# A Short and Efficient Synthesis of 3-{2-[2-(Bromomethyl)thiazol-4-yl]ethynyl}-5-fluorobenzonitrile: A Precursor for PET Radioligand [<sup>18</sup>F]SP203

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Abstract: An improved synthesis of 3-{2-[2-(bromomethyl)thiazol-4-yl]ethynyl}-5-fluorobenzonitrile, a precursor for PET radioligand [18F]SP203, is described, wherein a new synthon was employed for Sonogashira coupling with 3-bromo-5-fluorobenzonitrile. The new five-step synthesis provided the title compound in 56% overall yield starting from 4-bromo-2-formylthiazole.

Key words: PET ligand, fluorine, Sonogashira coupling, palladium, bromination

Glutamate is the principal excitatory neurotransmitter in the central nervous system (CNS), and regulates a variety of neuronal activities through interacting with specific receptors.<sup>1</sup> The metabotropic glutamate receptors (mGluRs) are G protein coupled receptors and classified as belonging to groups I, II, or III.<sup>2,3</sup> Group I mGluRs include mGluR1 and mGluR5 subtypes. Activation of mGluR5 stimulates phospholipase, leading to phosphoinositide hydrolysis and increase of intracellular Ca<sup>2+</sup> levels.<sup>2,3</sup> Development of specific mGluR5 antagonists is of current interest, which could lead to useful therapeutics for a variety of disorders.<sup>4-6</sup> 3-Fluoro-5-{2-[2-(fluoromethyl)thiazol-4-yl]ethynyl}benzonitrile (SP203, 1, Figure 1), a recently synthesized mGluR5 antagonist, was found to have exceptionally high affinity and potency in a phosphoinositol assay for mGluR5.6 The corresponding radioligand [<sup>18</sup>F]SP203 (2) was prepared from the bromomethyl analogue, 3-{2-[2-(bromomethyl)thiazol-4yl]ethynyl-5-fluorobenzonitrile (3), and [<sup>18</sup>F]fluoride ion.  $[^{18}F]SP203$  (2) was found to be effective as a positron emission tomography (PET) radioligand in rhesus monkey.<sup>7</sup> [<sup>18</sup>F]SP203 is now being studied with PET in human subjects since it shows excellent imaging properties devoid of issues from radiodefluorination seen in animals.<sup>8</sup>

As part of an ongoing research program, multigram quantities of 3 were required. Compound 3 was previously pre-



Figure 1 Structures of SP203 (1), [<sup>18</sup>F]SP203 (2), and 3

yield 18% overall pared in from 4-bromo-2formylthiazole (4) using a nine-step procedure (Scheme 1).<sup>6</sup> Reactions were carried out on milligram quantities and therefore difficulties in the scale-up reactions were anticipated. Of particular concern was the large-scale preparation and purification of the unstable stannyl intermediate 5, which was crucial for the success of the synthesis. Therefore, two alternative synthetic approaches for 3 were investigated.

The first approach is outlined in Scheme 2. Sonogashira coupling of 4-bromo-2-formylthiazole (4) with (trimethylsilyl)acetylene using bis(triphenylphosphine)palladium(II) chloride [(Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>)], CuI, and triethylamine afforded 4-trimethylsilylethynylthiazole-2-carbaldehyde (6) in 50% yield. When tetrakis(triphenylphosphine)palladium  $[Pd(PPh_3)_4]$  was used as catalyst, a 63% yield of 6 was realized. Coupling of 6 with 3-bromo-5-fluorobenzonitrile (7) using Pd(PPh<sub>3</sub>)<sub>4</sub>, CuI, and tetrabutylammonium fluoride (TBAF) in 1,2-dimethoxyethane (DME) then 3-fluoro-5-(2-formylthiazol-4-yl)benzonitrile provided





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Scheme 2 Attempted synthesis of 9

(8) in 37% yield. Unfortunately, subsequent sodium borohydride reduction of 8 did not afford the expected alcohol 9. Instead, a product without the triple bond, as judged by <sup>1</sup>H and <sup>13</sup>C NMR analyses, was isolated in 58% yield. It appeared that sodium borohydride reduced both the triple bond and the aldehyde group of 8.

Alternatively, reduction of aldehyde 4 with sodium borohydride in methanol at 0 °C afforded (4-bromothiazol-2yl)methanol (10) in 91% yield (Scheme 3).<sup>6</sup> The alcohol was then protected by treatment with tert-butyldimethylsilyl chloride (TBDMSCl) to give 4-bromo-2-(tert-butyldimethylsilyloxymethyl)thiazole (11) in 98% yield. Sonogashira coupling of 11 with (trimethylsilyl)acetylene using Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and CuI at 50 °C for 18 hours provided an 80% yield of 2-(tert-butyldimethylsilyloxymethyl)-4-[2-trimethylsilyl)ethynyl]thiazole (12).When  $Pd(PPh_3)_4$  was used as catalyst, the reaction was complete in 2.5 hours and 12 was obtained in 82% yield. Subsequent coupling of 12 with 7 using  $Pd(PPh_3)_4$ , CuI, triethylamine, and TBAF at 80 °C afforded 3-fluoro-5-{2-[2-(hydroxymethyl)thiazol-4-yl]ethynyl}benzonitrile (9) in 55% yield. In this reaction, TBAF was slowly added to the mixture containing 12, 7, and the catalysts over 45 minutes, and the reaction mixture was heated for another 50 minutes. Further optimization of the reaction conditions, including reduced TBAF, addition time (3 min), and the subsequent heating time (12 min) resulted in less by-product formation and increased the yield of 9 to 91%. Bromination of 9 was first attempted using 1.1 equivalents of triphenylphosphine and 20 equivalents of carbon tetrabromide in benzene following the reported procedure.<sup>6</sup> Unfortunately, column purification of the crude product gave only 31% yield of 3. The poor yield and use of a large excess of toxic carbon tetrabromide and benzene prompted investigation of an alternative bromination method, which would be applicable to the large scale reaction. Thus, pilot-scale reaction of 9 with 1.1 equivalents of N-bromo-(NBS) succinimide and 1.1 equivalents of triphenylphosphine in dichloromethane at 0 °C afforded 3 in 87% yield. Finally, scale-up bromination of 9 using these optimized reaction conditions furnished 3 in 74% vield.

In summary, significant improvements have been made to the previously reported synthesis of  $3-\{2-[2-(bromometh$  $yl)thiazol-4-yl]ethynyl\}-5-fluorobenzonitrile ($ **3**) via synthesis of a new synthon**12**for the Sonogashira coupling



Scheme 3 Synthesis of 3

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reaction. The improved five-step synthesis provided the title compound in 56% overall yield from 4-bromo-2formylthiazole (4). The present approach is general and 12 will be useful for preparing related ligands through Sonogashira cross-coupling reactions with substituted bromobenzenes.

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker Avance spectrometer (300 MHz) in CDCl<sub>3</sub> using TMS as internal standard. 4-Bromothiazol-2-carbaldehyde was purchased from Frontier Scientific. HRMS were performed at the University of Michigan, Ann Arbor. MS spectra (MS) were run on a Perkin-Elmer Sciex APR150 EX mass spectrometer outfitted with APCI (atmospheric pressure chemical ionization) or ESI (turbospray) sources. Flash column chromatography was done using E. Merck silica gel 60 (230-400 mesh). Analytical TLC was carried out using EMD silica gel 60 F<sub>254</sub> TLC plates. Elemental analyses were done by Atlantic Microlab Inc., Norcross, GA.

#### 4-Trimethylsilylethynylthiazole-2-carbaldehyde (6)

A solution of 4-bromothiazole-2-carbaldehyde (4; 0.96 g, 5.00 mmol) in Et<sub>3</sub>N (25 mL) was degassed with argon for 10 min. Afterwards, CuI (110 mg, 0.58 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (320 mg, 0.28 mmol), and (trimethylsilyl)acetylene (1.06 g, 10.8 mmol) were added. The reaction mixture was heated and stirred at 50 °C for 40 min under argon. After cooling to r.t., the mixture was filtered through a pad of Celite. The Celite pad was washed with Et<sub>3</sub>N (100 mL). The filtrate and the washings were combined and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel using 5  $\rightarrow$  10% EtOAc in hexane afforded 6 as a yellow solid (0.68 g, 63%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 0.29$  (s, 9 H), 7.83 (d, J = 1.4 Hz, 1 H), 9.97 (d, *J* = 1.2 Hz, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = -0.4$ , 96.6, 96.7, 129.5, 140.4, 165.0, 183.2.

MS (APCI):  $m/z = 210.1 [M + H]^+$ .

Anal. Calcd for C<sub>9</sub>H<sub>11</sub>NOSSi: C, 51.64; H, 5.30; N, 6.69. Found: C, 51.85; H, 5.37; N, 6.60.

#### 3-Fluoro-5-(2-formylthiazol-4-yl)benzonitrile (8)

A solution of 6 (419 mg, 2.00 mmol) and 3-bromo-5-fluorobenzonitrile (7; 479 mg, 2.39 mmol) in anhyd DME (14 mL) was degassed with argon for 10 min. Afterwards, CuI (29.4 mg, 0.15 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (85.7 mg, 0.07 mmol), and Et<sub>3</sub>N (0.99 g, 9.83 mmol) were added, and the reaction mixture was heated at 80  $^{\circ}\mathrm{C}$  for 10 min while argon was bubbled into the solution. TBAF (1 M solution in THF, 2 mL, 2.00 mmol) was added to the brown solution over 35 min. After addition, the dark solution was further stirred at 80 °C for 50 min, cooled to r.t., and concentrated under reduced pressure. The dark residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with H<sub>2</sub>O  $(2 \times 40 \text{ mL})$  and brine (40 mL). The organic phase was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel using  $5 \rightarrow 30\%$  EtOAc in hexane afforded 8 as an off-white solid (0.19 g, 37%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.40 (ddd, *J* = 7.8, 2.4, 1.3 Hz, 1 H), 7.53 (ddd, J = 8.7, 2.4, 1.3 Hz, 1 H), 7.68 (s, 1 H), 7.97 (d, *J* = 1.2 Hz, 1 H), 10.0 (d, *J* = 1.1 Hz, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 85.2, 86.4 (d, *J* = 3.3 Hz), 114.5 (d, *J* = 10.2 Hz), 116.6 (d, *J* = 3.3 Hz), 119.7 (d, *J* = 24.7 Hz), 123.3 (d, J = 22.9 Hz), 125.5 (d, J = 10.0 Hz), 130.4, 131.3 (d, J = 3.5 Hz), 139.1, 161.9 (d, J = 251.9 Hz), 165.7, 183.0.

HRMS (ESI): m/z [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>6</sub>FN<sub>2</sub>OS: 257.0185; found: 257.0185.

#### (4-Bromothiazol-2-yl)methanol (10)

To a stirred solution of 4 (1.97 g, 10.0 mmol) in MeOH (15 mL) at 0 °C was added NaBH<sub>4</sub> (0.39 g, 10.0 mmol) in portions over 10 min. After stirring at 0 °C for 15 min, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with  $H_2O(2 \times 50 \text{ mL})$  and brine (40 mL). The organic phase was dried (Na2SO4) and concentrated under reduced pressure to afford 10 as a colorless oil (1.76 g, 91%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 3.76$  (t, J = 6.0 Hz, 1 H), 4.94 (d, *J* = 5.9 Hz, 2 H), 7.21 (s, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 61.8, 117.0, 124.4, 173.0.

MS (ESI):  $m/z = 194.2 [M + H]^+ (^{79}Br), 196.2 [M + H]^+ (^{81}Br).$ 

#### 4-Bromo-2-(tert-butyldimethylsilyloxymethyl)thiazole (11)

To a stirred solution of 10 (1.73 g, 8.92 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at r.t. was added imidazole (0.67 g, 9.84 mmol) followed by TBDMSCl (1.48 g, 9.82 mmol). After stirring at r.t. for 90 min, the mixture was treated with aq sat. NH<sub>4</sub>Cl (10 mL) and stirred for additional 5 min. The organic layer was separated and the aqueous layer was further extracted with  $CH_2Cl_2$  (2 × 20 mL). The combined organic extracts were dried (Na2SO4) and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel using  $5 \rightarrow 10\%$  EtOAc in hexane afforded **11** as a colorless oil (2.70 g, 98%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 0.13$  (s, 6 H), 0.95 (s, 9 H), 4.94 (s, 2 H), 7.17 (s, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = -5.5$ , 18.2, 25.7, 63.0, 116.4, 124.3. 174.4.

MS (APCI):  $m/z = 308.4 [M + H]^+ (^{79}Br), 310.2 [M + H]^+ (^{81}Br).$ 

#### 2-(tert-Butyldimethylsilyloxymethyl)-4-[2-(trimethylsilyl)ethynyl]thiazole (12)

A solution of 11 (2.67 g, 8.66 mmol) in Et<sub>3</sub>N (50 mL) was degassed with argon for 10 min. Afterwards, CuI (177 mg, 0.93 mmol),  $Pd(PPh_3)_4$  (529 mg, 0.46 mmol), and (trimethylsilyl)acetylene (1.80 g, 18.3 mmol) were added, and the reaction mixture was stirred at 50 °C for 2.5 h under argon. After cooling to r.t., the mixture was filtered through a pad of Celite. The Celite pad was washed with Et<sub>3</sub>N (100 mL). The filtrate and the washings were combined and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel using  $0 \rightarrow 5\%$  EtOAc in hexane afforded 12 as a pale-brown oil (2.44 g, 87%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 0.12$  (s, 6 H), 0.24 (s, 9 H), 0.94 (s, 9 H), 4.93 (s, 2 H), 7.42 (s, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta = -5.5, -0.3, 18.2, 25.7, 63.1, 94.4,$ 98.4, 123.0, 137.1, 173.1.

HRMS (ESI): m/z [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>28</sub>NOSSi<sub>2</sub>: 326.1430; found: 326.1419.

#### 3-Fluoro-5-{2-[2-(hydroxymethyl)thiazol-4-yl]ethynyl}benzonitrile (9)

A solution of 12 (2.28 g, 7.00 mmol) and 7 (1.68 g, 8.37 mmol) in anhyd DME (55 mL) was degassed with argon for 10 min. Afterwards, CuI (99.0 mg, 0.52 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (308 mg, 0.27 mmol), and Et<sub>3</sub>N (3.56 g, 35.2 mmol) were added, and the reaction mixture was stirred at 80 °C for 10 min while argon was bubbled into the solution. TBAF (1 M solution in THF, 14 mL, 14.0 mmol) was added to the brown solution over 3 min. After addition, the dark solution was further stirred at 80 °C for 12 min, cooled to r.t., and concentrated under reduced pressure. The dark residue was dissolved in  $CH_2Cl_2$  (250 mL), and washed with  $H_2O$  (2 × 125 mL) and brine

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(150 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel using  $20 \rightarrow 50\%$  EtOAc in hexane afforded **9** as a white solid (1.65 g, 91%).

<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):  $\delta = 3.35$  (m, 1 H), 4.99 (d, J = 5.8 Hz, 2 H), 7.35 (ddd, J = 7.8, 2.4, 1.4 Hz, 1 H), 7.47 (ddd, J = 8.8, 2.4, 1.4 Hz, 1 H), 7.60 (s, 1 H), 7.62 (m, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 62.1, 85.5 (d, J = 3.2 Hz), 86.5, 114.3 (d, J = 10.2 Hz), 116.7 (d, J = 3.2 Hz), 119.2 (d, J = 24.8 Hz), 123.1 (d, J = 23.0 Hz), 124.5, 126.1 (d, J = 10.1 Hz), 131.2 (d, J = 3.5 Hz), 135.9, 161.9 (d, J = 251.5 Hz), 172.1.

MS (ESI):  $m/z = 259.5 [M + H]^+$ .

#### 3-{2-[2-(Bromomethyl)thiazol-4-yl]ethynyl}-5-fluorobenzonitrile (3)

To a stirred solution of **9** (1.55 g, 6.00 mmol) and Ph<sub>3</sub>P (1.71 g, 6.42 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (90 mL) at 0 °C was added NBS (1.16 g, 6.52 mmol), and the reaction mixture was stirred at 0 °C for 35 min. The mixture was adsorbed on silica gel by evaporation under reduced pressure. Subsequent flash column chromatography on silica gel using  $5 \rightarrow 15\%$  EtOAc in hexane afforded **3** as an off-white solid (1.42 g, 74%); mp 109–110 °C (Lit.<sup>6</sup> mp 102–104 °C).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.73 (s, 2 H), 7.36 (ddd, *J* = 7.8, 2.5, 1.4 Hz, 1 H), 7.48 (ddd, *J* = 8.7, 2.5, 1.4 Hz, 1 H), 7.63 (m, 1 H), 7.66 (s, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 26.0, 85.6 (d, *J* = 3.5 Hz), 86.2, 114.4 (d, *J* = 10.2 Hz), 116.7 (d, *J* = 3.3 Hz), 119.4 (d, *J* = 24.7 Hz), 123.2 (d, *J* = 22.8 Hz), 125.9 (d, *J* = 10.0 Hz), 126.2, 131.2 (d, *J* = 3.5 Hz), 136.3, 161.9 (d, *J* = 251.7 Hz), 166.2.

MS (ESI):  $m/z = 321.0 [M + H]^+ (^{79}Br), 323.1 [M + H]^+ (^{81}Br).$ 

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