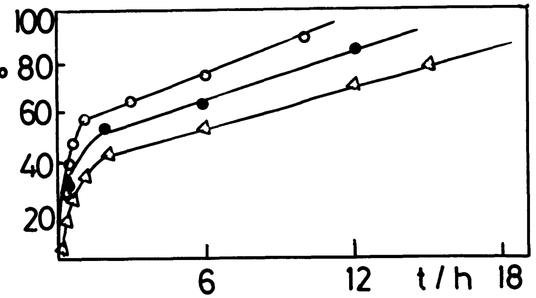


Fig. 1. Time-yield curves in the aminolysis of $Ph_3Sb(OAc)_2$ with *n*-hexylamine.
○ ; 50 °C, ● ; 40 °C, △ ; 37.5 °C.

$$\underset{\underline{1}}{Ph_3Sb(OAc)_2} \xrightarrow[fast]{RNH_2} \underset{(\underline{1})}{Ph_3Sb(OH)(OAc)} + RNHAc$$

$$\xrightarrow[slow]{RNH_2} Ph_3SbO + RNHAc + H_2O$$

Scheme 2.

In contrast to the triphenylantimony dicarboxylates, tetraphenylstibonium acetate[8)] and antimony triacetate gave *N*-*n*-hexylacetamide in only 16 and 15% yields, respectively. The bidentate acetate group in these antimony derivatives was considered to form a stable chelation[9,10)] which resisted against the aminolysis. Dibutyltin diacetate which possessed more bidentate and bridging acetate moieties[11)] could not react with hexylamine at 50-100 °C.

The organoantimony active esters should be more useful if they could be used as catalysts. We then attempted the amidation of carboxylic acids with amines in the presence of $Ph_3Sb(OAc)_2$ or Ph_3SbO as the catalysts. Recently, some organometallic reagents have been employed in amide syntheses,[12-13)] however, few was succeeded for their catalytic application.[14)] Thus, the reaction of 1 mmol of $Ph_3Sb(OAc)_2$ with 20 mmol of hexylamine in the presence of 2 mmol of acetic acid at 90 °C for 8h, and of 10 mmol of acetic acid with 12.5 mmol of hexylamine in the presence of 1 mmol of $Ph_3Sb(OAc)_2$ in 2 ml of pyridine at 100 °C for 10 h gave 3.9 and 12 mmol of hexylacetamide, respectively. These results evidenced the regeneration of $Ph_3Sb(OAc)_2$ *in situ*.

Table 2. Direct amidation catalyzed by organoantimony compounds [a,b)]

Catalysts	RCOOH R=	R'NH$_2$ R'=	T/°C	t/h	Yields of amides/%
none	CH_3	*n*-Hex [c)]	100	10	15
$Ph_3Sb(OAc)_2$			70	96	100 [d)]
			90	8	98 [d)]
			100	10	100
Ph_3SbO			100	10	88
		$PhCH_2$		6	99
		cyclo-Hex [c)]		24	81
		Ph	110	24	98
	Pr^n	*n*-Hex [c)]	100	8	70
		$PhCH_2$		7	97
	Ph	*n*-Hex [c)]		24	11
		Ph	130	24	85

a) Typical conditions, antimony catalyst/RCOOH/R'NH_2=1/10/12.5 mmol. b) Pyridine (2 ml) was used as solvent. c) Hex denotes hexyl. d) $Ph_3Sb(OAc)_2$/AcOH/HexNH_2=1/2/20 mmol.

Further, triphenylstibine oxide also offered a excellent catalytic activity for the amidation as shown in Table 2. Pyridine as a solvent was necessary to enforce this catalytic amidation effectively, because pyridine could dissolve well both $Ph_3Sb(OAc)_2$ and 1 and prevented the the formation of the chelation in 1 by coordination. Other solvents such as benzene and chloroform were less effective. The major advantages of the organoantimony catalysts are as following. The organoantimony active esters are readily obtainable and stable to handle. Further, the catalytic use of the organoantimony compounds are also capable.

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3) It is well known that Ph_3SbO readily reacts with carboxylic acids to give corresponding dicarboxylates, see for example, J. Havránek, J. M. Mleziva, and A. Lycka, *J. Organomet. Chem.*, 157, 163 (1978).
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5) Triphenylantimony diacetate and other dicarboxylates were prepared by the method reported by Havránek et al., see Ref. 3 and agreed well with analyses.
6) $Ph_3Sb(OGly\text{-}Z)_2$, mp 134-135 °C, IR (KBr) 3380 (NH) and 1723 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.75 (4H, d, CH_2), 4.98 (4H, s, benzyl), 5.11 (2H, t, NH) and 6.6-7.3 (25H, m, phenyl); ^{13}C NMR ($CDCl_3$) δ=44.1 (t), 66.8 (t), 127.9 (d), 128.0 (d), 128.5 (d), 129.7 (d), 131.7 (d), 133.8 (d), 134.0 (s), 136.1 (s), 156.0 (s), and 172.6 (s). HexNHGly-Z, mp 107-109 °C; IR (KBr) 1642 (amide) cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.62-1.1 (13H, m, hexyl), 3.25 (2H, q), 3.82 (2H, d, glycine CH_2), 5.15 (2H, s), 5.65-5.74 (1H, m), 5.84-6.14 (1H, m), 7.3-7.6 (5H, m, phenyl), satisfactory analytical results were obtained for these two compounds.
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