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COMMUNICATION

Triphenylstibine oxide–phosphorus(V) sulfide as a novel condensation catalyst system: application to the synthesis of dipeptides

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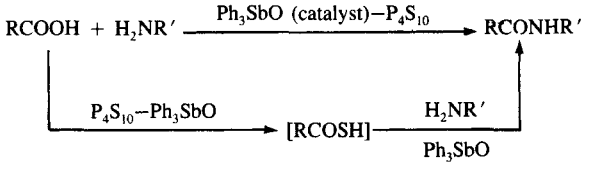
Triphenylstibine oxide (Ph_3SbO) and phosphorus(V) sulfide (P_4S_{10}) synergistically catalyzed the aminolysis of *N*-protected amino-acids with amino-acid esters in benzene. Ph_3SbO accelerated both the initial conversion of carboxylic moieties into the corresponding thiocarboxylic moieties by P_4S_{10} and the subsequent aminolysis of the resulting thiocarboxylic acids. Thus, dipeptides such as Z–A–A′–OEt (where Z = $PhCH_2OC(O)$— and A,A′ = Ala,Gly; Gly,Gly; Leu,Gly; Phe,Gly; Phe,Leu; Ser,Gly; Val,Gly, respectively) were conveniently prepared even at 35°C.

Keywords: Triphenylstibine oxide, phosphorus pentasulfide, catalytic peptide synthesis, amidation, thiocarboxylic acids

INTRODUCTION

In previous papers,[1,2] we have reported a catalytic amidation using triphenylantimony dicarboxylates as key intermediates. The amidation process consisted of the initial condensation step in which triphenylstibine oxide (Ph_3SbO) reacted with carboxylic acids to afford the intermediate triphenylantimony dicarboxylates, and a subsequent aminolysis step. However, the catalyst system possessed two disadvantages;[2] the first is low turnover numbers (not exceeding 11), and the second is a low reaction rate at below 50°C.

In our continuing efforts to enhance the catalytic activity of Ph_3SbO for the amidation, we have found that Ph_3SbO can catalyze the aminolysis of thiocarboxylic acids by primary and secondary amines.[3] This observation encouraged us to extend the applications of Ph_3SbO as catalysts; i.e. if the starting carboxylic acids could be conveniently converted into thiocarboxylic acids *in situ*, a novel direct amidation process would be realized. Now, we describe a novel sulfuration system consisting of phosphorus pentasulfide (P_4S_{10}) and catalytic amounts of Ph_3SbO which is applicable to the building up of dipeptide linkages as shown in Scheme 1.



Scheme 1 R and R′ indicate *N*-protected and *C*-protected amino-acids, respectively.

EXPERIMENTAL

General

Melting points are uncorrected. The values of $[\alpha]_D$ were measured by a Jasco DIP-181 polarimeter using ethanol (spectroscopic grade) as a solvent at 25°C. *N*-Protected aminoacids were prepared in the usual manner.[4] Triphenylstibine oxide was synthesized as reported previously.[2] Other reagents and solvents were used as received.

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Table 1 Dipeptide synthesis catalyzed by $Ph_3SbO-P_2S_5$ system[a]

Dipeptide	T (°C)	t (h)	Yield (%)	Mp (lit.) (°C)	$[\alpha]_D$ (lit.) (°)
Bz—LeuGly—OEt	35	2	66	156–157 (156–157)	−23.0 (−34.0[5])
Z—AlaGly—OEt	35	2	90	97–98 (97–98)	−19.6 (−21.0[9])
Z—GlyGly—OEt	35	0.5	83	81 (80–81[10])	
	35	7	tr[b]		
	35	7	tr[c]		
	35	7	25[d]		
	35	7	56[e]		
Z—LeuGly—OEt	35	2	75	100–102 (98–99)	−26.6 (−26.5[11])
Z—PheGly—OEt	40	2	81	111–113 (110–112)	−16.6 (−16.8[12])
Z—PheLeu—OEt	40	2	73	102–103 (110–111)	−22.9 (−24.7[13])
Z—SerGly—OEt	35	2	51	105–107 (106–107)	−5.6 (−5.9[13])
Z—ValGly—OEt	35	2	99	172–173 (163–164)	−26.9 (−27.2[10])

[a]Z—A—OH/H—A′—OEt/Ph_3SbO/P_4S_{10} = 5/5/0.5/1 mmol. [b]Absence of P_4S_{10}. [c]Absence of Ph_3SbO. [d]Ph_3SbO/P_4S_{10} = 2/1.25 mmol. [e]Ph_3SbO/P_4S_{10} = 0.5/0.6 mmol.

Dipeptide synthesis

Typical reaction procedure was as follows; into a suspension of Ph_3SbO (0.54 mmol) in benzene (30 cm^3), P_4S_{10} (1 mmol) and Z-aminoacid (5 mmol) were added and the mixture was stirred at 50°C for 0.5–1 h. After cooling to room temperature, the coupling aminoacid ethyl ester hydrochloride and triethylamine (5 mmol each) in benzene (20 mmol) were added dropwise. Work-up was done with general ethyl acetate extraction followed by washing with aqueous citric acid and neutralization. The dipeptides were crystallized from ethyl acetate/hexane.

RESULTS AND DISCUSSION

The results of the dipeptide synthesis using $Ph_3SbO-P_4S_{10}$ catalyst are summarized in Table 1. The coupling reactions of Z—Gly—OH with H—Gly—OEt proceeded even at 35°C in the presence of the $Ph_3SbO-P_4S_{10}$ system, and Z—Gly—Gly—OEt was obtained in 83% yield. In contrast, the reaction did not occur in the absence of Ph_3SbO and/or P_4S_{10} at the same temperature. Thus, it can be said that Ph_3SbO and P_4S_{10} synergistically accelerate the amidation and the optimal ratio of Ph_3SbO/P_4S_{10} was found to be 0.5/1 in molar terms. Other dipeptides could be also prepared under similar conditions by using the $Ph_3SbO-P_4S_{10}$ system without significant racemization occurring. Further, the Young test (preparation of Bz—LeuGly—OEt)[5] also shows only a small extent of racemization throughout this amidation process.

In our experience, P_4S_{10} is a less attractive phosphorus compound in synthetic chemistry and its use is almost solely limited to the preparation of thiocarbonyls from the corresponding carbonyls under somewhat severe conditions.[6] Recently, Davy and Metzner have reported that P_4S_{10} is useful for the synthesis of dithioesters directly from carboxylic acids and alcohols at above 170°C.[7] Thus, in this catalytic amidation, we consider that P_4S_{10} must convert carboxylic acid into thiocarboxylic moieties with the assistance of Ph_3SbO *in situ*. In addition, it is known that thiocarboxylic acids are accessible for peptide synthesis as active *C*-terminals[8] and Ph_3SbO can also accelerate such aminolysis.[3] Consequently, we felt Ph_3SbO was an effective catalyst in both the sulfuration and aminolysis steps.

Next we attempted to check whether the $Ph_3SbO-P_4S_{10}$ system could convert the carboxylic acids into thiocarboxylic ones or not. The reaction of acetic acid with the $Ph_3SbO-P_4S_{10}$ system in benzene was conducted and thioacetic acid was isolated in quantitative yield after reaction at 35°C for 1 h, whereas acetic acid did not react with P_4S_{10} in the absence of Ph_3SbO at below 80°C in benzene and the reagents could be recovered. These results support the view that the conversion of a carboxylic acid into the corresponding thiocarboxylic acid by P_4S_{10} was promoted with Ph_3SbO. It is interesting that Ph_3SbO assists the sulfuration by P_4S_{10} at such a low temperature in

contrast to the conventional sulfuration reaction which has to be carried out at 100–200°C.[6,7]

REFERENCES

1. Nomura, R, Wada, T, Yamada, Y and Matsuda, H *Chem. Lett.*, 1986, 1901
2. Nomura, R, Yamada, Y and Matsuda, H *Appl. Organomet. Chem.*, 1988, 2: 557
3. Nomura, R, Wada, T, Yamada, Y and Matsuda, H *Chem. Express*, 1988, 3: 543
4. Carter, H E, Frank, R L and Johnston, H W *Org. Synth.*, 1955, Coll. Vol. III: 168
5. Williams, M W and Young, G T *J. Chem. Soc.*, 1963, 881
6. Schwarz, G *Org. Synth.*, 1959, Coll. Vol. III: 332; Voss, J *Liebigs Ann. Chem.*, 1971, 746: 92
7. Davy, H and Metzner, P *Chem. Ind. (London)*, 1985, 824; *J. Chem. Res. (S)*, 1985, 272
8. Yamashiro, D and Blake, J *Int. J. Pept. Prot. Res.*, 1981, 18: 383
9. Ueda, M, Kawaharasaki, N and Imai, Y *Bull. Chem. Soc. Jpn*, 1984, 57: 85
10. Kinoshita, H, Inamoto, K, Miyano, O and Kotake, H *Bull. Chem. Soc. Jpn*, 1979, 52: 2619
11. Matsuda, F, Itoh, S, Hattori, N, Yanagiya, H and Matsumoto, T *Tetrahedron*, 1985, 41: 3625
12. Mukaiyama, T, Matsueda, R and Suzuki, M *Tetrahedron Lett.*, 1970, 1901
13. Yamada, S-I and Takeuchi, Y *Tetrahedron Lett.*, 1971, 3595