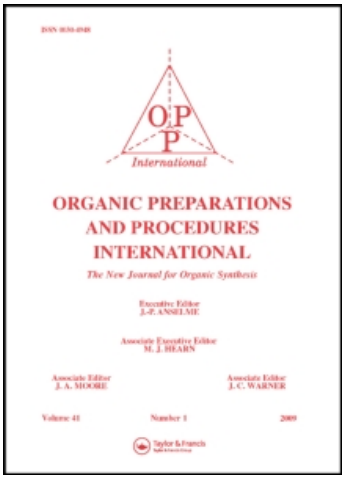

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SYNTHESIS OF 4-BORONO-2-FLUOROPHENYLALANINE

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SYNTHESIS OF 4-BORONO-2-FLUOROPHENYLALANINE

Submitted by (03/14/00) G. W. Kabalka*, N. K. Reddy, L. Wang and R. R. Malladi

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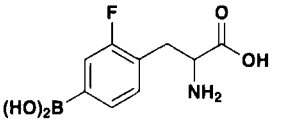
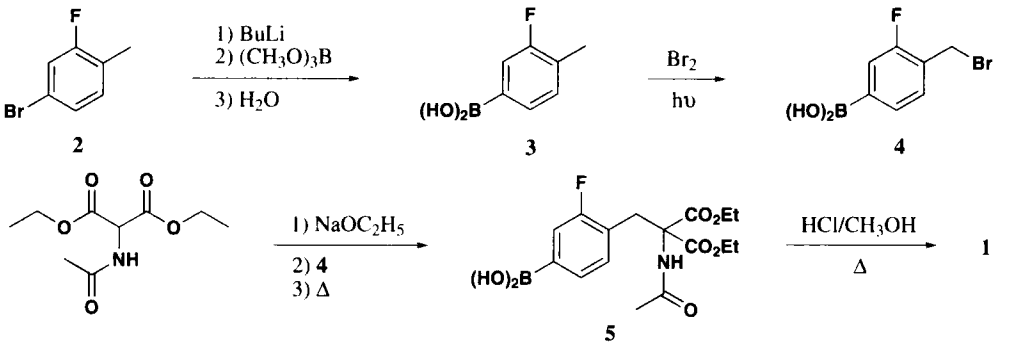
4-Boronophenylalanine (BPA) is one of only two boronated compounds approved for use in the U.S. Phase II Clinical Trials for boron neutron capture therapy.[1] This therapy is dependent on the interaction of boron-10 atoms with low energy (thermal) neutrons to generate cytotoxic alpha particles.[2] In an effort to determine the distribution of BPA *in vivo* utilizing both MRI[3] and positron emission tomography (PET),[4,5] 4-borono-2- fluorophenylalanine (**1**) was prepared. In MRI applications, **1**



1

can be detected *in vivo* through the use of multinuclear, fluorine-19 MRI. Its primary role in PET studies is to serve in preliminary biodistribution studies in which tissue samples obtained at the time of tumor biopsy are analyzed for both fluorine and boron content. This data can then used to validate the fluorine-18 labeled BPA *in vivo* studies.[4,5] We now report the details of our synthesis of **1** starting from 4-bromo-2-fluorotoluene (**2**) (*Scheme 1*).

4-Bromo-2-fluorotoluene (**2**) was converted to the corresponding boronic acid **3** in 91% yield. Boronic acid **3** was then brominated using molecular bromine to form benzyl bromide **4** which was added directly to the sodium salt of diethyl acetamidomalonate to form **5** in 68% yield. The desired product, **1**, was formed in 55% yield from **5** via a one step hydrolysis/decarboxylation sequence.



Scheme 1

EXPERIMENTAL SECTION

All reactions were carried out under an argon atmosphere. All glassware and syringes were oven-dried. Hexane was distilled over calcium hydride. THF was distilled from sodium benzophenone ketyl. All other materials were obtained from commercial suppliers and used as received. ^{1}H NMR and ^{13}C NMR data were recorded on 250 MHz or 400 MHz spectrometers. *J* values are given in Hz. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

3-Fluoro-4-methylphenylboronic Acid (3).- A solution of 4-bromo-2-fluorotoluene (**2**) (25.0 mmol, 4.74 g) in hexane and tetrahydrofuran (1:1 by volume, 30 mL) was added to *n*-butyllithium (30 mmol, 18.8 mL of a 1.6 M solution in hexane) dissolved in a mixture of hexane (11 mL) and tetrahydrofuran (30 mL) at -78°. The solution was stirred at -50° for 30 min. and then cooled to -78°. Trimethylborate (36 mmol, 4.0 mL) in tetrahydrofuran (15 mL) was added and the mixture stirred for 12 h at room temperature.[6] The reaction was quenched with aqueous 3 N HCl, extracted into ether (3 x 100 mL) and concentrated to obtain **3**. The product was recrystallized from water and air dried to obtain pure 3-fluoro-4-methylphenylboronic acid (3.5 g, 91%), mp. 234° as a white solid. IR (nujol): 3250 cm^{-1} (OH); ^{1}H NMR (250 MHz, CD_3OD): δ 7.34 (d, *J* = 6.87, 1 H), 7.27 (d, *J* = 10.8 Hz, 1H), 7.08 (t, *J* = 7.50 Hz, 1H), 2.17 (d, *J* = 1.57 Hz, 3 H). ^{13}C NMR (62.5 MHz, CD_3OD): δ 164.3, 160.5, 131.8, 130.4, 127.7 (d, *J* = 17.1 Hz), 120.5 (d, *J* = 20.6 Hz), 14.5.[11] B NMR (29 MHz, CH_3OH): δ 27.8. *Anal.* Calcd. for $C_7H_8BFO_2$: C, 54.61; H, 5.24; B, 7.02; F, 12.34

Found: C, 54.18; H, 4.99; B, 6.41; F, 12.46

2-[1-Acetylamino-2-(4-borono-2-fluorophenyl)ethyl]malonic Acid Diethyl Ester (5).- To a mixture of 3-fluoro-4-methylphenylboronic acid (85.4 mmol, 13.2 g) and dry carbon tetrachloride (200 mL) was added 2 mL of a solution of bromine (86.0 mmol, 4.4 mL in carbon tetrachloride, 70 mL).[7] The mixture was irradiated using an unfrosted 200-watt tungsten lamp. After an induction period (5-10 min.), the color of the bromine faded, and the remainder of the bromine solution was added over a period of 1 h with continued irradiation. The crude product **4**, obtained after removal of the solvent, was used in the next step without further purification.

To a solution of sodium ethoxide prepared from sodium (128 mmol, 3.00 g) and absolute ethanol (200 mL) was added diethyl acetamidomalonate (128 mmol, 28.0 g) in ethanol (100 mL) and the mixture stirred for 45 min. Crude **4** in ethanol (100 mL) was added to the yellow solution and the mixture refluxed for 12 h. The reaction was cooled to 0°, quenched with aqueous 3 N HCl (12 mL) and filtered to remove the precipitated salt. The filtrate was concentrated and a yellow semi-solid formed; the mixture was recrystallized from 30% ethanol to give **5** (21.4g, 68%), mp. 230° as a white solid; IR (nujol): 3350 (OH), 1790 (amide C=O), 1730 cm^{-1} (ester C=O). ^1H NMR (250 MHz, CD_3OD): δ 7.36 (d, *J* = 7.39 Hz, 1H), 7.27 (d, *J* = 11.0 Hz, 1H), 6.93 (t, *J* = 7.42 Hz, 1H), 4.19 - 4.09 (m, 4 H), 3.55 (s, 2 H), 1.89 (s, 3H), 1.18 (t, *J* = 7.11 Hz, 6 H). ^{13}C NMR (62.5 MHz, CD_3OD): δ 172.8, 168.7, 164.7, 160.8, 132.7, 130.5, 125.4 (d, *J* = 15.8 Hz), 121.0 (d, *J* = 20.81 Hz), 68.0, 63.6, 32.7, 22.2, 14.2. ^{11}B NMR (29 MHz, THF): δ 30.7. HR-FAB-MS (m + H -2 H_2O in glycerol matrix): Calcd. for $C_{19}H_{26}BFNO_8$: 426.174. Found: 426.173

Anal. Calcd. for $C_{16}H_{21}BFNO_7$: C, 52.1; H, 5.7; N, 3.8. Found: C, 51.9; H, 5.8; N 3.7

4-Borono-2-fluoro-D,L-phenylalanine (1).- Acetamidomalonate **5** (54.4 mmol, 20.1g) was added to a solution of methanol in 3 N HCl (1:3, 600 mL) and the mixture refluxed for 16 h. The solvent was removed and the residue dissolved in water (100 mL) and filtered. The pH of the solution was adjusted to 6.2 with ammonium hydroxide. After sitting overnight at 0°, the white solid was collected, washed with water and air dried to afford **1** (6.75g, 55%), mp. 270°; IR (KBr): 3294 (OH), 1595 (C=O); ^1H NMR (400 MHz, D_2O): δ 7.41 (d, *J* = 7.52, 1H), 7.35 (d, *J* = 10.88 Hz, 1H), 7.24 (t, *J* = 7.49 Hz, 1H), 3.89 (dd, *J* = 5.58 and 7.82 Hz, 1H), 3.25 (dd, *J* = 5.58 and 15.44 Hz, 1H), 3.04 (dd, *J* = 7.89 and 15.44 Hz, 1H). ^{11}B NMR (29 MHz, 0.5 N NaOH): δ 3.9. HR-FAB-MS (m +H-2H_2O in glycerol matrix): Calcd. for $C_{12}H_{16}BFNO_5$, 284.111. Found: 284.112

Anal. Calcd. for $C_9H_{11}BFNO_4$: C, 47.6; H, 4.9; N, 6.2. Found: C, 47.7; H, 4.9; N 6.3

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PREPARATION OF *bis*-[SPIROFLUORENE-9,4'-(1-AZA-2-CYCLOPENTENE)[1,5-a]INDOLINE-8'-YL]SULFONE

Submitted by (10/26/99)

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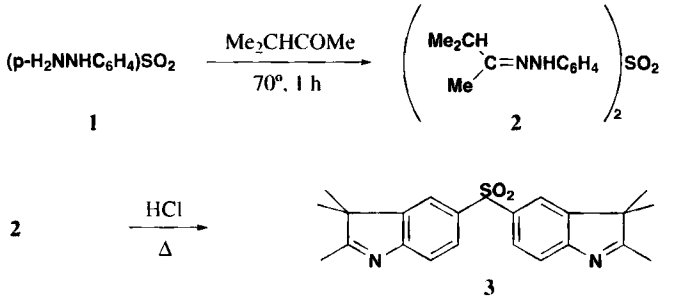
For many years, considerable attention has been directed toward the development of photochromic molecules. A large number of photochromic spiroindolines have been reported[1-4] and as a result, the preparation and study of their bichromophoric analogues are of great interest.[5] This communication describes the synthesis of symmetrical *bis*-(spiro[1,5-a]-indolines) **6a,b** containing isolated spiroindoline rings linked with a sulfone group.

The starting material, *bis*-[2,3,3-trimethylindolenin-5-yl]sulfone (**3**) was obtained by Fischer cyclization reaction of *bis*-[4-hydrazinophenyl]sulfone (**1**)[6] and methylisopropylketone in one step (*Scheme 1*), the *bis*-arylhydrazone **2** was not separated but used directly for further cyclization.



Scheme 1

Compound **2** in principle can lead to the two products on Fischer cyclization.[7] In particular, each hydrazone fragment of compound **2** possesses two sites for ring closure: the primary carbon atom of methyl group, producing 2-isopropylindole ring and the tertiary carbon atom of isopropyl group,