3,6-Diisopropyl-2-hydroxypyrazine and 3,6-Diisopropyl-2-pyrazinethiol as Carriers of Some Alkoxycarbonyl Groups

Akihiro Ohta, Yukiko Inagawa and Chie Mitsugi

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

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Some derivatives of benzyloxycarbonylated 3,6-diisopropyl-2-hydroxypyrazine and 3,6-diisopropyl-2-pyrazinethiol were prepared and shown to be the versatile benzyloxycarbonylation reagents for amines and amino acids. It was also ascertained that 3,6-diisopropyl-2-hydroxypyrazine and 3,6-diisopropyl-2-pyrazinethiol serve effectively as carriers of the β,β,β-trichloroethoxycarbonyl group.

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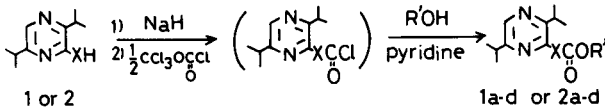
The benzyloxycarbonyl group has been widely employed for the protection of amino groups, especially of the amino moiety of amino acids, in company with the *t*-butoxycarbonyl group [1]. Derivation of the benzyl group has been also studied, and it was ascertained that the introduction of an electron donating group, such as the methoxyl group, makes easy the cleavage of benzyloxycarbonylated amines [2]. Efforts on finding the appropriate carriers of these groups were also made on the other side, and some aromatic *N*-heterocycles, such as pyridine [3] and pyrimidine [4], were observed to be competent carriers. The β,β,β-trichloroethoxycarbonyl group is known also to be a convenient protecting group for amines [5]. In continuation of the investigation on the utilization of pyrazinols and pyrazinethiols as acyl carriers, we recently reported that 3,6-dialkyl-2-hydroxypyrazines and 3,6-dialkyl-2-pyrazinethiols constitute versatile carriers of the *t*-butoxycarbonyl group for the protection of amino groups [6]. Following these works, the present report deals with the utilization of 3,6-diisopropyl-2-hydroxypyrazine and 3,6-diisopropyl-2-pyrazinethiol as carriers of some types of benzyloxycarbonyl groups and the β,β,β-trichloroethoxycarbonyl group.

Table 1

Alkoxycarbonylated Pyrazinols **1a-d** and Pyrazinethiols **2a-d**



Compounds	R'	X	Yield (%)
1a	$CH_2C_6H_5$	O	48
2a	$CH_2C_6H_5$	S	55
1b	$CH_2C_6H_4CH_3$	O	45
2b	$CH_2C_6H_4CH_3$	S	57
1c	$CH_2C_6H_4NO_2$	O	56
2c	$CH_2C_6H_4NO_2$	S	61
1d	CH_2CCl_3	O	53
2d	CH_2CCl_3	S	62

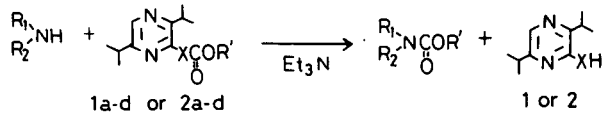
In similar manner as reported [6], 3,6-diisopropyl-2-hydroxypyrazine (**1**) [7] and 3,6-diisopropyl-2-pyrazinethiol (**2**) [8] were treated with sodium hydride, trichloromethyl chloroformate, and benzyl alcohol, successively. The resulting benzyloxycarbonylated products **1a** and **2a** were purified by column chromatography and obtained as oils. Although *p*-methyl (**1b** and **2b**) and *p*-nitro derivatives (**1c** and **2c**) of **1** and **2** were prepared in the same way, the *p*-methoxyl derivatives of both pyrazines were so unstable that these products could not be obtained in a pure state. The β,β,β-trichloroethoxycarbonylated 3,6-diisopropyl-2-hydroxypyrazine (**1d**) and 3,6-diisopropyl-2-pyrazinethiol (**2d**) were also prepared without difficulty. These results were summarized in Table 1.

For a start, the alkoxycarbonylation of amines was studied, using the alkoxycarbonylated pyrazinols **1a-d** and pyrazinethiols **2a-d** thus prepared. In the presence of triethylamine, a reagent was stirred for 10 minutes with an amine in an acetonitrile solution at room temperature. As amine, benzylamine, *N*-methylbenzylamine, aniline, and *N*-methylaniline were adopted. Interestingly, only the two former compounds were alkoxycarbonylated, and in the case of the reaction of the two latter compounds, the reagent was completely recovered. Namely, these reagents were surely available only for alkoxycarbonylation of aliphatic amines.

Next, the L-amino acids were submitted to the reaction with the six benzyloxycarbonylating reagents (**1a-c** and **2a-c**). The reaction was carried out in a mixture of acetonitrile and water in the presence of triethylamine, and the satisfactory results were obtained as shown in Table 3. The values of optical rotation of the benzyloxycarbonylated L-alanine and L-tryptophan, and the *p*-nitrobenzyloxycarbonylated L-tryptophan were consistent with the ones reported, respectively. Namely, the protection reaction proceeded without racemization. Although the values of the other products could not be found in the literature, these products were probably obtained without racemization.

Table 2

Alkoxycarbonylation of Amines

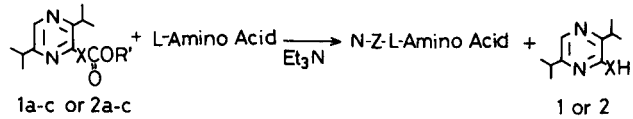


1a-d or 2a-d 1 or 2

Amines	R_1	R_2	Reagents	R′	X	Products Yield (%)
Benzylamine	$C_6H_5CH_2$	H	**1a**	$CH_2C_6H_5$	O	95 [9]
Benzylamine	$C_6H_5CH_2$	H	**2a**	$CH_2C_6H_5$	S	89 [9]
Benzylamine	$C_6H_5CH_2$	H	**1b**	$CH_2C_6H_4CH_3$	O	93
Benzylamine	$C_6H_5CH_2$	H	**2b**	$CH_2C_6H_4CH_3$	S	91
Benzylamine	$C_6H_5CH_2$	H	**1c**	$CH_2C_6H_4NO_2$	O	92
Benzylamine	$C_6H_5CH_2$	H	**2c**	$CH_2C_6H_4NO_2$	S	85
Benzylamine	$C_6H_5CH_2$	H	**1d**	CH_2CCl_3	O	86
Benzylamine	$C_6H_5CH_2$	H	**2d**	CH_2CCl_3	S	88
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**1a**	$CH_2C_6H_5$	O	90 [10]
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**2a**	$CH_2C_6H_5$	S	90 [10]
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**1b**	$CH_2C_6H_4CH_3$	O	82
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**2b**	$CH_2C_6H_4CH_3$	S	86
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**1c**	$CH_2C_6H_4NO_2$	O	95
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**2c**	$CH_2C_6H_4NO_2$	S	88
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**1d**	CH_2CCl_3	O	85
N-Methylbenzylamine	$C_6H_5CH_2$	CH_3	**2d**	CH_2CCl_3	S	90

Table 3

N-Benzyloxycarbonylation of L-Amino Acids



1a-c or 2a-c 1 or 2

L-amino Acids		Reagents R′	X	Products Yield (%)	$[\alpha]_D$ Found	Reported
L-Alanine	**1a**	$CH_2C_6H_5$	O	87	−15.1° [a]	−13.9° [a] [10]
L-Alanine	**2a**	$CH_2C_6H_5$	S	94	−14.6° [a]	−13.9° [a] [10]
L-Alanine	**1b**	$CH_2C_6H_4CH_3$	O	92	−14.4° [a]	
L-Alanine	**2b**	$CH_2C_6H_4CH_3$	S	89	−13.8° [a]	
L-Alanine	**1c**	$CH_2C_6H_4NO_2$	O	86	−14.7° [a]	
L-Alanine	**2c**	$CH_2C_6H_4NO_2$	S	90	−14.2° [a]	
L-Tryptophan	**1a**	$CH_2C_6H_5$	O	90	+3.3° [a]	+3.2° [a] [11]
L-Tryptophan	**2a**	$CH_2C_6H_5$	S	95	+3.5° [a]	+3.2° [a] [11]
L-Tryptophan	**1b**	$CH_2C_6H_4CH_3$	O	90	+3.9° [a]	
L-Tryptophan	**2b**	$CH_2C_6H_4CH_3$	S	91	+3.0° [a]	
L-Tryptophan	**1c**	$CH_2C_6H_4NO_2$	O	85	−40.0° [b]	−43.5° [b] [12]
L-Tryptophan	**2c**	$CH_2C_6H_4NO_2$	S	87	−42.9° [b]	−43.5° [b] [12]

[a] In acetic acid. [b] In *N*,*N*-dimethylformamide.

As described above, the benzyloxycarbonylated and β,β,β-trichloroethoxycarbonylated 3,6-diisopropyl-2-hydroxypyrazines **1a-d** and 3,6-diisopropyl-2-pyrazinethiols **2a-d** are convenient reagents for the corresponding alkoxycarbonylation of amines. After the reaction, the mother pyrazines **1** and **2** are able to be recovered in high yields. As reported before, **1** and **2** can be prepared from L-valine without difficulty [7,8]. In conclusion, 3,6-dialkyl-2-hydroxypyrazines and 3,6-dialkyl-2-pyrazinethiols might be used as carrier of the benzyloxycarbonyl and β,β,β-trichloroethoxycarbonyl groups.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro-melting point apparatus and are uncorrected. Boiling points are also uncorrected. All uv spectra were taken in 95% ethanol using Hitachi Model 323 and 557 spectrometers, ir spectra on a Shimadzu IR-400 spectrometer, and pmr spectra in deuteriochloroform using JEOL PS-100 and Varian EM-360 instruments with tetramethylsilane as an internal standard. Mass spectra were obtained with Hitachi RMU-7L and M-80 spectrometers.

General Procedure for Preparation of Benzyloxycarbonylated 3,6-Diisopropyl-2-hydroxypyrazines **1a-c** and 3,6-Diisopropyl-2-pyrazinethiols **2a-c**.

To a solution of **1** (10 mmoles) or **2** (10 mmoles) in dioxane (50 ml), sodium hydride (480 mg, 10 mmoles) was added and the reaction mixture was stirred at room temperature, until the generation of hydrogen gas ceased. Under ice-cooling, trichloromethyl chloroformate (0.9 ml, 7.5 mmoles) was added at once to the reaction mixture, which was stirred overnight at room temperature. After addition of a solution of benzylalcohol (15 mmoles) in pyridine (2.5 ml) under ice-cooling, the reaction mixture was stirred further for 3 hours and then allowed to stand overnight at room temperature. In order to decompose trichloromethyl chloroformate, the reaction mixture was stirred with powdered activated charcoal (50 mg) for one hour, and filtered. After removing the solvent of the filtrate by distillation *in vacuo*, the resulting oil was purified by chromatography on silica gel (Wakogel C-200, 35 g), eluting with hexane containing an increasing amount of chloroform.

2-Benzyloxycarbonyloxy-3,6-diisopropylpyrazine (**1a**).

This compound had the following physical properties: colorless oil, bp 90-95°/3 torr; uv: λ max 273.5 (log ε = 4.11), 293 (3.64, shoulder) nm; ir (liquid film): 1770 (C=O) cm^{-1}; pmr: δ 1.20 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.23 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 3.00 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.10 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 5.27 (2H, s, $CH_2C_6H_5$), 7.25-7.45 (5H, m, benzene H), 8.40 (1H, s, pyrazine H) ppm; ms: m/e 315 ($M^+ + 1$), 179 (M^+-$COOCH_2C_6H_5$), 91 ($CH_2C_6H_5^+$).

Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.98; H, 7.09; N, 9.09.

3,6-Diisopropyl-2-*p*-methylbenzyloxycarbonyloxypyrazine (**1b**).

This compound had the following physical properties: colorless oil, bp 102-104°/2 torr; uv: λ max 273 (log ε = 3.91), 294 (3.48, shoulder) nm; ir (liquid film): 1770 (C=O) cm^{-1}; pmr: δ 1.20 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.27 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 2.33 (3H, s, $C_6H_4CH_3$), 3.00 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.13 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 5.23 (2H, s, $CH_2C_6H_4CH_3$), 7.13-7.38 (4H, m, benzene H), 8.37 (1H, s, pyrazine H) ppm; ms: m/e 329 ($M^+ + 1$), 328 (M^+), 179 (M^+-$COOCH_2C_6H_4CH_3$), 105 ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.74; H, 7.37; N, 8.58.

3,6-Diisopropyl-2-*p*-nitrobenzyloxycarbonyloxypyrazine (**1c**).

This compound had the following physical properties: colorless oil, bp 115-118°/2 torr; uv: λ max 272 (log ε = 4.19), 296 (3.74, shoulder), 330 (3.08, shoulder) nm; ir (liquid film): 1780 (C=O) cm^{-1}; pmr: δ 1.23 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.30 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 3.03 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.17 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 5.37 (2H, s, $CH_2C_6H_4NO_2$), 7.57 (2H, d, J = 9 Hz, benzene H), 8.22 (2H, d, J = 9 Hz, benzene H), 8.33 (1H, s, pyrazine H) ppm; ms: m/e 360 ($M^+ + 1$), 359 (M^+), 179 (M^+-$COOCH_2C_6H_4NO_2$), 136 ($CH_2C_6H_4NO_2^+$).

Anal. Calcd. for $C_{18}H_{21}N_3O_5$: C, 60.15; H, 5.89; N, 11.69. Found: C, 60.52; H, 6.23; N, 11.64.

Benzyl *S*-3,6-diisopropylpyrazin-2-ylthiolcarbonate (**2a**).

This compound had the following physical properties: colorless oil, bp 145-150°/2 torr; uv: λu max 284 (log ε = 3.80), 311 (3.07, shoulder) nm; ir (liquid film): 1730 (C=O) cm^{-1}; pmr: δ 1.20 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.27 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 3.07 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.53 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 5.23 (2H, s, $CH_2C_6H_5$), 7.37 (5H, s, benzene H), 8.48 (1H, s, pyrazine H) ppm; ms: m/e 331 ($M^+ + 1$), 330 (M^+), 195 (M^+-$COOCH_2C_6H_5$), 91 ($CH_2C_6H_5^+$).

Anal. Calcd. for $C_{18}H_{22}N_2O_2S$: C, 65.42; H, 6.71; N, 8.48. Found: C, 65.68; H, 6.77; N, 8.27.

p-Methylbenzyl *S*-3,6-Diisopropylpyrazin-2-ylthiolcarbonate (**2b**).

This compound had the following physical properties: colorless oil, bp 132-139°/2 torr; uv: λ max 284 (log ε = 3.92), 310 (3.21, shoulder) nm; ir (liquid film): 1730 (C=O) cm^{-1}; pmr: δ 1.23 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.30 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 2.33 (3H, s, $C_6H_4CH_3$), 3.10 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.55 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 5.20 (2H, s, $CH_2C_6H_4CH_3$), 7.20 (4H, broad s, benzene H), 8.47 (1H, s, pyrazine H) ppm; ms: m/e 345 ($M^+ + 1$), 344 (M^+), 195 (M^+-$COOCH_2C_6H_4CH_3$), 105 ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 66.54; H, 7.13; N, 8.30.

p-Nitrobenzyl *S*-3,6-Diisopropylpyrazin-2-ylthiolcarbonate (**2c**).

This compound had the following physical properties: colorless needles (from hexane), mp 59-60°; uv: λ max 277 (log ε = 4.53) nm; ir (potassium bromide): 1715 (C=O) cm^{-1}; pmr: δ 1.23 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.30 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 3.07 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.50 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 5.30 (2H, s, $CH_2C_6H_4NO_2$), 7.45 (2H, d, J = 9 Hz, benzene H), 8.17 (2H, d, J = 9 Hz, benzene H), 8.43 (1H, s, pyrazine H) ppm; ms: m/e 375 (M^+), 195 (M^+-$COOCH_2C_6H_4NO_2$), 136 ($CH_2C_6H_4NO_2^+$).

Anal. Calcd. for $C_{18}H_{21}N_3O_4S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.69; H, 5.66; N, 11.29.

Preparation of 3,6-Diisopropyl-2-β,β,β-trichloroethoxycarbonyloxypyrazine (**1d**) and β,β,β-Trichloroethyl *S*-3,6-Diisopropylpyrazin-2-ylthiolcarbonate (**2d**).

To a solution of **1** (10 mmoles) or **2** (10 mmoles) in dioxane (50 ml), sodium hydride (480 mg, 10 mmoles), trichloromethyl chloroformate (0.9 ml, 7.5 mmoles) and a solution of β,β,β-trichloroethanol (2.24 g, 15 mmoles) in pyridine (2.5 ml) were successively added in the same manner as cited in the previous paragraph. The products were purified by silica gel chromatography (Wakogel C-200, 35 g) eluting with hexane containing an increasing amount of chloroform.

3,6-Diisopropyl-2-β,β,β-trichloroethoxycarbonyloxypyrazine (**1d**).

This compound had the following physical properties: colorless oil, bp 105-107°/2 torr; uv: λ max 273.5 (log ε = 4.06), 293.5 (3.65, shoulder) nm; ir (liquid film): 1790 (C=O) cm^{-1}; pmr: δ 1.30 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.33 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 3.07 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.23 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 4.90 (2H, s, CH_2CCl_3), 8.40 (1H, s, pyrazine H) ppm; ms: m/e 356 ($M^+ + 2$), 354 (M^+), 179 (M^+-$COOCH_2CCl_3$).

Anal. Calcd. for $C_{13}H_{17}Cl_3N_2O_3$: C, 43.90; H, 4.82; N, 7.88. Found: C, 44.15; H, 4.85; N, 7.95.

β,β,β-Trichloroethyl *S*-3,6-Diisopropylpyrazin-2-ylthiolcarbonate (**2d**).

This compound had the following physical properties: colorless needles, bp 170-180°/5 torr (bath temperature), mp 62-64°; uv: λ max 283 (log ε = 3.77), 315 (2.91, shoulder) nm; ir (potassium bromide): 1730 (C=O) cm^{-1}; pmr: δ 1.23 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 1.32 (6H, d, J = 6 Hz, $CH(CH_3)_2$), 3.10 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 3.57 (1H, m, J = 6 Hz, $CH(CH_3)_2$), 4.82 (2H, s, CH_2CCl_3), 8.52 (1H, s, pyrazine H) ppm; ms: m/e 372 ($M^+ + 2$), 370 (M^+), 195 (M^+-$COOCH_2CCl_3$).

Anal. Calcd. for $C_{13}H_{17}Cl_3N_2O_2S$: C, 42.00; H, 4.61; N, 7.54. Found: C, 42.06; H, 4.61; N, 7.45.

General Procedure for Alkoxycarbonylation of Amines.

To a solution of an amine (1 mmole) and triethylamine (121 mg, 1.2 mmoles) in acetonitrile (10 ml), an alkoxycarbonylated derivative of **1** (1

mmole) or **2** (1 mmole) was added and the reaction mixture was stirred for 10 minutes at room temperature. The solvent was removed by distillation *in vacuo* and the residue was dissolved in ether. The ether solution was washed with 10% hydrochloric acid, 10% potassium hydroxide and water, successively. An usual work-up of the ether layer gave the product, which was purified by distillation or recrystallization. From the 10% potassium hydroxide layer, the starting pyrazinol and pyrazinethiol were recovered in *ca.* 80% yields.

p-Methylbenzyl Benzylaminoformate.

This compound had the following physical properties: colorless needles (from hexane), mp 72-74°; ir (potassium bromide): 1695 (C=O) cm^{-1}; pmr: δ 2.30 (3H, s, $C_6H_4CH_3$), 4.33 (2H, d, J = 6 Hz, $C_6H_5CH_2NH$), 5.00 (1H, broad s, NH), 5.07 (2H, s, $COOCH_2C_6H_4CH_3$), 7.10-7.40 (4H, m, benzene H), 7.28 (5H, s, benzene H) ppm; ms: m/e 255 (M^+), 150 ($OOCNHCH_2C_6H_5^+$), 105 ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.50; H, 6.75; N, 5.65.

p-Nitrobenzyl Benzylaminoformate.

This compound had the following physical properties: colorless needles (from hexane), mp 109-110°; uv: λ max 366 (log ϵ = 4.12) nm; ir (potassium bromide): 1690 (C=O) cm^{-1}; pmr: δ 4.35 (2H, d, J = 6 Hz, $C_6H_5CH_2NH$), 5.15 (1H, broad s, NH), 5.20 (2H, s, $COOCH_2C_6H_4NO_2$), 7.28 (5H, s, benzene H), 7.46 (2H, d, J = 7.5 Hz, benzene H), 8.16 (2H, d, J = 7.5 Hz, benzene H) ppm; ms: m/e 287 ($M^+ + 1$), 150 ($OOCNHCH_2C_6H_5^+$).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.23; H, 4.89; N, 9.97.

β,β,β-Trichloroethyl Benzylaminoformate.

This compound had the following physical properties: colorless needles (from hexane), mp 70-71°; ir (potassium bromide): 1700 (C=O) cm^{-1}; pmr: δ 4.38 (2H, d, J = 6 Hz, $C_6H_5CH_2NH$), 4.73 (2H, s, $COOCH_2CCl_3$), 5.43 (1H, broad s, NH), 7.33 (5H, s, benzene H) ppm; ms: m/e 285 ($M^+ + 4$), 281 (M^+), 150 ($OOCNHCH_2C_6H_5^+$), 91 ($CH_2C_6H_5^+$).

Anal. Calcd. for $C_{10}H_{10}Cl_3NO_2$: C, 42.51; H, 3.57; N, 4.96. Found: C, 42.93; H, 3.60; N, 5.00.

p-Methylbenzyl Benzylmethylaminoformate.

This compound had the following physical properties: colorless oil, bp 160-165°/2 torr; ir (liquid film): 1700 (C=O) cm^{-1}; pmr: δ 2.32 (3H, s, $C_6H_4CH_3$), 2.83 (3H, s, NCH_3), 4.67 (2H, s, $C_6H_5CH_2N$), 5.13 (2H, s, $COOCH_2C_6H_4CH_3$), 7.07-7.50 (9H, m, benzene H) ppm; ms: m/e 270 ($M^+ + 1$), 269 (M^+), 164 ($OOCN(CH_3)CH_2C_6H_5^+$), 105 ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.85; H, 7.28; N, 5.06.

p-Nitrobenzyl Benzylmethylaminoformate.

This compound had the following physical properties: colorless needles (from hexane), mp 71-73°; uv: λ max 266.5 (log ϵ = 3.86) nm; ir (potassium bromide): 1695 (C=O) cm^{-1}; pmr: δ 2.93 (3H, s, NCH_3), 4.52 (2H, s, $C_6H_5CH_2N$), 5.27 (2H, s, $COOCH_2C_6H_4NO_2$), 7.30 (5H, broad s, benzene H), 7.50 (2H, d, J = 9 Hz, benzene H), 8.18 (2H, d, J = 9 Hz, benzene H) ppm; ms: m/e 301 ($M^+ + 1$), 300 (M^+), 164 ($OOCN(CH_3)CH_2C_6H_5^+$), 136 ($CH_2C_6H_4NO_2^+$).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.09; H, 5.33; N, 9.37.

β,β,β-Trichloroethyl Benzylmethylaminoformate.

This compound had the following physical properties: colorless oil, bp 110-115°/2 torr; ir (liquid film): 1730 (C=O) cm^{-1}; pmr: δ 2.93 (3H, s, NCH_3), 4.53 (2H, broad s, $C_6H_5CH_2N$), 4.80 (2H, s, $COOCH_2CCl_3$), 7.32 (5H, broad s, benzene H) ppm; ms: m/e 299 ($M^+ + 4$), 295 (M^+), 164 ($OOCN(CH_3)CH_2C_6H_5^+$), 91 ($CH_2C_6H_5^+$).

Anal. Calcd. for $C_{11}H_{12}Cl_3NO_2$: C, 44.55; H, 4.08; N, 4.72. Found: C, 44.98; H, 4.13; N, 4.75.

General Procedure for Benzyloxycarbonylation of L-Amino Acids.

To a solution of an L-amino acid (2 mmoles) and triethylamine (303 mg, 3 mmoles) in water (10 ml), a benzyloxycarbonylated derivative of **1** (2.4 mmoles) or **2** (2.4 mmoles), dissolved in acetonitrile (10 ml), was added at once. The reaction mixture was stirred for 24 hours at room temperature, diluted with water (50 ml) and then extracted with ethyl acetate. The water layer was acidified to *p*H 4 with 1% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried with sodium sulfate and the solvent was evaporated *in vacuo* to give the product, which was purified by recrystallization.

L-*N*-(*p*-Methylbenzyloxycarbonyl)alanine.

This compound had the following physical properties: colorless needles (from chloroform-hexane), mp 93-94°; ir (potassium bromide): 1710, 1700 (C=O) cm^{-1}; pmr: δ 1.45 (3H, d, J = 6 Hz, $CHCH_3$), 2.35 (3H, s, $C_6H_4CH_3$), 4.42 (1H, m, J = 6 Hz, $CHCH_3$), 5.10 (2H, s, $CH_2C_6H_4CH_3$), 7.23 (4H, m, benzene H) ppm; ms: m/e 237 (M^+), 122 ($HOCH_2C_6H_4CH_3^+$), 105 ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.89; H, 6.50; N, 5.86.

L-*N*-(*p*-Nitrobenzyloxycarbonyl)alanine.

This compound had the following physical properties: colorless fine prisms (from ether-pentane), mp 74-77°; uv: λ max 268 (log ϵ = 3.95) nm; ir (potassium bromide): 1700 (C=O) cm^{-1}; pmr: δ 1.48 (3H, d, J = 7 Hz, $CHCH_3$), 4.40 (1H, m, J = 7 Hz, $CHCH_3$), 5.23 (2H, s, $CH_2C_6H_4NO_2$), 5.43 (1H, broad s, NH or COOH), 7.53 (2H, d, J = 9 Hz, benzene H), 8.07 (1H, broad s, COOH or NH), 8.25 (2H, d, J = 9 Hz, benzene H) ppm; ms: m/e 268 (M^+), 223 (M^+-COOH), 136 ($CH_2C_6H_4NO_2^+$).

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44. Found: C, 49.23; H, 4.69; N, 10.17.

L-N^{α}-(*p*-Methylbenzyloxycarbonyl)tryptophan.

This compound had the following physical properties: colorless fine prisms (from chloroform-hexane), mp 126-127°; uv: λ max 273 (log ϵ = 3.68, shoulder), 282 (3.71), 289.5 (3.65) nm; ir (potassium bromide): 1750, 1730, 1680 (C=O) cm^{-1}; pmr: δ 2.33 (3H, s, $C_6H_4CH_3$), 3.30 (2H, broad d, J = 6 Hz, $CHCH_2$), 4.73 (1H, m, $CHCH_2$), 5.07 (2H, s, $CH_2C_6H_4CH_3$), 5.30 (1H, broad s, NH or COOH), 6.93-7.63 (9H, m, benzene H and indole H), 8.03 (1H, broad s, NH or COOH) ppm; ms: m/e 334 (M^+-H_2O), 130 (M^+-COOH-$NHCOOCH_2C_6H_4CH_3$), 105 ($CH_2C_6H_4CH_3^+$).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.28; H, 5.73; N, 7.99.

REFERENCES AND NOTES

[1] T. W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, 1981.

[2] K. Noda, S. Terada and N. Izumiya, *Bull. Chem. Soc. Japan*, **43**, 1883 (1970).

[3] S. Kim and J. I. Lee, *Chem. Letters*, 237 (1984).

[4] T. Nagasawa, K. Kuroiwa and K. Narita, *Bull. Chem. Soc. Japan*, **46**, 1269 (1973).

[5] H. Yajima, H. Watanabe and M. Okamoto, *Chem. Pharm. Bull.*, **19**, 2185 (1971).

[6] A. Ohta, Y. Inagawa, M. Inoue, M. Shimazaki and Y. Mamiya, *J. Heterocyclic Chem.*, in press.

[7] A. Ohta, M. Shimazaki, H. Tamamura, Y. Mamiya and T. Watanabe, *J. Heterocyclic Chem.*, **20**, 951 (1983).

[8] A. Ohta, M. Shimazaki, N. Tanekura and S. Hayashi, *Heterocycles*, **20**, 797 (1983).

[9] E. Fujita, Y. Nagao, K. Seno, S. Takao and T. Miyasaka, *J. Chem. Soc., Perkin Trans. I*, 914 (1970).

[10] Y. Kita, J. Haruta, K. Fukunaga, Y. Shirouchi and Y. Tamura, *J. Org. Chem.*, **47**, 2697 (1982).

[11] J. R. Vaughan, Jr. and J. A. Eichler, *J. Am. Chem. Soc.*, **76**, 2474 (1954).

[12] O. Nishimura, C. Kitada and M. Fujino, *Chem. Pharm. Bull.*, **26**, 1576 (1978).