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SHORT PAPER

An organoantimony catalyst for peptide synthesis; preparation and aminolysis of triphenylantimony bis(aminoacylate)s

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Triphenylantimony bis(aminoacylate)s [$Ph_3Sb(O-A)_2$, A=Z—Gly, Z—Phe, Z—Leu, Bz—Phe] were prepared by direct condensation between triphenylstibine oxide and *N*-protected amino-acids in acetone. The aminolysis of these antimony aminoacylates by amino-acid esters gave corresponding dipeptides, which lead to a catalytic dipeptide synthesis using triphenylstibine oxide as a catalytic precursor of the antimony aminoacylate *in situ*.

Keywords: Triphenylstibine oxide, triphenylantimony bis(aminoacylate)s, catalytic peptide synthesis, aminolysis, dipeptides

INTRODUCTION

Recently, we pointed out the possibility of catalytic amidation using triphenylantimony diacylates as key intermediates.[1] Triphenylantimony diacylates, which can be formed *in situ* from triphenylstibine oxide and carboxylic acids, possessed high reactivities towards aminolysis and were able to be recycled. Meanwhile, direct amidation is a rather primitive synthetic reaction, although some modification has been done with the introduction of activated esters and condensation agents, etc,[2,3] but they are rather stoichiometric routes.

Some efforts have been given to an organometallic approach in direct amidation. Although certain complexes containing copper,[4] cobalt,[5,6] chromium,[7] tungsten,[7] rhenium,[8] platinum,[9] and palladium[9] are used in peptide synthesis, they merely behave as activators for condensation agents or protecting groups against racemization, but they do not function as catalysts. In addition, organotin compounds are also utilized in amidation, but they have been restricted to use in transesterification[10] or amidation under severe conditions.[11,12] Thus, in our knowledge, no successful organometallic catalyst for the amidation is known. In this paper, we will describe a novel catalyst for amide and peptide synthesis using Ph_3SBO as a precursor and catalyst for the diacylates as active intermediates (Scheme 1).

$$Ph_3Sb(O-A)_2 + RNH_2 \longrightarrow 2\ RNH-A + H_2O + Ph_3SbO$$

A = Z—Gly, Z—Phe, Z—Leu;

R = n-Hex, Gly—OEt, Leu—OEt.

Scheme 1

EXPERIMENTAL

General

Melting points were uncorrected. IR and NMR spectra were recorded on a Hitachi 260–30 spectrophotometer and on a Hitachi R90H FT spectrometer respectively. Triphenylstibine oxide (Ph_3SbO) was prepared by means of a hydrogen peroxide (H_2O_2) oxidation of triphenylstibine.[13] *N*-Protected amino-acids were prepared in the usual manner.[14]

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Preparation of triphenylantimony bis(*N*-protected aminoacylate)s

Into a suspension of Ph_3SbO (5.2 g) in acetone (200 cm^3) the stoichiometric amounts of *N*-protected amino-acids were added slowly. The precipitates of Ph_3SbO disappeared gradually, and the mixture became homogeneous after stirring at room temperature for two hours. Then the mixture was filtered off and the filtrate was evaporated *in vacuo*. A highly viscous oil was obtained and was dissolved in chloroform. Pure triphenylantimony dicarboxylates were crystallized from the chloroform and hexane. Exceptionally, the di(Z-leucinate) derivative did not crystallize and was purified by continuous washing with hexane (Table 1).

Aminolysis of triphenylantimony diacylates

Solvents and the triphenylantimony diacylates of *N*-protected amino-acids were placed in a 50 cm^3 flask, and the mixture was heated with stirring by a small bar magnet. After the reaction (Scheme 1) was finished, the mixture was poured into 100 cm^3 water and extracted by ethyl acetate, followed by evaporation. The residues were then chromatographed on silica gel eluted by ethyl acetate/hexane (1:1). The amino products were obtained by evaporation and crystallization.

Table 1 Yields and properties of organoantimony amino-acid esters

$Ph_3Sb(O—A)_2$[a,b]	Yield (%)	M.p. (°C)	δC OOSb ($\Delta\delta$)[c,d]	νC=O (cm^{-1})
A=Z—Gly	95	134–135	172.6 (+0.4)	1723
A=Z—Phe	50	49–51	174.0 (−1.6)	1715
A=Bz—Phe	70	166–169	173.9 (−1.1)	1710
A=Z—Leu	95	Oil	175.8 (−1.2)	1720

[a] Z, benzyloxycarbonyl, $C_6H_5CH_2OCO$. [b] The triphenylantimony bis(aminoacylate)s obtained give satisfactory elemental analysis data. [c] $\Delta\delta = \delta$C OOSb − δC OO free *N*-protected amino-acids. [d] $\Delta\delta$ of $Ph_3Sb(OAc)_2$ is ±0.

Catalytic aminolysis

Into a suspension of triphenylstibine oxide in the solvents, *N*-protected amino-acids and amino-acid ethyl esters were added slowly in this order and at the concentrations and ratios shown in Table 2. The mixture was stirred at the previously prescribed temperatures. After the reaction, the mixtures were worked-up as described above.

RESULTS AND DISCUSSION

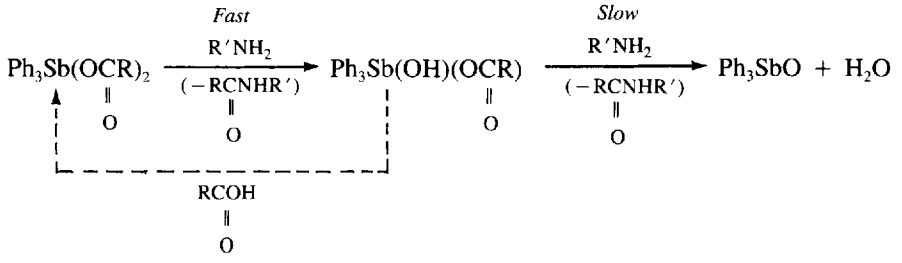
It is well known that triphenylantimony diacylates are easily accessible via alkoxy–carboxylate exchange reactions; i.e. the apparent condensation reaction of triphenylstibine oxide and carboxylic acids occurs usually in methanol solution.[15] However, because of significant methanolysis of triphenylantimony bis(aminoacylate)s, the apparent condensation should be carried out in aprotic solvents such as acetone.

Thus, we prepared four types of triphenylantimony bis(*N*-protected aminoacylate)s as shown in Table 1. In the previous paper, we reported that the

Table 2 Aminolysis of triphenylantimony di(aminoacylate)s

$Ph_3Sb(O—A)_2$[a]	Amine	Ratio[b]	Solvent	Temp(°C)	Time(h)	Yield[c] (%)
A=Z—Gly	n-$HexNH_2$[d]	1/20	—	60	1	93
		1/ 2	$CHCl_3$	60	24	75
	HGly—OEt	1/ 2	Et_3N	50	1	45
		1/ 2	$CHCl_3/Et_3N$[e]	50	10	60
	HLeu—OEt	1/ 2	$CHCl_3/Et_3N$[e]	60	24	95
A=Z—Phe	n-$HexNH_2$	1/20	—	60	1	85
		1/ 2	$CHCl_3$	60	24	65
	HLeu—OEt	1/ 2	Et_3N	60	24	12
		1/ 2	$CHCl_3/Et_3N$[e]	60	4	38
A=Z—Leu	n-$HexNH_2$	1/20	—	60	1	86
		1/ 2	$CHCl_3$	60	24	tr

[a] Z, benzyloxycarbonyl. [b] Molar ratio of $Ph_3Sb(O—A)_2$/amine. [c] Peptide product. [d] Hex, hexyl. [e] $CHCl_3/Et_3N$=3/7 by vol.



Scheme 2

organometallic carboxylates reactive to aminolysis possessed an ester-like linkage and that their IR νCOOSb and NMR δCOOSb appeared at around 1700 cm^{-1} and 172 ppm, respectively. Since the list of their δCOOSb and νC=O shown in Table 1 indicates the presence of ester-type antimony–carboxylate linkages, the aminoacylates of triphenylantimony are also considered to be reactive towards aminolysis as well as unfunctionalized carboxylates.[1]

The aminolysis of triphenylantimony bis(aminoacylate)s by hexylamine and ethyl esters of glycine and leucine was carried out and the results are shown in Table 2. In these reactions, a homogeneous solution at the starting of the aminolysis gradually became opaque and triphenylstibine oxide precipitated and was removed. The aminolysis of the aminoacylates using large excesses of n-hexylamine gave corresponding amides in good yields in 1 h. For aminolysis using stoichiometric amounts of n-hexylamine it was necessary to use solvents such as chloroform and long reaction periods. Further, the use of amino-acid esters was needed to add tertiary amines as a component of solvent systems, and the yields were relatively low. Steric hindrance around the acylate moieties was considered to affect the aminolysis significantly.

As stated in the preliminary report,[1] the aminolysis of triphenylantimony diacylates proceeds in two steps (Scheme 2): the second acylate group reacts with amines just after the end of consumption of the first acylate.[1] In addition, the reaction of the first acylate is very fast, in contrast to the second one. The overall aminolysis seemed to be an ineffective procedures as determined by the slow second step. Thus, we considered that if only the first acylate could be employed, the catalytic amidation and peptide synthesis will become facile (consult Scheme 2).

The catalytic dipeptide synthesis was attempted using the coupling of Z—glycine and glycine ethyl ester, and the results are presented in Table 3. Fortunately, we obtained partially successful results. Thus, triphenylstibine oxide behaved as an amidation catalyst and Z—GlyGly—OEt was obtained in good-to-moderate yields. The turnover numbers were still low (not exceeding 11); however, triphenylstibine oxide was also applicable to the coupling of Z—PheOH and HGly—OEt in a similar turnover number without significant racemization. Now we are attempting to improve the catalytic activity of triphenylstibine oxide and some modification will be reported.

Table 3 Synthesis of Z—GlyGly—OEt catalysed by Ph_3SbO[a]

Ph_3SbO (mol %)[b]	Solvent	Temp(°C)	Time(h)	Yield (%)[c]
25	$CHCl_3$/DBU[d]	50	2	100
10	$CHCl_3/Et_3N$[e]	50	3	25
5	$CHCl_3/Et_3N$[e]	50	3	57
5[f]	$CHCl_3/Et_3N$[e]	50	3	51

[a] Z—GlyOH/HGly—OEt = 0.5/0.5 mmol; 2 cm^3 of solvents were used. [b] With respect to Z—Gly—OH. [c] Turnover numbers are 4, 2.5, 11 and 10 (respectively). [d] DBU, 1, 7-diazabicyclo[5,4,0]undec-7-ene; $CHCl_3$/DBU = 3/7 by vol. [e] $CHCl_3/Et_3N$ = 3/7 by vol. [f] Z—Phe—OH was used in place of Z—Gly—OH and Z—PheGly—OEt was obtained.
Z = benzyloxycarbonyl.

CONCLUSIONS

The condensation of triphenylstibine oxide and *N*-protected amino-acids easily occur in aprotic media and corresponding di(aminoacylate)s are isolated in good yields. Catalytic dipeptide synthesis via the triphenylantimony bis(aminoacylate)s as key intermediates has been shown to occur.

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