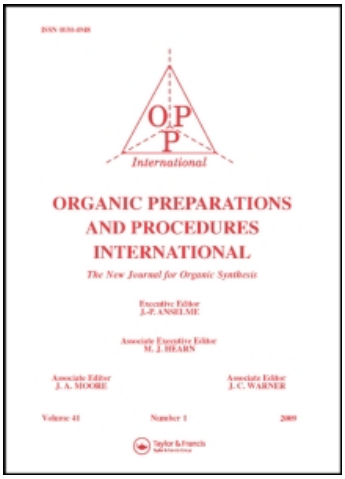

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AN IMPROVED PREPARATION OF 3-(5-BENZOFURANYL)-L-ALANINE

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(175); 111 (9%); 99 (100%); 83 (19%); 71 (27%); 55 (31%); 43 (35%).

HRMS: Calcd for $C_{16}H_{30}O_2$, *m/z*, 254.22458. Found: 254.22857

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(06/15/01)

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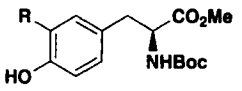
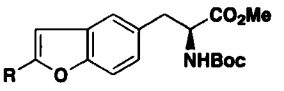
3-(5-Benzofuranyl)-L-alanine (**3a**) has recently emerged as a highly promising non-canonical amino acid in the development of strategies for the site-specific *in vivo* incorporation of photoreactive amino acids.[1] The synthesis of **3a** in five steps and ~10% overall yield has involved the non-

selective preparation of the D,L-form followed by enzymatic resolution. In the last fifteen years, a large variety of 3-aryl and 3-heteroarylalanines have been prepared as valuable tools in the design of selective peptide ligands exploiting transition metal-catalyzed reactions.[2] In particular, Crisp has used the Sonogashira reaction[3] to attach a series of fluorescent and enzymatic labels containing a terminal alkyne to suitably protected iodophenylalanines.[4] Annulation of Sonogashira adducts of *o*-halophenols and 1-alkynes, either as starting materials or as reaction intermediates, represents a very useful procedure for the synthesis of benzofurans.[5] The use of a similar chemistry to obtain the title compound from commercially available 3-iodo-L-tyrosine is described herein.



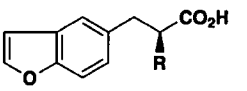
1

a) R = I
b) R = C≡C–$SiMe_3$
c) R = C≡CH



2

a) R = $SiMe_3$
b) R = H



3

a) R = NH_2
b) R = $NH_3^+Cl^-$
c) R = NHBoc

The reaction of fully protected 3-iodo-L-tyrosine **1a**[6] with (trimethylsilyl)acetylene in the presence of $Pd(OAc)_2/PPh_3$ as the catalyst, CuI as cocatalyst, and Et_3N as the base in DMF proceeded smoothly at 45° to give the protected 3-ethynyl-L-tyrosine **1b** in 90% yield. Less satisfactory results were obtained at 60° using piperidine as the base (56%)[5d] or at 90° in Et_3N (74%)[5c]. No benzofuran **2a** resulting from cyclization of **1b** could be observed in these syntheses.[7] Desilylation of **1b** with KF in MeOH and *in situ* cyclization of **1c** by the catalytic action of CuI at room temperature provided protected 3-(5-benzofuranyl)-L-alanine **2b** in 83% yield. When $Pd(OAc)_2$ was used as catalyst in the cyclisation step, **2b** was isolated in only 19% yield. The free amino acid was obtained nearly quantitatively by saponification of **2b** with a mixture NaOH/MeOH/H_2O at room temperature followed by the removal of the Boc protecting group using a solution of dry HCl in ethyl acetate. Physical data for the hydrochloride salt **3b** (mp, optical rotation, ^1H and ^{13}C NMR) were in good agreement with the values reported in literature.[1]

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at 25° with a Schmidt-Haensch Polartronic D polarimeter (1 dm-cell). IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 spectrometer.

***N*-Boc-3-[(trimethylsilyl)ethynyl]-L-tyrosine Methyl Ester (1b).**- A mixture of **1a**[6] (421 mg, 1 mmol), (trimethylsilyl)acetylene (0.21 mL, 1.5 mmol), Et_3N (0.56 mL, 4 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (16 mg, 0.06 mmol), and CuI (11 mg, 0.06 mmol) in DMF (4 mL) was stirred at 45° for 3 h under nitrogen. The reaction mixture was then cooled, diluted with water, and extracted with Et_2O. The organic solution was washed twice with water, dried (Na_2SO_4), and evaporated. The residue

(459 mg) was purified by chromatography on silica gel (14 g) using CH_2Cl_2/hexane = 7/3 as eluent to give 352 mg (90%) of **1b**: oil; $[\alpha]_D$ +39° (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3517, 3437, 2953, 2145, 1742, 1710, 1488, 1366, 1164 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.27 (9H, s, $SiMe_3$), 1.43 (9H, s, *t*-Bu), 2.92 (1H, dd, J = 14.0, 6.3 Hz, CHH), 3.03 (1H, dd, J = 14.0, 5.6 Hz, CHH), 3.72 (3H, s, CO_2Me), 4.51 (1H, m, α-CH), 4.99 (1H, d, J = 8.1 Hz, NH), 5.82 (1H, br s, OH), 6.86 (1H, d, J = 8.1 Hz, ArH), 6.99 (1H, dd, J = 8.1, 2.1 Hz, ArH), 7.11 (1H, br s, ArH); ^{13}C NMR: δ 0.05, 28.35, 37.41, 52.30, 54.55, 80.06, 98.90, 102.45, 109.70, 114.81, 127.86, 131.59, 132.39, 155.09, 156.24, 172.31.

Anal. Calcd for $C_{20}H_{29}NO_5Si$: C, 61.35; H, 7.47; N, 3.58. Found: C, 61.26; H, 7.54; N, 3.63

***N*-Boc-3-(5-benzofuranyl)-L-alanine Methyl Ester (2b).**- To a stirred solution of **1b** (391 mg, 1 mmol) in MeOH (4 mL) was added KF (116 mg, 2 mmol) and the resulting mixture was stirred at 20-25°. The desilylation reaction followed by TLC (CH_2Cl_2/AcOEt = 9/1, R_f of **1b** and **1c** 0.43 and 0.32, respectively) was complete in 6 h. CuI (19 mg, 0.1 mmol) was added and the stirring was continued at 20-25° for additional 36 h. The reaction mixture was then diluted with water and extracted with Et_2O. The organic solution was washed with water, dried (Na_2SO_4), and evaporated. The residue (308 mg) was purified by chromatography on silica gel (10 g) using CH_2Cl_2/hexane = 7/3 as eluent to give 265 mg (83%) of **2b**, R_f 0.72 (CH_2Cl_2/AcOEt = 9/1): oil; $[\alpha]_D$ +45° (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3437, 2977, 1740, 1707, 1602, 1500, 1367, 1170 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (9H, s, *t*-Bu), 3.17 (2H, m, β-CH_2), 3.71 (3H, s, CO_2Me), 4.61 (1H, m, α-CH), 5.03 (1H, d, J = 7.6 Hz, NH), 6.71 (1H, d, J = 2.2 Hz, ArH), 7.05 (1H, dd, J = 8.4, 1.4 Hz, ArH), 7.35 (1H, br s, ArH), 7.42 (1H, d, J = 8.4 Hz, ArH), 7.60 (1H, d, J = 2.2 Hz, ArH); ^{13}C NMR: δ 28.36, 38.32, 52.25, 54.88, 80.01, 106.50, 111.42, 121.78, 125.60, 127.82, 130.53, 145.44, 154.27, 155.21, 172.52.

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.83; H, 6.70; N, 4.45

3-(5-Benzofuranyl)-L-alanine Hydrochloride (3b).- A solution of **2b** (319 mg, 1 mmol) in MeOH (3 mL) and 2N NaOH (1 mL) was stirred at 20-25° for 2 h, then concentrated under reduced pressure, acidified with a slight excess of 2N HCl, and extracted with AcOEt. The organic phase was washed twice with water, dried (Na_2SO_4), and evaporated. The residue (316 mg) was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH = 95/5 as eluent to give 298 mg (98%) of **3c**,[1] R_f 0.41 (CH_2Cl_2/MeOH = 9/1): oil; $[\alpha]_D$ +43° (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3434, 2938, 1706, 1500, 1369, 1164 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (9H, s, *t*-Bu), 3.17 (1H, dd, J = 13.5, 5.7 Hz, CHH), 3.28 (1H, dd, J = 13.5, 5.7 Hz, CHH), 4.64 (1H, m, α-CH), 5.00 (1H, d, J = 7.5 Hz, NH), 6.71 (1H, d, J = 2.1 Hz, ArH), 6.97 (1H, br s, CO_2H), 7.11 (1H, d, J = 8.4 Hz, ArH), 7.40 (1H, br s, ArH), 7.42 (1H, d, J = 8.4 Hz, ArH), 7.60 (1H, d, J = 2.1 Hz, ArH); ^{13}C NMR: δ 28.22, 37.62, 54.59, 80.18, 106.27, 111.21, 121.63, 125.40, 127.54, 130.02, 145.09, 153.96, 154.90, 175.95. To a solution of **3c** (298 mg, 0.98 mmol)) in AcOEt (2 mL) was added a saturated solution of anhydrous HCl in AcOEt (4 mL). The solution was stirred at 20-25° for 3 h and evaporated to afford **3b** as a white solid (234 mg, 99%), mp 225-226°; $[\alpha]_D$ -14° (c 1.0, H_2O) [*lit.*[1] mp 234-236°; $[\alpha]_D$ -12.9° (c 1.0, H_2O)]; IR (KBr): 3420, 2901, 1734, 1483, 1212 cm^{-1}; ^1H NMR (D_2O): δ 3.29 (1H, dd, J = 14.7, 7.5 Hz, CHH), 3.45 (1H, dd, J = 14.7, 5.5 Hz, CHH), 4.32 (1H, dd, J = 7.5, 5.5 Hz, α-CH), 6.90 (1H, d, J = 2.1 Hz, ArH), 7.26 (1H, d,

J = 8.4 Hz, ArH), 7.57 (1H, d, J = 8.4 Hz, ArH), 7.59 (1H, br s, ArH), 7.79 (1H, d, J = 2.1 Hz, ArH); ^{13}C NMR: δ 35.43, 54.58, 106.35, 111.66, 121.98, 125.29, 127.87, 128.41, 146.23, 153.98, 171.72.

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7. *o*-Alkynylphenols are known to cyclise under basic conditions (refs. 5a,b), but some authors have reported that the reaction does not proceed to an appreciable extent without transition metals catalysis (ref. 5c). Indeed, we found that **1b** could be converted into **2a** in 44% yield by treatment with Et_3N (2 equivalents) and a catalytic amount of $Pd(OAc)_2$ (5 mol%) in MeOH at 45° for 4.5 h. **2a**: oil; $[\alpha]_D$ +38° (c 1.0, $CHCl_3$); IR ($CHCl_3$): 3437, 2953, 2927, 1740, 1707, 1498, 1368, 1252, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.34 (9H, s, $SiMe_3$), 1.41 (9H, s, *t*-Bu), 3.17 (2H, m, β-CH_2), 3.71 (3H, s, CO_2Me), 4.59 (1H, m, α-CH), 4.97 (1H, d, J = 5.6 Hz, NH), 6.90 (1H, d, J = 0.6 Hz, ArH), 7.02 (1H, dd, J = 8.5, 1.6 Hz, ArH), 7.31 (1H, br s, ArH), 7.41 (1H, d, J = 8.5 Hz, ArH); ^{13}C NMR: δ 1.83, 30.12, 39.95, 53.99, 56.62, 81.72, 113.04, 117.68, 123.28, 127.44, 130.23, 131.71, 157.02, 159.23, 166.00, 174.28.
Anal. Calcd for $C_{20}H_{29}NO_5Si$: C, 61.35; H, 7.47; N, 3.58. Found: C, 61.25; H, 7.55; N, 3.65
2-(Trimethylsilyl)benzofurans have been previously obtained by flash vacuum pyrolysis of *o*-[(trimethylsilyl)ethynyl]phenols: T. J. Barton and B. L. Groh, *J. Org. Chem.*, **50**, 158 (1985) and by metallation of benzofurans followed by quenching with Me_3SiCl [M. Gill, *Tetrahedron*, **40**, 621 (1984)].