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### CONVENIENT N-PROTECTION OF L-PYROGLUTAMIC ACID ESTERS

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### CONVENIENT *N*-PROTECTION OF L-PYROGLUTAMIC ACID ESTERS<sup>†</sup>

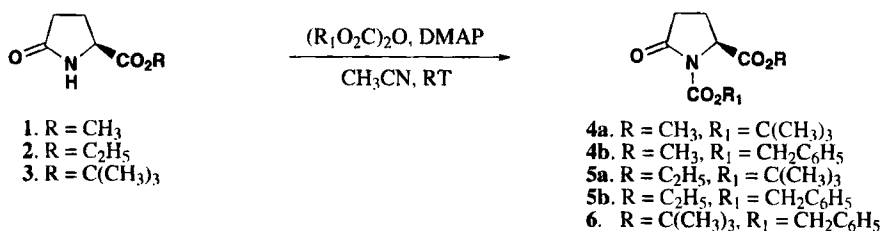
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(01/17/01)

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Non-genetically coded pyroglutamic acid is an important component of many biological important natural peptides,<sup>1</sup> and *N*-protected-L-pyroglutamic acid esters are important substrates for the synthesis of non-proteinogenic amino acids, natural products, and  $\gamma$ -homologation reactions.<sup>2-5</sup> Direct syntheses of these compounds from pyroglutamic acid esters without significant racemization is an arduous task. Therefore, *N*-benzyloxycarbonyl-L-pyroglutamic acid is consistently prepared by the classical old method of ring cyclization of benzyloxycarbonyl-L-glutamic acid.<sup>6</sup> Furthermore, there is only one example of direct introduction of benzyloxycarbonyl (Z) group at the ring-nitrogen of pyroglutamic acid.<sup>7</sup> However, when attempted in our laboratory, the method proved inadequate with substantial racemization of the product. Additionally, the use of the method fails to introduce *tert*-butoxycarbonyl (*t*-Boc) group directly at the nitrogen of pyroglutamic acid esters. Kikugawa *et al.*<sup>8</sup> reported recently the use of LiHMDS in THF at -78° to prepare Z, *t*-Boc, and other functional groups protected L-pyroglutamic acid esters. However, the method is ineffective on a preparative scale due to complicated reaction conditions, and the use of low temperature. Hence, there is a need to develop methodologies suitable for large-scale synthesis without much difficulty and racemization of the product. A literature survey revealed that, Grieco *et al.*<sup>9</sup> have used molar equivalents of di-*tert*-

butyl dicarbonate, 4-dimethylaminopyridine (DMAP) and triethylamine in THF for the nitrogen protection of lactam and amides. In yet another report, Effenberger *et al.*<sup>10</sup> have prepared *N*-acetyl pyroglutamic acid esters using acid chlorides in triethylamine. This paper reports the extension of these methodologies to prepare *N*-protected L-pyroglutamates without any apparent racemization.

In the **Method A**, reaction of L-pyroglutamates acid esters (**1-3**)<sup>11</sup> with di-*tert*-butyl dicarbonate or dibenzyl dicarbonate in acetonitrile at ambient temperature and catalytic amounts of dimethylaminopyridine (DMAP) provided compounds **4-6** in 70-98% yield (**Scheme 1, Table**). It is important to note that the use of excess amount of DMAP during the reaction did not shorten the reaction time nor increase the yield.



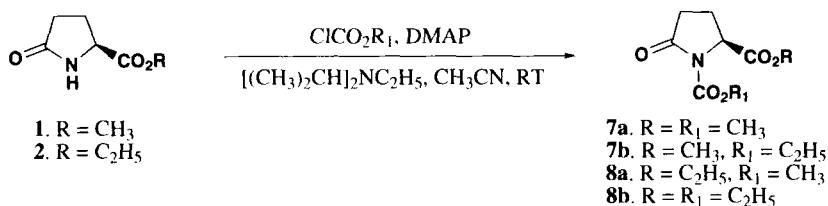
**Scheme 1**

**Table:** Yield and Optical Rotation of Compounds 4-8

No.	R	R <sub>1</sub>	Yield (%)	[α] <sub>D</sub> <sup>20</sup>	Lit.
<b>4a</b>	CH <sub>3</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	90 <sup>a</sup>	-44.9° (c = 1.89, CH <sub>3</sub> OH)	-44.3° (c = 1.0, C <sub>2</sub> H <sub>5</sub> OH) <sup>6</sup>
<b>4b</b>	CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	75 <sup>a</sup>	-45.0° (c = 3.5, CH <sub>3</sub> OH)	-41.3° (c = 1, C <sub>2</sub> H <sub>5</sub> OH) <sup>6</sup>
<b>5a</b>	C <sub>2</sub> H <sub>5</sub>	C(CH <sub>3</sub> ) <sub>3</sub>	98 <sup>a,2</sup>	-46.3° (c = 1.4, CH <sub>3</sub> OH)	
<b>5b</b>	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	70 <sup>a</sup> , 60 <sup>b</sup>	-44.5° (c = 2.0, CH <sub>3</sub> OH)	
<b>6</b>	C(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	85 <sup>a</sup>	-37.4° (c = 1.0, CH <sub>3</sub> OH)	-35.9° (c = 0.91, CHCl <sub>3</sub> ) <sup>8</sup>
<b>7a</b>	CH <sub>3</sub>	CH <sub>3</sub>	60 <sup>b</sup>	-45.2° (c = 2.1, CH <sub>3</sub> OH)	
<b>7b</b>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	90 <sup>b</sup>	-40.8° (c = 2.0, CH <sub>3</sub> OH)	
<b>8a</b>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	95 <sup>b</sup>	-46.0° (c = 5.0, CH <sub>3</sub> OH)	
<b>8b</b>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	88 <sup>b</sup>	-39.5° (c = 2.0, CH <sub>3</sub> OH)	

<sup>a</sup>Method A, <sup>b</sup>Method B

In the **Method B**, L-pyroglutamates (**1-2**) were treated with commercially available alkyl chloroformates in the presence of dimethylaminopyridine and *N,N*-diisopropylethylamine (DIEA) for 8 h at ambient temperature in acetonitrile and gave compounds **7-8** in 60-95% yield (**Scheme 2, Table**).



Scheme 2

*tert*-Butoxycarbonyl and benzyloxycarbonyl functions are versatile orthogonal protecting groups widely used in peptide synthesis for the protection of amino functionality. Therefore, selective deblocking of compound **6** [R = C(CH<sub>3</sub>)<sub>3</sub>, R<sub>1</sub> = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>] with TFA/CH<sub>2</sub>Cl<sub>2</sub> would give *N*-benzyloxycarbonyl-L-pyrroglutamic acid (R = CO<sub>2</sub>H, R<sub>1</sub> = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), compound suitable for peptide synthesis.

In summary, we have developed two mild and facile procedures for the synthesis of *N*-protected-L-pyrroglutamic acid esters from L-pyrroglutamates. Both of these methods allow easy and direct introduction of a variety of important protecting groups like *t*-Boc, Z, CO<sub>2</sub>Me, CO<sub>2</sub>Et at the ring-nitrogen of L-pyrroglutamic acid esters.

## EXPERIMENTAL SECTION

<sup>1</sup>H NMR spectra were recorded on a Bruker 300 (300 MHz) spectrometer. The Central Instrumentation Section of the NIPER provided Mass spectra. Elemental analysis was performed by Atlantic Micro lab, Norcross, GA or by Galbraith Laboratories, Knoxville, TN. Melting points were recorded on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 MC Polarimeter. Chromatographic purification was performed with silica gel 60 (230-400 mesh). All TLC (silica gel) development was performed by use of 0.5% CH<sub>3</sub>OH in CHCl<sub>3</sub>. All reagents were obtained from commercial sources and were of analytical grade.

**General Method for the Synthesis of *N*-Protected-L-pyrroglutamic acid Esters (4-8). Method A. Synthesis of Methyl *N*-*tert*-Butoxycarbonyl-L-pyrroglutamate (4a).** To a mixture of methyl L-pyrroglutamate (**1**, 1 g, 7 mmol) and DMAP (50 mg) in acetonitrile (25 mL) was added di-*tert*-butyl dicarbonate (10.5 mmol) in one portion and the reaction mixture was stirred at room temperature for 3h. The solvent was removed *in vacuo*, and the residue was chromatographed over silica gel using ethyl acetate/hexanes (40:60) to afford 1.52 g (90%) of methyl *N*-*tert*-butoxycarbonyl-L-pyrroglutamate (**4a**) as colorless viscous oil (*Scheme 1, Table*).

HPLC was performed using a Supelcosil 25 cm x 4.6 mm ID, 5 mm particle chiral column, on a Hewlett Packard 1090 model (UV detection at 235 nm) with hexane/isopropanol (1:1) as eluant. HPLC analysis of **1** gave **1**(*S*-enantiomer):**1**(*R*-enantiomer) isomeric ratio of 98.2:1.8. After synthesis of **4a** from **1**, the isomeric ratio of 98.2:1.8 for **4a**(*S*-enantiomer) and **4a**(*R*-enantiomer) was observed from the HPLC analysis indicating the absence of racemization during the protection step. Retention time of 11 and 13 minutes are observed for **4a**(*S*-enantiomer) and **4a**(*R*-enantiomer) respectively, that was confirmed by synthesizing authentic **4a**(*R*-enantiomer).<sup>12</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.49 (s, 9H, 3 x CH<sub>3</sub>), 2.0-2.7 (m, 4H, 2 x CH<sub>2</sub>), 3.78 (s, 3H, CH<sub>3</sub>), 4.62 (m, 1H,

CH); MS (CI-NH<sub>3</sub>): *m/z* 261 (M+18).

*Anal.* Calcd for C<sub>11</sub>H<sub>17</sub>NO<sub>5</sub>: C, 54.31; H, 7.04; N, 5.75. Found: C, 54.55; H, 7.10; N, 5.73

**Methyl N-Benzoyloxycarbonyl-L-pyroglutamate (4b).** Yield: 75%; mp 71-72°; light yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.47 (m, 2H, CH<sub>2</sub>), 2.61 (m, 2H, CH<sub>2</sub>), 3.67 (s, 3H, CH<sub>3</sub>), 4.57 (m, 1H, CH), 4.70 (m, 2H, CH<sub>2</sub>), 7.36 (m, 5H, Ar-H); MS (CI-NH<sub>3</sub>): *m/z* 295 (M+18).

*Anal.* Calcd for C<sub>14</sub>H<sub>15</sub>NO<sub>5</sub>: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.63; H, 5.47; N, 5.21

**Ethyl N-tert-Butoxycarbonyl-L-pyroglutamate (5a).** Yield: 98%; mp 53-54°; white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (t, 3H, CH<sub>3</sub>, J= 7.3 Hz), 1.49 (s, 9H, 3 x CH<sub>3</sub>), 1.9-2.7 (m, 4H, 2 x CH<sub>2</sub>), 4.24 (q, 2H, CH<sub>2</sub>, J= 7.2 & 14.2 Hz), 4.59 (m, 1H, CH); MS (CI-NH<sub>3</sub>): *m/z* 275 (M+18).

*Anal.* Calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>5</sub>: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.12; H, 7.47; N, 5.48

**Ethyl N-Benzoyloxycarbonyl-L-pyroglutamate (5b).** Yield: 70%; colorless viscous oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.19 (t, 3H, CH<sub>3</sub>, J= 7.2 Hz), 2.0-2.65 (m, 4H, 2 x CH<sub>2</sub>), 4.15 (m, 2H, CH<sub>2</sub>), 4.67 (m, 1H, CH), 5.28 (m, 2H, CH<sub>2</sub>), 7.36 (m, 5H, C<sub>6</sub>H<sub>5</sub>); MS (CI-NH<sub>3</sub>): *m/z* 309 (M+18).

*Anal.* Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>5</sub>: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.66; H, 5.85; N, 4.77

**tert-Butyl N-Benzoyloxycarbonyl-L-pyroglutamate (6).** Yield: 85%; colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.47 (s, 9H, 3 x CH<sub>3</sub>), 2.03-2.65 (m, 4H, 2 x CH<sub>2</sub>), 4.58 (m, 1H, CH), 5.17 (s, 2H, CH<sub>2</sub>), 7.33 (m, 5H, Ar-H); Mass (CI-NH<sub>3</sub>): *m/z* 337 (M+18).

*Anal.* Calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>5</sub>: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.87; H, 6.81; N, 4.32

**Method B. Synthesis of Methyl N-Methoxycarbonyl-L-pyroglutamate (7a).**- To a mixture of methyl L-pyroglutamate (1, 1 g, 7 mmol), DMAP (3.1 mmol) and *N,N*-diisopropylethylamine (9.5 mmol) in acetonitrile (25 mL) was added methyl chloroformate (10.5 mmol) drop wise during 10 minutes. The reaction mixture was stirred for 8 h at room temperature. The solvent was removed and residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with saturated NaCl solution (2 x 20 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* to afford crude product. Purified by flash column chromatography using ethyl acetate/hexanes (40:60) to provide 1 g (60%) of compound **7a** as a thick oil (*Scheme 2, Table*).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.0-2.7 (m, 4H, 2 x CH<sub>2</sub>), 3.80 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, CH<sub>3</sub>), 4.70 (m, 1H, CH); MS (CI-NH<sub>3</sub>): *m/z* 219 (M+18).

*Anal.* Calcd for C<sub>8</sub>H<sub>11</sub>NO<sub>5</sub>: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.69; H, 5.42; N, 6.77

**Methyl N-Ethoxycarbonyl-L-pyroglutamate (7b).** Yield: 90%; colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.32 (t, 3H, CH<sub>3</sub>, J= 7.0 Hz), 2.0-2.71 (m, 4H, 2 x CH<sub>2</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 4.32 (m, 2H, CH<sub>2</sub>), 4.68 (m, 1H, CH); MS (CI-NH<sub>3</sub>): *m/z* 233 (M+18).

*Anal.* Calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>5</sub>: C, 50.23; H, 6.08; N, 6.50. Found: C, 50.22; H, 6.10; N, 6.44

**Ethyl N-Methoxycarbonyl-L-pyroglutamate (8a).** Yield: 95%; colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.29 (t, 3H, CH<sub>3</sub>, J= 7.5 Hz), 2.10-2.73 (m, 4H, 2 x CH<sub>2</sub>), 3.78 (s, 3H, CH<sub>3</sub>), 4.25 (m, 2H, CH<sub>2</sub>), 4.67 (m, 1H, CH); MS (CI-NH<sub>3</sub>): *m/z* 233 (M+18).

*Anal.* Calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>5</sub>: C, 50.23; H, 6.08; N, 6.50. Found: C, 50.29; H, 6.20; N, 6.42

**Ethyl N-Ethoxycarbonyl-L-pyroglutamate (8b).** Yield: 88%; colorless oil, <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ

1.32 (m, 6H, 2 x CH<sub>3</sub>), 2.0-2.75 (m, 4H, 2 x CH<sub>2</sub>), 4.3 (m, 4H, 2 x CH<sub>2</sub>), 4.66 (m, 1H, CH); MS (CI-NH<sub>3</sub>): 247 (M+18).

*Anal.* Calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>5</sub>: C, 52.40; H, 6.60; N, 6.11. Found, C, 52.13; H, 6.58; N, 5.96

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  - Methyl D-pyroglutamate required for the synthesis of authentic sample of **4a**(*R*-enantiomer) was synthesized from D-pyroglutamic acid {[α]<sub>D</sub><sup>20</sup> +10.2° (c = 1.5, H<sub>2</sub>O)} following a literature procedure;<sup>11</sup> it was converted to methyl *N*-*tert*-butoxycarbonyl-D-pyroglutamate [**4a**(*R*-enantiomer)] using *Method A*. Yield: 83%; colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.49 (s, 9H, 3 x CH<sub>3</sub>), 2.05-2.73 (m, 4H, 2 x CH<sub>2</sub>), 3.79 (s, 3H, CH<sub>3</sub>), 4.65 (m, 1H, CH); MS (CI-NH<sub>3</sub>): m/z 261 (M+18); *Anal.* Calcd for C<sub>11</sub>H<sub>17</sub>NO<sub>5</sub>: C, 54.31; H, 7.04; N, 5.75; Found: C, 54.37; H, 7.13; N, 5.79. The HPLC analysis of methyl *N*-*tert*-butoxycarbonyl-D-pyroglutamate on a Hewlett Packard 1090 model analyzer (UV detection at 235 nm) using Supelcosil 25 cm x 4.6 mm ID, 5 mm particle chiral column, with hexane/isopropanol (1:1) as eluent indicated the isomeric ratio of 3:97 for **4a**(*S*-enantiomer) and **4a**(*R*-enantiomer) with retention time of 11.2 and 13.1 minutes respectively.