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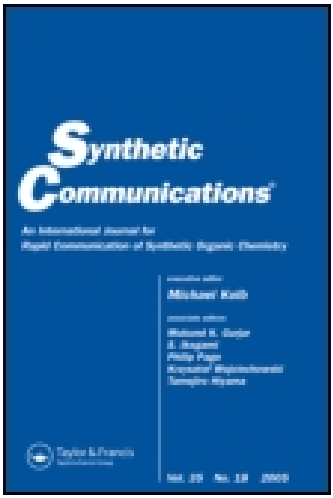

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A Convenient Preparation of 4-t-Butyl-L-phenylalanine

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A Convenient Preparation of 4-*t*-Butyl-L-phenylalanine

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Abstract: A convenient preparation of 4-t-butyl-L-phenylalanine and N-Fmoc-4-t-butyl-L-phenylalanine are described.

We required 4-*t*-butyl-L-phenylalanine as a replacement for phenylalanine in the preparation of a peptide. 4-*t*-Butyl-L-phenylalanine was reported in the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives displaying angiotensin-converting enzyme inhibitory activity[1], artificial transaminases linking pyridoxamine to binding cavities[2] and synthesis of glycyl(β-aryl)dehydroalanines.[3]

We chose Fmoc-4-*t*-Bu-Phe-OH as the protected amino acid for building the peptide by solid phase peptide synthesis[4]. The preparation[5,6] of the amino acid (Scheme 1) began with deprotonation of diethyl acetamidomalonate (**1**) with sodium ethoxide in ethanol at refluxing temperature, followed by addition of para-*t*-butyl benzyl bromide to form compound **2** in 87% yield. After saponification of both ethyl esters, decarboxylation at refluxing temperature afforded *N*-acetyl-4-*t*-butyl-D,L-phenylalanine (**3**, 59% yield). An enzymatic resolution using porcine kidney acylase I[7-9] at room temperature resulted in the selective separation of 4-*t*-butyl-L-phenylalanine (**4**, 92% yield) from *N*-acetyl-4-*t*-butyl-D-phenylalanine (**5**) with high efficiency. The 4-*t*-butyl-L-phenylalanine (**4**) was protected using Fmoc-OSu under basic conditions to yield *N*-Fmoc-4-t-butyl-L-phenylalanine (**6**, 53% yield).

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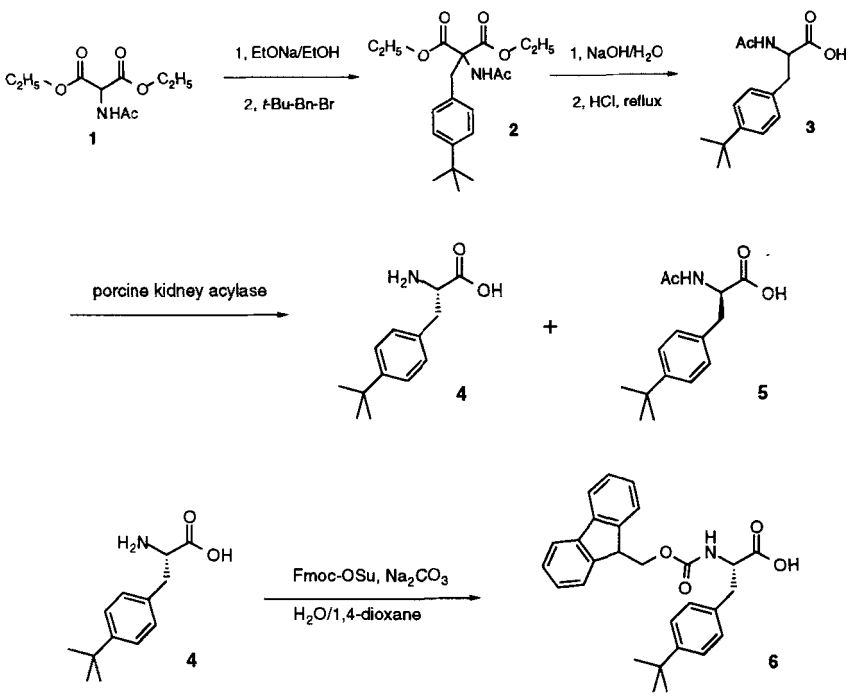
Scheme 1 Preparation of Fmoc-4-*t*-Butyl-L-Phenylalanine



This is a straightforward route to prepare gram quantities of 4-*t*-butyl-L-phenylalanine and *N*-Fmoc-4-*t*-butyl-L-phenylalanine from readily available starting materials.[10]

EXPERIMENTAL SECTION

General Experimental. The NMR spectra were obtained on a GE QE-300, and are reported in ppm downfield from TMS. The mass spectra were obtained on a Hewlett Packard 5989B mass spectrometer. All melting points were determined using a Mel-Temp II device and have not been corrected. Reagents used were all analytical grade.

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Diethyl *t*-Butylbenzylacetamidomalonate (2):

Sodium metal (0.5 g, 21.4 mmol.) was dissolved in ethanol (35 mL) at 45 °C under a nitrogen atmosphere and the solution mixed 1 hour. Diethyl acetamidomalonate (4.65 g, 21.4 mmol.) was added to the sodium ethoxide solution, and the reaction mixture refluxed at 85 °C for one hour with formation of a white solid. The reaction mixture was cooled to 0-5 °C. *t*-Butylbenzyl bromide (5.0 g, 22.0 mmol.) was added, followed by stirring at 0 to 5 °C for four hours. The reaction was quenched with water (50 mL) and the solution mixed at ambiant temperature one hour. After evaporating ethanol under reduced pressure, a white solid was collected by filtration and washed with water to afford 6.79 g (87% yield); mp: 76-78 °C; ^{1}H NMR: δ 1.26-1.35 (m, 15H), 2.05 (s, 3H), 3.61 (s, 2H), 4.25-4.33 (m, 4H), 6.55 (s, 1H), 6.90-7.28 (m, 4H)); ^{13}C NMR δ 14.0, 23.0, 31.3, 37.3, 62.5, 125.2, 129.5; MS: $(M+H)^+$ at m/z 364; Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.12; H, 8.05; N, 3.86. Found: C, 66.15; H, 8.06; N, 3.77.

***N*-Acetyl-4-*t*-Butyl-D,L-phenylalanine (3):**

To a solution of **2** (6.79 g, 18.7 mmol.) in ethanol (40 mL) and H_2O (40 mL) was added sodium hydroxide (0.75 g, 37.4 mmol.) at ambiant temperature. The mixture was stirred at reflux for 21 hours. After the reaction mixture was cooled to ambiant temperature, 4 mL 6 M HCl was added to the reaction mixture at 0 °C. The pH was the adjusted to 2 by concentrated HCl. The mixture was heated at 80 °C until ethanol was distilled (about 20 mL). An oil was separated from the aqueous solution overnight at room temperature. The oil was dissolved in hot ethanol, and then slowly stirred to afford a white solid (2.72 g, 59% yield); mp: 226-228 °C; ^{1}H NMR δ 1.30 (s, 9H), 1.95 (s, 3H), 2.92-3.20 (m, 2H), 4.65-4.72 (m, 1H), 5.05 (s, 1H), 7.13-7.35 (m, 4H); ^{13}C NMR δ 20.8, 30.1, 35.9, 53.0, 124.4, 128.0; MS: $(M+H)^+$ at m/z 264; Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.44; H, 8.05; N, 5.32. Found: C, 68.51; H, 7.93; N, 5.14.

4-*t*-Butyl-L-phenylalanine (4):

A suspension of **3** (3.33 g, 12.6 mmol) in distilled water (2000 mL) was sparged with nitrogen at 40 °C, and the pH adjusted to 7.2-7.5 with 1 M LiOH.

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During the LiOH addition, the solid gradually dissolved. Porcine kidney acylase (40 mg, Sigma A-3010) was added and the mixture stirred at 40 °C over 48 h. The reaction was monitored by HPLC (C4, Kromasil, 20 to 75% B 40 min; solvent A: 0.1% H_3PO_4 in water, solvent B: acetonitrile) with the final ratio of 4-*t*-Bu-L-Phe-OH to *N*-Ac-4-*t*-Bu-D-Phe-OH 47:53. The pH was adjusted to 1.5 by concentrated HCl. The aqueous solution was extracted with EtOAc (6 x 100 mL) until HPLC analysis indicated that the aqueous layer contained only 4-*t*-Bu-L-Phe-OH. The aqueous layer was concentrated *in vacuo* to yield 1.5 g white solid (92% yield, 99.9 % ee[11]). mp 216-219 °C; ^{1}H NMR δ 1.38 (s, 9H), 3.40-3.60 (m, 2H), 7.26-7.42 (m, 4H); MS: $(M+H)^+$ at m/z 222; Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.67; N, 6.33. Found: C, 69.98; H, 8.29; N, 6.02.

***N*-Fmoc-4-*t*-Butyl-L-phenylalanine (6):**

A solution of L-4-*t*-Bu-Phe-OH (0.84 g, 3.8 mmol) and sodium carbonate (0.81 g, 7.6 mmol) in 100 mL water was cooled to 0 to 5 °C while Fmoc-OSu (1.28 g, 3.8 mmol) in 1,4-dioxane (30 mL) was added dropwise over 2 hours. After the addition was complete, the ice bath was removed and mixture allowed to warm to ambiant temperature over 1.5 hours. Ethyl acetate (250 mL) and 1.0 M HCl (until pH of the aqueous layer was 1.5) were added. The ethyl acetate was separated, and the aqueous layer was extracted with 100 mL of ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over $MgSO_4$, and evaporated to afford a white solid, 0.90 g (92% area percent by HPLC, 53% yield) mp 65-67 °C; ^{1}H NMR δ 1.30 (s, 9H), 3.08-3.24 (m, 2H), 4.16-4.44 (m, 3H), 4.65-4.75 (m, 1H), 5.15-5.25 (m, 1H), 7.06-7.78 (m, 12H); ^{13}C NMR δ 31.3, 34.5, 37.1, 47.1, 54.5, 67.1, 120.0, 125.0, 125.6, 127.7, 129.0, 132.2, 141.3, 143.7, 150.2, 155.8, 175.3; MS: $(M+H)^+$ at m/z 444; Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.84; H, 6.60; N, 3.16. Found: C, 75.62; H, 6.54; N, 3.24.

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