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A CONVENIENT *N*-PROTECTION OF PYROGLUTAMATE DERIVATIVES

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Abstract: Esters of pyroglutamic acid were *N*-protected by conventional protective groups (Z, Boc, and COOMe) in high yield, without racemization, using LiHMDS in THF at -78 °C and ZCl, Boc_2O, and ClCOOMe, respectively.

Pyroglutamic acid is recognized as an internal protection of the γ-carboxyl group of glutamic acid; furthermore, the *N*-acylated esters have received much attention because of their importance as a chiral source and also because they serve to activate the lactam carbonyl group in synthesis.[1,2] In our current work, we needed an easy access to esters of *N*-benzyloxycarbonyl(Z)pyroglutamic acid. The nitrogen substitution without racemization is rather difficult and the

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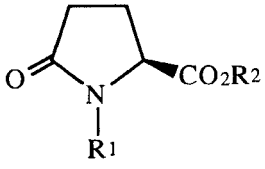
syntheses of all the *N-tert*-butoxycarbonyl(Boc)- and *N*-methoxycarbonylpyroglutamic acid derivatives have been performed using two methods.[3]



1-6

R2 \ R1	H	Z	Boc	CO_2Me
Me	**1**	**2a**	**2b**	**2c**
Bn	**3**	**4a**	**4b**	**4c**
t-Bu	**5**	**6a**	**6b**	**6c**

1, 3, 5 $\xrightarrow[2\quad \text{Acylating reagent}]{1\quad \text{LiHMDS in THF, -78°C}}$ **2, 4, 6**

On the other hand, only one example of direct introduction of Z-group at the ring nitrogen of *tert*-butyl pyroglutamate (**5**) without racemization has been reported[5] using sodium hydride as a base; in our hands, however, low chemical yield and racemization were observed under the similar reaction conditions in the case of benzyloxycarbonylation of methyl and benzyl pyroglutametes (**1** and **3**) (See experimental). It was reported that *N*-benzylation of **1** by use of sodium hydride brought about racemization.[6] Recently, (*S*)-*N*-Z-pyroglutamic acid derivatives[1c,2] were prepared by cyclization of (*S*)-Z-glutamic acid according to the classical method.[7]

We have undertaken a direct introduction of the Z group to **1**. Initially, we applied the method of *tert*-butoxycarbony-

lation of **1**, using Z-Cl instead of di-*tert*-butyl dicarbonate (Boc_2O),[3a] but in vain. Finally, we have used lithium hexamethyldisilazide (LiHMDS) in tetrahydrofuran (THF) at -78 °C, which gave significantly high yields without racemization. Several pyroglutamate derivatives were reacted in this way, and the results are presented in table 1.

Not only the Z group, but also conventional protective groups (Boc and COOMe) are introduced directly in a similar way using Boc_2O and ClCOOMe, respectively.

Experimental

All melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured at 60 MHz on a JEOL JNM-PMX60SI spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent. IR spectra were recorded on a JASCO IR810 spectrometer. Electron-impact mass spectra and fast atom bombardment mass spectra were obtained with a JEOL JMX-DX300 spectrometer. HPLC was performed on a 0.46 cmϕ x 25 cm 10 micron Chiralcel OD column, using a Waters model 6000A (UV detection at 235 nm). 2-Propanol-n-hexane (*1* : *1*) was used as the eluent. Optical rotations were taken on a JASCO DIP-181 digital polarimeter. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Esters of pyroglutamic acid were prepared from pyroglutamic acid {$[\alpha]^{23}_D$ -10.45° (c 4.44, H_2O)} purchased from

Table 1. Acylation of Pyroglutamates

Starting Comp.	Product	Yield (%)	$[\alpha]^{25}_D$	Lit.
1	**2a**	89.5	-45.5° (*c* 2.42, EtOH)	-41.3°(*c* 1.0, EtOH)[4]
	2b	90.5	-44.3° (*c* 1.0, EtOH)	-44.3°(*c* 1.0, EtOH)[4]
	2c	62.9	-44.1° (*c* 1.0, CH_2Cl_2)	
3	**4a**	84.7	-42.8° (*c* 1.0, $CHCl_3$)	-47.6°(*c* 1.1, $CHCl_3$)[2]
	4b	91.4	-31.9° (*c* 1.0, CH_2Cl_2)	
	4c	80.4	-40.4° (*c* 1.0, CH_2Cl_2)	
5	**6a**	92.6	-40.7° (*c* 0.75, $CHCl_3$)	-40.4°(*c* 2.4, CH_2Cl_2)[5]
	6b	94.4	-35.9° (*c* 0.91, $CHCl_3$)	-33.2°(*c* 0.9, $CHCl_3$)[2] -35.1°(*c* 0.9, $CHCl_3$)[4]
	6c	87.3	-38.8° (*c* 1.0, CH_2Cl_2)	

Tokyo Kasei Kogyo Co., Ltd. by the literature methods to give **1**[7,8], **3**[4,9], and **5**[2,5].

Compounds **4a**[2], **6a**[5], **2b**[4], and **6b**[2] are known.

A Typical Procedure for *N*-Protection of Esters of Pyroglutamic Acid: To **3** (233 mg, 1.06 mmol) in anhydrous THF (5 ml) was added a solution of LiHMDS in hexane (1 M, 1.1 ml, 1.1 mmol) under argon at -78 °C over 5-10 min, and reaction mixture was stirred for 20 min. Then Z-Cl (0.17 ml,

1.1 mmol) was added over 5-10 min, and reaction mixture was stirred for 20 min. Saturated NH_4Cl solution (2 ml) and H_2O (15 ml) were added and the mixture was extracted with AcOEt (25 ml x 2). The combined organic layers were washed with saturated brine (25 ml), dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel with benzene-AcOEt (3 : 1) as the eluent to give **4a**[2]; yield: 318 mg (84.7 %). HPLC analyses of **4a** and **3** gave **4a**(S) : **4a**(R) and **3**(S) : **3**(R) ratios of 97.3 : 2.7 and 97.4 : 2.6, respectively, which indicates no racemization occurred during *N*-protection.

Esters of *N*-BOC-pyroglutamic Acid (2b, 4b, and 6b): Prepared using 1.5 molar equivalents of Boc_2O with **1**, **3** or **5** in a similar manner to that described above.

Esters of *N*-Methoxycarbonylpyroglutamic Acid (2c, 4c, and 6c): Prepared using 1.1 molar equivalents of methyl chloroformate with **1**, **3**, or **5** in a similar manner to that described above.

Methyl L-*N*-Methoxycarbonylpyroglutamate (2c). A colorless oil. IR (neat): ν = 1800, 1750, 1735 (C=O) cm^{-1}. ^{1}H-NMR: δ = 1.83-2.80 (m, 4H, CH_2 x 2), 3.74 (s, 3H, $COOCH_3$), 3.81 (s, 3H, $COOCH_3$), 4.50-4.80 (m, 1H, C_2-H). MS: m/z (%) = 201 (M^+, 4.3), 142 (100).

Benzyl L-*N*-*tert*-Butoxycarbonylpyroglutamate (4b). A colorless turbid oil. IR (neat): ν = 1790, 1750, 1720 (C=O) cm^{-1}. ^{1}H-NMR: δ = 1.40 (s, 9H, $C(CH_3)_3$), 1.85-2.73 (m, 4H, CH_2 x 2),

4.46-4.71(m, 1H, C_2-H), 5.13 (s, 2H, $PhCH_2$), 7.25 (s, 5H, Harom). MS (positive ion FAB, 3-nitrobenzyl alcohol matrix): m/z = 342 (M + Na).

Benzyl L-*N*-Methoxycarbonylpyroglutamate (4c). Recrystallized from benzene-hexane (2:3) as colorless prisms; mp 100.5-102°C. IR (KBr): ν = 1760, 1750, 1720 (C=O) cm^{-1}. ^1H-NMR: δ = 1.93-2.81 (m, 4H, CH_2 x 2), 3.73 (s, 3H, $COOCH_3$), 4.51-4.77 (m, 1H, C_2-H), 5.14 (s, 2H, $PhCH_2$), 7.25 (s, 5H, Harom). MS: m/z (%) = 277 (M^+, 6.5), 142 (100). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.77; H, 5.51; N, 4.99.

***tert*-Butyl L-*N*-Methoxycarbonylpyroglutamate (6c).** A colorless oil. IR (neat): ν = 1800, 1760, 1735 (C=O) cm^{-1}. ^1H-NMR: δ = 1.47 (s, 9H, $COOC(CH_3)_3$), 1.90-2.68 (m, 4H, CH_2 x 2), 3.83 (s, 3H, $COOCH_3$), 4.39-4.63(m, 1H, C_2-H). MS: m/z (%) = 170 (M^+-73), 142 (89.8), 57 (100).

Benzyl L-*N*-Benzyloxycarbonylpyroglutamate (4a). To 60% NaH (in oil, 52 mg, 1.406 mmol) in anhydrous THF (5 ml) was added **3** (257 mg, 1.172 mmol) in anhydrous THF (2 ml) under argon with ice cooling, and reaction mixture was stirred for 20 min. Then Z-Cl (0.23 ml, 1.406 mmol) was added, and reaction mixture was stirred for 0.5 h. 10% HCl (1 ml) and H_2O (25 ml) were added and the mixture was extracted with AcOEt (25 ml x 2). The combined organic layers were washed with saturated brine (25 ml), dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column

of silica gel with benzene- AcOEt (3 : 1) as the eluent to give **4a**[2]; yield: 159.6 mg (38.4 %). HPLC analysis of **4a** gave a **4a**(*S*) : **4a**(*R*) ratio of 81.2 : 18.8.

References

(1) a) Collado, I.; Ezquerra, J.; Vaquero, J. J.; Pedregal, C., *Tetrahedron Lett.*, **1994**, *35*, 8037; Moody, C. M.; Young, D. W.; *ibid.*, **1994**, *35*, 7277; Panday, S. K.; Griffart-Brunet, D.; Langlois, N., *ibid.*, **1994**, *35*, 6673; Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; Navio, J. L. G.; Alvarez-Builla, J.; Vaquero, J. J., *ibid.*, **1993**, *34*, 6317; Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S., *ibid.*, **1993**, *34*, 5743; Moody, C. M.; Young, D. W., *ibid.*, **1993**, *34*, 4667; Nakamura, H.; Oba, Y.; Murai, A., *ibid.*, **1993**, *34*, 2779; Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sanchez-Ferrando, F., *Tetrahedron*, **1993**, *49*, 8665; Ezquerra, J.; Mendoza, J.; Pedregal, C.; Ramfrez, C., *Tetrahedron Lett.*, **1992**, *33*, 5589; August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W., *ibid.*, **1992**, *33*, 4617; Avent, A. G.; Bowler, A. N.; Doyle, P. M.; Marchand, C. M.; Young, D. W., *ibid.*, **1992**, *33*, 1509; Bowler, N.; Doyle, P. M.; Hitchcock, P. B.; Young, D. W., *ibid.*, **1991**, *32*, 2679; Schoenfelder, A.; Mann, A., *Synth. Commun.*, **1990**, *20*, 2585; Ohta, T.; Hosoi, A.; Nozoe, S., *Tetrahedron Lett.*, **1988**, *29*, 329; b) Griffart-Brunet, D.; Langlois, N., *Tetrahedron Lett.*, **1994**, *35*, 119; Langlois, N.; Rojas, A.,

ibid., **1993**, *34*, 2477; *idem*, *Tetrahedron*, **1993**, *49*, 77; c) Altmann, K.-H., *Tetrahedron Lett.*, **1993**, *34*, 7721.

(2) Baldwin, J. E.; Miranda, T.; Moloney, M.; Hokelek, T., *Tetrahedron*, **1989**, *45*, 7459.

(3) a) Flynn, D. L.; Zelle, R. E.; Grieco, P. A., *J. Org. Chem.*, **1983**, *48*, 2424; b) Effenberger, F.; Muller, W.; Isak, H., *Chem. Ber.*, **1987**, *120*, 45.

(4) Yoshifuji, S.; Tanaka, K.; Kawai, T.; Nitta, Y., *Chem. Pharm. Bull.*, **1986**, *34*, 3873.

(5) Kolasa, T.; Miller, M. J., *J. Org. Chem.*, **1990**, *55*, 1711.

(6) Rigo, B.; Gautret, P.; Legrand, A.; Ghammarti, S. El; Couturier, D., *Synth. Commun.*, **1994**, *24*, 2609.

(7) H. Gibian, H.; Klieger, E., *Liebigs Ann. Chem.*, **1961**, *640*, 145.

(8) Saijo, S.; Wada, M.; Himizu, J.; Ishida, A., *Chem. Pharm. Bull.*, **1980**, *28*, 1449.

(9) Drauz, K.; Kleemann, A.; Martens, J.; Scherberich, P.; Effenberger, F., *J. Org. Chem.*, **1986**, *51*, 3494.

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