

The Pentafluorophenyl Sulfonate Ester as a Protecting Group for the Preparation of Biaryl- and Heterobiaryl-Sulfonate Esters

Barbara G. Avitabile^{*,†}, Clive A. Smith and
Duncan B. Judd

[†]Marie Curie Post Doctoral student

GlaxoSmithKline, New Frontiers Science Park, Third
Avenue, Harlow, Essex, UK CM19 5AW

barbara.g.avitabile@gsk.com

Supporting Information

General. Reagents for synthesis were purchased from Sigma-Aldrich, Lancaster, Boron Molecular, and Strem. Anhydrous solvents were purchased from Romil. All reactions were performed under an argon atmosphere.

Medium pressure chromatography was carried out on pre-packed Isco RediSep silica cartridges, using the ISCO SQ16X instrument. Analytical (TLC) was performed using silica gel 60 (Merck, 1 mm). ¹H and ¹⁹F NMR spectra were recorded on a Bruker 400 MHz spectrometer and reported as chemical shifts (δ) in ppm relative to TMS, and CFCl₃ respectively (δ= 0). Spin multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), double-doublet (dd) or multiplet (m); coupling constants (*J*) are given in Hz. The permanent presence of solvent in analytical samples was corroborated by ¹H NMR spectroscopy. MP were recorded using the Perkin-Elmer Electrothermal melting point apparatus (IA6304).

4-Bromobenzenesulfonic acid pentafluorophenyl ester (2). To a solution of pentafluorophenol (82g, 0.445 mol) in DCM (3.5 L) was added TEA (135.09g, 1.335 mol). The mixture was stirred at room temperature for 10 minutes; during which time a change of colour occurred from pale yellow to an intense orange colour indicative of the anion formation. A solution of 4-bromobenzenesulfonyl chloride (113.7g, 0.445 mol) in DCM was then added. The reaction mixture was allowed to stir at room temperature for one hour. The solvent was evaporated

under vacuum and the white solid was then washed with acetone and filtered; the organic filtrate was evaporated under vacuum to give a white solid.

Crystallisation from ether-hexane gave pure **2** (171g, 95 %) as a white solid. TLC (CH₂Cl₂/hexane 1:4): R_f 0.6 ¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, ²J = 4.62 Hz, H-C (2/6), H-C (3/5)), 7.83 (d, ²J = 4.62 Hz, H-C (3/5), H-C (2/6)). ¹⁹F NMR (400 MHz, CFCl₃): δ 150.45 (d, ²J = 6.308 Hz), 155.21 (d, ²J = 6.308 Hz), 160.90 (d, ²J = 6.308 Hz). MP 63.8-64.9 °C. Analysis calc'd for C₁₂H₄BrF₅O₃S: C, 35.75; H, 1.00; found: C, 35.71; H, 1.01

4-Biaryl-benzenesulfonic acid pentafluorophenyl esters (4-8).

Method A: To a solution of 4-bromobenzenesulfonic acid pentafluorophenyl ester **2** (1g, 2.48 mmol) in 1,4-dioxane (20 ml) were added Pd(PPh₃)₄ (0.052g, 0.0744 mmol, 3 mol%), Na₂CO₃ (0.785g, 7.44 mmol), and a solution of the boronic acid **3a-e** (2.98 mmol) in EtOH (4 ml). The reaction mixture was allowed to reflux at 104 °C for 12 hours. The inorganic residue was filtered off on a celite pad and washed with DCM (3 x 50 ml). The organic filtrate was evaporated under vacuum giving a dark residue which was further purified by column chromatography on a gradient of CH₂Cl₂/hexane.

Method B: To a solution of 4-bromobenzenesulfonic acid pentafluorophenyl ester **2** (1g, 2.48 mmol) in 1,4-dioxane (5 ml) were added solid Pd(PPh₃)₄ (0.052g, 0.0744 mmol, 3 mol%), Na₂CO₃ (0.785g, 7.44 mmol), and a solution of the boronic acid **3a-e** (2.98 mmol) in EtOH (1 ml). The reaction mixture was subjected to microwave irradiation at 180 °C for 1 hour. The inorganic residue was filtered off on a celite pad and washed with DCM (3 x 50 ml). The organic filtrate was evaporated under vacuum giving a dark residue which was further purified by column chromatography on a gradient of CH₂Cl₂/hexane.

Method C: To a solution of 4-bromobenzenesulfonic acid pentafluorophenyl ester **2** (1g, 2.48 mmol) in 1,4-dioxane (20 ml) were added Pd(PPh₃)₄ (0.052g, 0.0744 mmol, 3 mol%), K₂CO₃ (1.03g, 7.44 mmol), and a solution of the boronic acid **3a-e** (2.98 mmol) in EtOH (4 ml). The reaction mixture was allowed to reflux at 104 °C for 12 hours. The inorganic residue was filtered off on a celite pad and washed with DCM (3 x 50 ml). The organic filtrate was evaporated under vacuum giving a dark residue which was further purified by column chromatography on a gradient of CH₂Cl₂/hexane.

Method D: To a solution of 4-bromobenzenesulfonic acid pentafluorophenyl ester **2** (1g, 2.48 mmol) in 1,4-dioxane (20 ml) were added Pd(PPh₃)₄ (0.052g, 0.0744 mmol, 3 mol%), Na₂B₄O₇ (1.5g, 7.44 mmol), and a solution of the boronic acid **3a-e** (2.98 mmol) in EtOH (4 ml). The reaction mixture was allowed to reflux at 104 °C for 12 hours. The inorganic residue was

filtered off on a celite pad and washed with DCM (3 x 50 ml). The organic filtrate was evaporated under vacuum giving a dark residue which was further purified by column chromatography on a gradient of CH₂Cl₂/hexane.

3',4'-Dichloro-biphenyl-4-sulfonic acid pentafluorophenyl ester (4). The derivative was synthesised using the procedure described in **Method D**.

The product **4** was initially purified by column chromatography using the Isco SQ16X and further crystallised from 1,4-dioxane/EtOH obtaining a white solid (0.861g, 74%). TLC (CH₂Cl₂/hexane 1: 4): R_f 0.4 ¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, ²J = 4.4 Hz, H-C (2/6), H-C (3/5)), 7.69 (d, ²J = 4.2 Hz, H-C (3/5), H-C (2/6)), 7.66 (d, ¹J = 1 Hz, H-C' (2), H-C' (6)), 7.52 (d, ¹J = 4.2 Hz, H-C' (5), H-C' (6)), 7.41 (dd, ¹J = 4.2 Hz, H-C' (6), H-C' (2), ²J = 1 Hz, H-C' (6), H-C' (5)). ¹⁹F NMR (400 MHz, CFCl₃): δ 150.46, 154.98, 160.70. MP 120.4-121.2 °C Analysis calc'd for C₁₈H₇Cl₂F₅O₃S: C, 46.08; H, 1.50; found: C, 45.64; H, 1.25

4'-Methyl-biphenyl-4-sulfonic acid pentafluorophenyl ester (5). The derivative was synthesised using the procedure described in **Method D**.

The product **5** was initially purified by column chromatography using the ISCO SQ16X and further crystallised from 1,4-dioxane/EtOH obtaining a white solid (0.349g, 68%). TLC (CH₂Cl₂/hexane 1: 4): R_f 0.4 ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, ²J = 7 Hz, H-C' (2/6), H-C' (3/5)), 7.82 (d, ²J = 6.55 Hz, H-C (3/5), H-C (2/6)), 7.56 (d, ²J = 6.55 Hz, H-C (2/6), H-C (3/5)), 7.32 (d, ²J = 6.31 Hz, H-C' (3/5), H-C' (2/6)), 2.43 (s, 3). ¹⁹F NMR (400 MHz, CFCl₃): δ 150.45, 155.21, 160.90. MP 73.8-74 °C Analysis calc'd for C₁₉H₁₁F₅O₃S: C, 55.08; H, 2.68; found: C, 55.12; H, 2.72

4'-Methoxy-biphenyl-4-sulfonic acid pentafluorophenyl ester (6). The derivative was synthesised using the procedure described in **Method D**.

The product **6** was initially purified by column chromatography using the Isco SQ16X and further crystallised from 1,4-dioxane/EtOH obtaining a white solid (0.446g, 71%). TLC (CH₂Cl₂/hexane 1: 4): R_f 0.4 ¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, ²J = 8.05 Hz, H-C' (2/6), H-C' (3/5)), 7.78 (d, ²J = 8.08 Hz, H-C (3/5), H-C (2/6)), 7.61 (d, ²J = 7.07 Hz, H-C (2/6), H-C (3/5)), 7.01 (d, ²J = 7.07 Hz, H-C' (3/5), H-C' (2/6)), 3.88 (s, 3). ¹⁹F NMR (400 MHz, CFCl₃): δ 150.45, 155.21, 160.90. MP 96.2-97.3 °C Analysis calc'd for C₁₉H₁₁F₅O₄S: C, 53.03; H, 2.58; found: C, 52.93; H, 2.53

4-Pyridin-3-yl-benzenesulfonic acid pentafluorophenyl ester (7). The derivative was synthesised using the procedure described in **Method D**.

The product **7** was initially purified by column chromatography using the Isco SQ16X and further crystallised from 1,4-dioxane/EtOH obtaining a white solid (0.657g, 66%). TLC (CH₂Cl₂/hexane 1: 4): R_f 0.4 ¹H NMR (400 MHz, CDCl₃): δ 8.92 (d, ¹J = 1.57 Hz, H-C' (2), H-C' (6)), 8.75 (dd, ¹J = 4.52 Hz, H-C' (3), H-C' (4), ²J = 3.88 Hz, H-C' (3), H-C' (3), H-C' (6)), 8.17 (d, ²J = 6.75 Hz, H-C (2/6),

H-C (3/5), 7.98 (dd, ${}_1J = 1.55$ Hz, H-C' (5), H-C' (2), $J = 4.58$ Hz, H-C' (5), H-C' (4)), 7.84 (d, ${}_2J = 6.75$ Hz, H-C (3/5), H-C (2/6)), 7.47 (m, ${}_1$). ^{19}F NMR (400 MHz, CFCl_3): d 150.46, 154.97, 160.78. MP 121.6-122 $^\circ\text{C}$ Analysis calc'd for $\text{C}_{17}\text{H}_8\text{F}_5\text{NO}_3\text{S}$: C, 50.88; H, 2.01; N, 3.49; found: C, 50.57; H, 1.96; N, 3.38

4-(6-Methoxy-pyridin-3-yl)-benzenesulfonic acid pentafluorophenyl ester (8).

The derivative was synthesised using the procedure described in **Method D**.

The product **8** was initially purified by column chromatography using the Isco SQ16X and further crystallised from 1,4-dioxane/EtOH obtaining a white solid (0.748g, 70%). TLC (CH_2Cl_2 /hexane 1: 4): R_f 0.4 ^1H NMR (400 MHz, CDCl_3): δ 8.48 (d, ${}_1J = 2.09$ Hz, H-C' (2), H-C' (5)), 8.08 (d, ${}_2J = 5.53$ Hz, H-C (2/6), H-C (3/5)), 7.84 (dd, ${}_1J = 2.08$ Hz, H-C' (5), H-C' (2), $J = 6.9$ Hz H-C' (5), H-C' (4)), 7.77 (d, ${}_2J = 5.55$ Hz, H-C (3/5), H-C (2/6)), 6.90 (d, ${}_1J = 6.92$ Hz, H-C' (4), H-C' (5)), 4.01 (s, ${}_3$). ^{19}F NMR (400 MHz, CFCl_3): δ 150.46, 155.17, 160.89. MP 138.3-139.5 $^\circ\text{C}$ Analysis calc'd for $\text{C}_{18}\text{H}_{10}\text{F}_5\text{NO}_4\text{S}$: C, 50.12; H, 2.34; N, 3.25; found: C, 50.12; H, 2.34; N, 3.18