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New Amino-protective Reagents for *t*-Butoxycarbonylation and Benzyloxycarbonylation of Amines and Amino Acids

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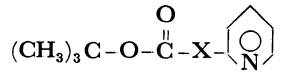
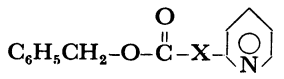
New amino-protective reagents for *t*-butoxycarbonylation and benzyloxycarbonylation of amines and amino acids have been developed. *t*-Butyl 2-pyridyl carbonate and *t*-butyl *S*-(2-pyridyl) thiocarbonate react cleanly with various amines and amino acids to afford *N*-Boc amines and *N*-Boc amino acids in high yields. Benzyl 2-pyridyl carbonate and *O*-benzyl *S*-(2-pyridyl) thiocarbonate are also found to be very effective in the benzyloxycarbonylation of amino acids.

The *t*-butoxycarbonyl (Boc) group is one of the most important amino-protective groups along with benzyloxycarbonyl (Cbz) group in peptide synthesis because the *t*-butoxycarbonyl group is cleanly cleaved by cold trifluoroacetic acid, hot formic acid, or hydrochloric acid and *N*-Boc amino acids are resistant to racemization during peptide synthesis.[1] Since *t*-butyl chloroformate is only fairly stable below 10 °C,[2] considerable efforts have been devoted to the development of a variety of useful and reliable reagents for the preparation of *N*-Boc amino acids during last 30 years.[3] In view of the great importance of the *t*-butoxycarbonyl group in peptide synthesis, a great need still exists for an efficient and stable reagent for the *t*-butoxycarbonylation of amines and amino acids.

Since it has been found that *S*-(2-pyridyl) thioates and 2-pyridyl esters are very useful active esters as acylating agents in the synthesis of peptides,[4] ketones,[5] and carboxylic esters,[6] we have been interested in the utilization of 2-pyridyl ester moieties for the *t*-butoxycarbonylation and the benzyloxycarbonylation of amino acids. Recently, we have communicated that *t*-butyl 2-pyridyl carbonate (BPC) is very effective in the *t*-butoxycarbonylation of amino acids.[7] The present paper describes a full detail of (i) the preparation of BPC, *O*-*t*-butyl *S*-(2-pyridyl) thiocarbonate (BPT), benzyl 2-pyridyl carbonate (BZBC), and *O*-benzyl *S*-(2-pyridyl) thiocarbonate (BZPT) and (ii) their use for the *t*-butoxycarbonylation and the benzyloxycarbonylation of amines and amino acids.



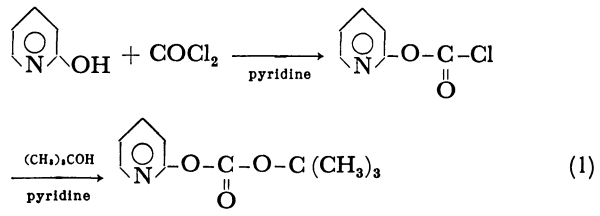
BPC: X = O
BPT: X = S



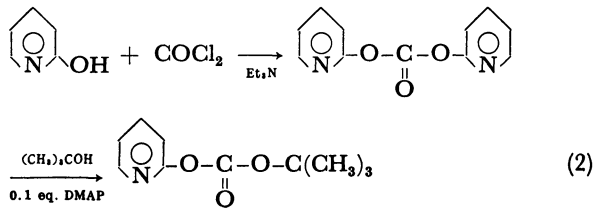
BZPC: X = O
BZPT: X = S

Results and Discussion

t-Butyl 2-Pyridyl Carbonate (BPC). BPC was originally prepared by the reaction of 2-pyridyl chloroformate, generated from an excess amount of phosgene and 2-pyridinol in the presence of pyridine, with equimolar amounts of *t*-butyl alcohol and pyridine in dichloromethane at room temperature and obtained in 65—70% yield along with a small amount of di-2-pyridyl carbonate (Eq. 1). In order to avoid the formation of di-2-pyridyl carbonate, we attempted to isolate 2-pyridyl chloroformate but it decomposed rapidly during usual workup, yielding 2-pyridinol as a major product. Thus, di-2-pyridyl carbonate was removed by filtration through a short column of silica gel with dichloromethane as an eluant. Recently, we have found that BPC can be prepared by the reaction of di-2-pyridyl carbonate[8] with an equimolar amount of *t*-butyl alcohol in the presence of 0.1 equiv of 4-dimethylaminopyridine[9] in dichloromethane at room temperature for 24 h in 80% yield. Di-2-pyridyl carbonate was conveniently prepared in 90% yield by treatment of phosgene with 2 equiv of 2-pyridinol in the presence of 2 equiv of triethylamine in dichloromethane (Eq. 2).



(1)

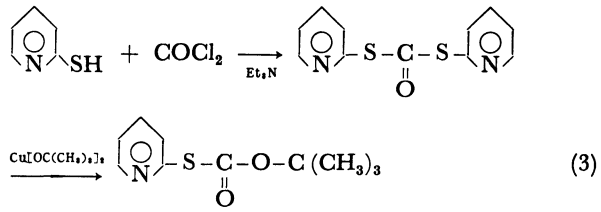


(2)

O-t-Butyl S-(2-Pyridyl) Thiocarbonate (BPT). The preparation of BPT was turned out to be very difficult. First, we adopted a similar scheme utilized in the preparation of BPC. (2-Pyridylthio)carbonyl chloride was prepared by a known procedure.[10] Unexpectedly, reaction of (2-pyridylthio)carbonyl chloride with equimolar amounts of *t*-butyl alcohol and triethylamine did not give the desired product. Instead *S*,*S*-di(2-pyridyl) dithiocarbonate was isolated in an essentially quantitative yield. Furthermore, the reaction of (2-pyridylthio)carbonyl chloride with equimolar amounts of *t*-butyl alcohol and pyridine did not occur to an observable extent, though the similar type of a reagent, *O*-*t*-butyl *S*-(4,6-dimethyl-2-pyrimidinyl) thiocarbonate, has been prepared in a high yield by use of pyridine as a base in a similar manner.[11]

Recently, we have found that *S*-(2-pyridyl) thioates are rapidly and cleanly esterified with alcohols in the presence of copper(II) bromide in acetonitrile.[6c] Thus, reaction of *S,S*-di(2-pyridyl) dithiocarbonate, which was prepared in 91% yield by the reaction of phosgene with 2 equiv of 2-pyridinethiol in the presence of 2 equiv of triethylamine in dichloromethane, with *t*-butyl alcohol in the presence of 1 equiv of copper(II) bromide in acetonitrile at room temperature was attempted. However, a desired product was not obtained. Furthermore, on the basis of a previous result obtained with BPC, we attempted the reaction of *S,S*-di(2-pyridyl) dithiocarbonate with equimolar amounts of *t*-butyl alcohol and 4-dimethylaminopyridine. However, the reaction did not proceed to an observable extent in dichloromethane, tetrahydrofuran, or *N,N*-dimethylformamide (DMF) at room temperature for 5 h.

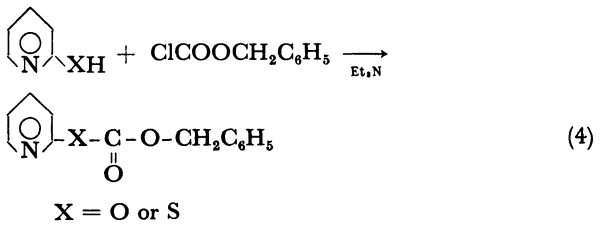
Finally, we were able to prepare BPT by treatment of *S,S*-di(2-pyridyl) dithiocarbonate with 0.5 equiv of copper(II) *t*-butoxide in tetrahydrofuran at room temperature for 2 h (Eq. 3). BPT was obtained in 79%



(3)

yield as a relatively stable oily compound. Attempts to crystallize the product were failed.

Benzyl 2-Pyridyl Carbonate (BZPC) and O-*Benzyl* S-*(2-Pyridyl) Thiocarbonate (BZPT).* BZPC was easily prepared in 80% yield as an oil by the reaction of benzyl chloroformate with equimolar amounts of 2-pyridinol and triethylamine in dichloromethane (Eq. 4). Similarly, BZPT was prepared in a high yield from equimolar amounts of benzyl chloroformate and 2-pyridinethiol in the presence of triethylamine in dichloromethane and obtained as an oil (Eq. 4).



(4)

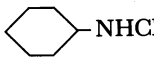
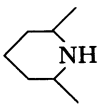
X = O or S

t-*Butoxycarbonylation of Amines and Amino Acids.* First, reaction of BPC with a variety of structurally different amines was examined. Simple amines such as propylamine, benzylamine, and piperidine were rapidly and quantitatively converted into the corresponding *t*-butyl carbamates in dichloromethane at room temperature within 2 h. However, the *t*-butoxycarbonylation of sterically hindered secondary amines such as diisopropylamine and 2,6-dimethylpiperidine, and relatively unreactive amines like aniline did not occur in dichloromethane to an observable extent, even after forcing conditions such as prolonged stirring at elevated temperatures. Thus, proper conditions to effect the *t*-butoxycarbonylation of sterically hindered amines were studied. Among the solvents employed, acetonitrile and DMF gave the best results in terms of the rapidity and the yield of the reaction and are generally recommended, though DMF is considered to be slightly better than acetonitrile. Reaction of diisopropylamine with BPC in DMF at 80 °C for 48 h afforded *N*-(*t*-butoxycarbonyl)diisopropylamine in 83% yield, whereas the reaction in acetonitrile at 80 °C required 60 h for completion of the reaction. Similarly, aniline was converted into *N*-(*t*-butoxycarbonyl)-aniline in high yields in DMF or acetonitrile at 80 °C. The *t*-butoxycarbonylation of imidazole and benzimidazole with BPC in DMF or acetonitrile did not occur under forcing conditions. The results obtained with several amines are summarized in Table 1.

In order to find out optimum conditions for the *t*-butoxycarbonylation of amino acids with BPC, we briefly examined the effects of bases, solvents, and reaction time by use of L-phenylalanine as a model compound. With aqueous DMF as the solvent, the effect of four bases was briefly examined at room temperature and it was found that the yield of Boc–Phe was the highest using 1.5 equiv of triethylamine (96% isolated yield): Sodium hydrogencarbonate (75%), sodium carbonate (72%), and sodium hydroxide (70%), though the reason for these results are unclear. However, the *t*-butoxycarbonylation proceeded much more rapidly with sodium hydroxide (1 h for complection of the reaction): sodium carbonate (5 h), sodium hydrogencarbonae (16 h), and triethylamine (12 h). Although aqueous DMF and aqueous dioxane were found to be equally effective in the *t*-butoxycarbonylation of amino acids, the reaction occurred more rapidly in aqueous DMF than in aqueous dioxane. For example, the reaction of L-phenylalanine with equimolar amounts of BPC in the presence of 1.5 equiv of triethylamine in aqueous DMF at room temperature afforded *N*-Boc–Phe in 96% yield in 12 h, whereas the reaction in aqueous dioxane required 16 h. The pronounced difference in the reaction rate was observed in L-leucine. The reaction in aqueous DMF required 4 h for completion of the reaction, whereas the reaction in aqueous dioxane required 16 h.

On the basis of these results obtained, the standard conditions employed for the *t*-butoxycarbonylation of amino acids with BPC involved the use of 1.5 equiv of triethylamine and aqueous DMF at room temperature. As shown in Table 2, the *t*-butoxycarbonylation of various amino acids used in this study was normally complete within 12 h at room temperature and the corresponding *N*-Boc amino acids were isolated in high yields. The identities of

Table 1. Preparation of *N*-Boc amines[a]

Amine	Solvent	Temp/°C	Time/h	Isolated Yield/%[b]
$CH_3CH_2CH_2NH_2$	CH_2Cl_2	r.t	0.25	97
$C_6H_5CH_2NH_2$	CH_2Cl_2	r.t	2	95
$(CH_3CH_2)_2NH$	CH_2Cl_2	r.t	1.5	94
	CH_2Cl_2	r.t	0.25	95
$CH_3CH_2C(CH_3)_2NH_2$	CH_2Cl_2	r.t	36	92
$C_6H_5NH_2$	CH_3CN	80	60	92
	DMF	80	48	92
	DMF	80	12	80
$(CH_3)_2CHNHCH(CH_3)_2$	CH_3CN	80	60	86
	DMF	80	48	83
	DMF	80	30	86
	DMF	80	36	81

a) The reaction was carried out on an 1—3 mmol scale of amine with 1.0 equiv of the reagent. b) Yields were based on the amine.

Table 2. Preparation of *N*-Boc amino acids in aqueous DMF[a]

Amino acid	*t*-Butyl 2-pyridyl carbonate (BPC) Time/h	Yield/%	Mp/θ_m/°C	$[\alpha]_D$/°	*O*-*t*-Butyl *S*-(2-pyridyl) thiocarbonate (BPT) Time/h	Yield/%	Mp/θ_m/°C	$[\alpha]_D$/°
Ala	8	90	145—147[b]	−23.8 (0.9, AcOH)	16	84	76—77	−23.6 (1.5, AcOH)
Cys[b]	10	85	173—176	−57.1 (1.3, AcOH)	12	84	173—175	−55.2 (1.0, AcOH)
Cys-Cys	8	87	140—142	−112.0 (0.7, AcOH)	20	83	141—143	−109.7 (1.4, AcOH)
Leu	4	94	70—74[c]	−23.1 (1.1, AcOH)	12	95	70—74[c]	−25.5 (1.1, AcOH)
Met[b]	7	96	137—139	+17.5 (1.4, MeOH)	8	90	136—139	+17.7 (1.7, MeOH)
Phe[b]	12	96	221—224	+28.0 (1.3, MeOH)	16	89	221—224	+27.8 (2.2, MeOH)
Pro	6	98	133—135	−60.7 (0.9, AcOH)	4	95	134—135	−61.0 (0.7, AcOH)
Ser[b]	7	93	139—141	+13.1 (1.2, DMF)	10	85	139—141	+12.9 (0.4, DMF)
Thr[b]	8	98	152—155	+10.2 (1.7, MeOH)	12	92	152—154	+9.8 (2.7, MeOH)
Try	4	98	137—138	−21.5 (1.0, AcOH)	8	89	136—138	−20.9 (0.8, AcOH)
Tyr[b]	6	88	212—215	+3.8 (1.1, AcOH)	16	92	206—208	+3.4 (3.2, AcOH)
Val	9	92	141—143[b]	−5.9 (1.1, AcOH)	12	80	77—78	−5.1 (1.5, AcOH)

a) Mp and $[\alpha]_D$ values of the known compounds were within the limit of error in comparison with the reported data and $[\alpha]_D$ values were measured at room temperature (15—25 °C). See Refs. 3, 11, and 12 for the reported data. b) Dicyclohexylammonium salt. c) Monohydrate.

N-Boc amino acids were confirmed by comparison of mp, NMR, and IR data and $[\alpha]_D$ values with reported data.[12] Furthermore, it is noteworthy that a by-product, water-soluble 2-pyridinol, can be easily removed from the reaction mixture by simple aqueous workup.

The *t*-butoxycarbonylation using BPT was performed on several amino acids under the similar conditions employed in the *t*-butoxycarbonylation of amino acids using BPC. In general, the reaction occurred smoothly but somewhat slowly in aqueous DMF at room temperature, when compared with reaction using BPC. Some experimental results are summarized in Table 2. It is noteworthy that 2-pyridinethiol, generated from the reaction, can be easily removed from the reaction mixture by washing with aqueous $CuSO_4$ solution. However, di-2-pyridyl disulfide was sometimes formed to some extent due to oxidation of 2-pyridinethiol during the reaction and it was removed by column chromatographic separation in such cases. In comparison with BPC, BPT has several disadvantages over BPC with respects to the difficulty of its preparation, an oily nature of BPT, and workup procedures.

Benzyloxycarbonylation of Amino Acids. Although benzyl chloroformate has been widely used for the preparation of *N*-Cbz amino acids, it is thermally unstable and decomposes to yield carbon dioxide and benzyl chloride when it is stored at room temperature over a long period of time. In view of

Table 3. Preparation of *N*-Cbz amino acids in aqueous DMF[a)]

Amino acid	Benzyl 2-pyridyl carbonate (BZPC) Time/h	Yield/%	Mp/θ_m/°C	$[\alpha]_D$/°	*O*-Benzyl *S*-(2-Pyridyl) Thiocarbonate (BZPT) Time/h	Yield/%	Mp/θ_m/°C	$[\alpha]_D$/°
Ala	0.3	85	83—85	−14.1 (1.5, AcOH)	0.5	87	84—85	−13.9 (1.5, AcOH)
Cys-Cys	1	95	68—69	−81.2 (1.3, AcOH)	1	90	68—69	−81.2 (1.3, AcOH)
Ile	0.5	86	42—43	+5.5 (1.2, EtOH)	0.5	87	42—44	+5.6 (1.9, EtOH)
Met	0.5	82	67—68	−21.1 (2.5, MeOH)	0.5	85	65—67	−19.8 (1.8, MeOH)
Phe	0.5	90	86—88	+5.4 (0.4, AcOH)	0.5	92	86—88	+5.4 (0.4, AcOH)
Pro	0.3	88	75—76	−58.3 (0.2, AcOH)	1	85	75—76	−59.0 (0.2, AcOH)
Ser	0.3	90	110—111	+5.0 (2.3, AcOH)	0.3	95	110—111	+5.0 (2.3, AcOH)
Thr[b)]	0.5	86	185—187	−2.8 (1.7, AcOH)	0.5	78	183—186	−2.7 (1.7, AcOH)
Try	0.3	97	Oil	+2.1 (2.4, AcOH)	0.3	94	Oil	+2.1 (2.4, AcOH)

a) Mp and $[\alpha]_D$ values of the known compounds were within the limit of error in comparison with the reported data and $[\alpha]_D$ values were measured at room temperature (15—25 °C). See Refs. 3c and 13 for the reported data. b) Dicyclohexylammonium salt.

encouraging results obtained with BPC, we turned our attention to BZPC and BZPT for the introduction of benzyloxycarbonyl group in amino acids under mild conditions. Thus, the reaction of BZPC and BZPT with several amino acids was briefly examined under similar conditions employed for the *t*-butoxycarbonylation of amino acids with BPC and the results are summarized in Table 3.[13)]

It was found that the benzyloxycarbonylation with BZPC and BZPT proceeded much faster than the *t*-butoxycarbonylation with BPC. The reaction was normally complete within 0.5 h in aqueous DMF at room temperature and the corresponding *N*-Cbz amino acids were isolated in excellent yields.

Experimental

NMR spectra were recorded with a Varian T-60A spectrometer, and chemical shifts are expressed as δ units relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 267 and the frequences are given in reciprocal centimeters. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Reported boiling points are those observed during distillation with a Kugelrohr apparatus and uncorrected. Optical rotations were measured with an automatic polarimeter AUTOPOL III. Elemental analysis were performed by Korea Research Institute of Chemical Technology and Lucky Central Research Institute.

Commercially available amines and amino acids were used without further purification and all amino acids used in this study were L-configuration.

Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples.

Di-2-pyridyl Carbonate. To a diluted solution of phosgene (2.5 M† in toluene, 2 ml, 5.0 mmol) with dichloromethane (8 ml) at 0 °C was added a solution of 2-pyridinol (950 mg, 10 mmol) and triethylamine (1.214 g, 10.2 mmol) in dichloromethane (20 ml). The reaction mixture was stirred at 0 °C for 1 h, washed with cold 5% $NaHCO_3$ (20 ml), cold saturated NaCl (20 ml), dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness to give di-2-pyridyl carbonate (972 mg) in 90% yield. Di-2-pyridyl carbonate could be recrystallized from dichloromethane–petrolem ether (811 mg, 75%). Mp 84—86 °C. NMR($CDCl_3$) δ=7.10—7.46 (m, 4H), 7.64—8.00 (m, 2H), 8.36—8.52 (m, 2H); IR(KBr) 1770 cm^{-1}. Found: C, 61.03; H, 3.45; N, 13.15%. Calcd for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.73; N, 12.96%.

t-Butyl 2-Pyridyl Carbonate (BPC). *A*: The procedure using 2-pyridyl chloroformate is as follows. To a diluted solution of phosgene (2.5 M in toluene, 20 ml, 50 mmol) with dichloromethane (20 ml) at −10—0 °C was slowly added a solution of 2-pyridinol (951 mg, 10 mmol) and pyridine (870 mg, 11 mmol) in dichloromethane (40 ml). After being stirred at −10—0 °C for 15 min, excess phosgene and solvents were evaporated under reduced pressure and then the residue was dissolved with dichloromethane (30 ml). A solution of *t*-butyl alcohol (815 mg, 11 mmol) and pyridine (830 mg, 10.5 mmol) in dichloromethane (20 ml) was added to the flask at room temperature. The reaction mixture was stirred at room temperature for 5 h and diluted with dichloromethane (30 ml). The resulting solution was washed with saturated $NaHCO_3$ (30 ml) and brine (30 ml), dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The crude product was purified by filtration through a short column of silica gel using dichloromethane as an eluant to afford *t*-butyl 2-pyridyl carbonate (1.37 g, 70%). The product could be recrystallized from hexane. Mp 48—49 °C. NMR($CDCl_3$) δ=1.60 (s, 9H), 7.00—7.39 (m, 2H), 7.62—7.97 (m, 1H), 8.30—8.50 (m, 1H); IR(KBr) 1755 cm^{-1}. Found: C, 62.13; H, 6.86; N, 6.98%. Calcd for $C_{10}H_{13}O_3N$: C, 61.53; H, 6.71; N, 7.17%.

B: The procedure using di-2-pyridyl carbonate is as follows. To a stirred solution of di-2-pyridyl carbonate (1.08 g, 5.0 mmol) in dichloromethane (15 ml) at room temperature were added *t*-butyl alcohol (370 mg, 5.0 mmol) and 4-dimethylaminopyridine (61 mg, 0.5 mmol) and stirring was continued at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (30 ml), washed with saturated NH_4Cl (30 ml) and brine (20 ml), dried over $MgSO_4$, and concentrated to dryness. The crude product was purified by filtration through a short column of silica gel using dichloromethane as an eluant to afford *t*-butyl 2-pyridyl carbonate (780 mg, 80%).

S,S-Di(2-pyridyl) Dithiocarbonate. To a solution of 2-pyridinethiol (1.112 g, 10 mmol) and triethylamine (1.02 g, 10 mmol) in dichloromethane (40 ml) at 0 °C was slowly added a solution of phosgene (2.5 M in toluene, 2 ml, 5 mmol). After being stirred at 0 °C for 1 h, the reaction mixture was washed with saturated $NaHCO_3$ (30 ml) and brine (30 ml), dried over $MgSO_4$, and evaporated to

† 1 M=1 mol dm^{-3}.

dryness to afford the desired product (1.13 g) in 91% yield as an oil. The crude product was pure enough using for further reactions. NMR($CDCl_3$) δ=6.66—6.97 (m, 2H), 7.10—7.33 (m, 4H), 8.03—8.30 (m, 2H); IR(film) 1715 cm^{-1}. Found: C, 53.31; H, 3.13; N, 11.42%. Calcd for $C_{11}H_8ON_2S_2$: C, 53.21; H, 3.25; N, 11.28%.

O-t-Butyl S-(2-Pyridyl) Thiocarbonate (BPT). To a solution of *t*-butyl alcohol (371 mg, 5 mmol) in tetrahydrofuran (7 ml) at 0°C under nitrogen was added butyllithium (1.6 M in hexane, 3.2 ml, 5 mmol). After being stirred at 0°C for 10 min, the solution was added to the suspended solution of copper(II) bromide (560 mg, 2.5 mmol) in tetrahydrofuran (4 ml) and the resulting mixture was stirred at room temperature for 0.5 h. To a solution of *S,S*-di(2-pyridyl) dithiocarbonate (1.24 g, 5 mmol) in tetrahydrofuran (4 ml) at 0°C was added a solution of copper(II) *t*-butoxide and the resulting solution was allowed to warm to room temperature with stirring for 2 h. After the reaction mixture was evaporated to dryness, the residue was dissolved in dichloromethane (40 ml). The dichloromethane solution was washed with saturated NH_4Cl (30 ml) and brine (30 ml), dried over $MgSO_4$, and concentrated. The residue was subjected to silica-gel column chromatography with hexane-ethyl acetate (2:1) as an eluent to affors *O-t*-butyl *S*-(2-pyridyl) thiocarbonate (834 mg) in 79% yield as an oil. NMR ($CDCl_3$) δ=1.66 (s, 9H), 7.13—7.40 (m, 1H), 7.64—7.81 (m, 2H), 8.47—8.64 (m, 1H); IR(film) 1730 cm^{-1}. Found: C, 56.29; H, 6.43; N, 6.53%. Calcd for $C_{10}H_{13}O_2NS$: C, 56.85; 6.20; N, 6.63%.

Benzyl 2-Pyridyl Carbonate (BZPC). To a solution of benzyl chloroformate (1.71 g, 10 mmol) in dichloromethane (10 ml) at 0°C was added a solution of 2-pyridinol (1.00 g, 10.5 mmol) and triethylamine (1.06 g, 10.5 mmol) in dichloromethane (20 ml). After being stirred at room temperature for 1 h, the reaction mixture was diluted with dichloromethane (30 ml) and washed with saturated NH_4Cl (20 ml) and brine (20 ml). The dichloromethane solution was dried over $MgSO_4$ and evaporated to give benzyl 2-pyridyl carbonate (2.20 g, 96%). The crude product was purified by filtration through a short column of silica gel with ethyl acetate-hexane (1:3) as an eluant to give benzyl 2-pyridyl carbonate (1.83 g) in 80% yield as an oil. NMR($CDCl_3$) δ=5.32 (s, 2H), 7.00—7.39 (m, 2H), 7.41 (b.s, 5H), 7.61—7.96 (m, 1H), 8.30—8.50 (m, 1H); IR(film) 1750 cm^{-1}. Found: C, 68.40; H, 4.89; N, 5.69%. Calcd for $C_{13}H_{11}O_3N$: C, 68.12; H, 4.84; N, 6.11%.

O-Benzyl S-(2-Pyridyl) Thiocarbonate (BZPT). To a solution of benzyl chloroformate (1.71 g, 10 mmol) in dichloromethane (10 ml) at 0°C was added a solution of 2-pyridinethiol (1.17 g, 10.5 mmol) and triethylamine (1.06 g, 10.5 mmol) in dichloromethane (20 ml). After being stirred at room temperature for 1 h, the reaction mixture was diluted with dichloromethane (30 ml) and washed with saturated NH_4Cl (20 ml) and brine (20 ml). The dichloromethane solution was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by filtration through a short column of silica gel with ethyl acetate-hexane (1:3) as an eluant to afford *O*-benzyl *S*-(2-pyridyl) thiocarbonate (2.06 g) in 84% yield as an oil. NMR($CDCl_3$) δ=5.29 (s, 2H), 7.09—7.32 (m, 1H), 7.34 (b.s, 5H), 7.57—7.82 (m, 2H), 8.42—8.63 (m, 1H); IR(film) 1720 cm^{-1}. Found: C, 63.93; H, 4.38; N, 6.04%. Calcd for $C_{13}H_{11}O_2NS$: C, 63.66; H, 4.52; N, 5.71%.

Preparation of N-Boc-Benzylamine. To a stirred solution of benzylamine (215 mg, 2.0 mmol) in dichloromethane (6 ml) at room temperature was added BPC (391 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane (30 ml), and washed with saturated $NaHCO_3$ (20 ml). The dichloromethane solution was dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized from dichloromethane-petroleum ether to give *N*-Boc-benzylamine (390 mg) in 95% yield. Mp 53—54°C (lit,[3a] 53—54°C); NMR($CDCl_3$) δ=1.50 (s, 9H), 4.30 (d, 2H, *J*=6 Hz), 4.64—5.31 (m, 1H), 7.28 (b.s, 5H); IR (KBr) 1680 cm^{-1}.

Preparation of N-Boc-2,6-Dimethylpiperidine. To a stirred solution of 2,6-dimethylpiperidine (115 mg, 1.0 mmol) in DMF (4 ml) at room temperature was added BPC (200 mg, 1.0 mmol). The reaction mixture was stirred at 80°C for 36 h, diluted with diethyl ether (30 ml), and washed with saturated $NaHCO_3$ (20 ml) and water (20 ml). The aqueous layer was extracted with diethyl ether (30 ml×2). The combined ether extracts were dried over $MgSO_4$ and evaporated to dryness. The curde product was distilled to give *N*-Boc-2,6-dimethylpiperidine (173 mg, 81%): Bp 102—108°C/38.5 mm Hg[†]); NMR ($CDCl_3$) δ=1.25 (d, 2H, *J*=7 Hz), 1.54 (s, 9H), 1.38—2.00 (m, 6H), 4.04—4.63 (m, 2H); IR(film) 1690 cm^{-1}. Found: C, 67.35; H, 10.62; N, 6.40%. Calcd for $C_{12}H_{12}O_2N$: C, 67.57; H, 10.87; N, 6.57%.

Preparation of N-Boc-Proline. *(A) BPC Method*: To a solution of L-proline (230 mg, 2.0 mmol) in DMF-water (2:1, 12 ml) was added triethylamine (303 mg, 3.0 mmol). After the reaction mixture was stirred at room temperature for 10 min, BPC (392 mg, 2.0 mmol) was added and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was adjusted to pH 3.5 by addition of 0.025 M oxalic acid and extracted with dichloromethane (30 ml×3). The dichloromethane solution was washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, and evaported to dryness *in vacuo* to give *N*-Boc-proline (424 mg, 98%) as a syrup, which can be crystallized from ethyl acetate-petroleum ether. Mp 133—135°C (lit,[3c] 136—137°C); $[\alpha]]_D$ −60.7° (0.9, AcOH, 20°C) [lit,[3c] $[\alpha]_D$ −60.57° (0.974, AcOH, 25°C)].

(B) BZPC Method: To a solution of L-proline (232 mg, 2.0 mmol) and triethylamine (303 mg, 3.0 mmol) in DMF-water (1:1, 8 ml) was added a solution of BZPC (423 mg, 2.0 mmol) in DMF (2 ml). The reaction mixture was stirred at room temperature for 4 h, acidified with 0.025 M oxalic acid (pH 3.5), and extracted with ethyl acetate (30 ml×3). The extracts were washed with saturated $CuSO_4$ (20 ml×2) and brine (30 ml), dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was crystallized from ethyl acetate-petroleum ether to give *N*-Boc-proline (408 mg, 95%). Mp 134—135°C; $[\alpha]_D$ −61.0° (0.7, AcOH, 18°C).

Preparation of N-Cbz-Phenylalanine. To a solution of L-phenylalanine (330 mg, 2.0 mmol) and triethylamine (301 mg, 3.0 mmol) in DMF-water (1:1, 8 ml) was added a solution of BZPT (492 mg, 2.0 mmol) in DMF (2 ml). The reaction mixture was stirred at room temperature for 0.5 h, acidified with 0.025 M oxalic acid (pH 3.5) and extracted with ethyl acetate (30 ml×3). The combined extracts were washed with saturated $CuSO_4$ (20 ml×2) and brine (20 ml), dried over $MgSO_4$, and evaporated to dryness. The crude product was crystallized from dichloromethane-petroleum ether to give *N*-Cbz-phenylalanine (534 mg, 89%). Mp 86—88°C (lit,[3c] 86—87°C); $[\alpha]_D$ +5.4° (0.4, AcOH, 20°C) [lit, [3c] $[\alpha]_D$ +5.54° (0.361, AcOH, 18°C)]. In the case of using BZPC, the com-

[†] 1 mmHg=133.322 Pa.

bined extracts were washed with water and brine. Otherwise, the experimental procedure is almost same as described above.

Spectral Data of N-*Boc Amines.* *N*-Boc-propylamine: Bp 65—70 °C/38 mmHg; NMR ($CDCl_3$) δ=1.00 (t, 3H, J=6 Hz), 1.56 (s, 9H), 1.25—1.94 (m, 2H), 3.06 (q, 2H, J=6 Hz), 4.50—5.07 (m, 1H); IR (film) 1700 cm^{-1}. *N*-Boc-diethylamine: Bp 74—76 °C/38 mmHg; NMR ($CDCl_3$) δ=1.25 (t, 6H, J=7 Hz), 1.57 (s, 9H), 3.26 (q, 4H, J=7 Hz); IR (film) 1690 cm^{-1}. *N*-Boc-piperidine: Bp 92—95 °C/38 mmHg; NMR ($CDCl_3$) δ=1.50 (s, 9H), 1.40—1.76 (m, 6H), 3.12—3.58 (m, 4H); IR (film) 1685 cm^{-1}. *N*-Boc-di-*s*-butylamine: Bp 92—95 °C/38 mmHg; NMR ($CDCl_3$) δ=0.85 (t, 3H, J=7 Hz), 1.28 (s, 6H), 1.50 (s, 9H), 1.53 (q, 2H, J=7 Hz), 4.19—4.63 (m, 1H); IR (film) 1705 cm^{-1}. *N*-Boc-aniline: Mp 133—135 °C (lit,[14] 135.5—138 °C); NMR ($CDCl_3$) δ=1.60 (s, 9H), 6.49—7.40 (m, 6H); IR (KBr) 1685 cm^{-1}. *N*-Boc-4-aminopyridine: Mp 139—142 °C; NMR ($CDCl_3$) δ=1.56 (s, 9H), 7.25—7.50 (m, 2H), 8.06—8.80 (m, 3H); IR (KBr) 1715 cm^{-1}. Found: C, 61.88; H, 7.47; N, 14.15%. Calcd for $C_{10}H_{14}O_2N_2$: C, 61.84; H, 7.27; N, 14.42%. *N*-Boc-diisopropylamine: Bp 70—75 °C/26 mmHg; NMR ($CDCl_3$) δ=1.20 (d, 12H, J=7 Hz), 1.51 (s, 9H), 3.40—4.10 (m, 2H); IR(film) 1685 cm^{-1}. *N*-Boc-*N*-isopropylcyclohexylamine: Bp 95—100 °C/48 mmHg; NMR ($CDCl_3$) δ=1.22 (d, 6H, J=6 Hz), 1.54 (s, 9H), 1.60—2.14 (m, 10H), 3.33—4.02 (m, 2H); IR (film) 1680 cm^{-1}. Found: C, 69.65; H, 11.87; N, 5.60%. Calcd for $C_{14}H_{27}O_2N$: C, 69.67; H, 11.27; N, 5.80%.

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