Fluoride Protects Boronic Acids in Copper (I)-mediated Click Reaction

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Experimental Section

General methods and materials
1H and 13C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer in deuterated chloroform (CDCl3), methanol-d4 (CD3OD), and DMSO-d6 ((CD3)2SO) with either tetramethylsilane (TMS) (0.00 ppm) or the NMR solvent as the internal reference unless otherwise specified. HPLC purification was carried out using a Shimadzu LC-10AT VP system, a Pinnacle C8 reverse phase column (10 mm × 250 mm, No. 9413571, for B-iii to I-iii) and a YMC-Pack SIL normal phase column (10 mm × 250 mm, No. 102505809, for purification and analysis of A-iii). HPLC analytical studies (stability and model reaction yield studies except for A-iii) were carried out using a Shimadzu LC-10AT VP system and a Pinnacle C8 reverse phase column (4.6 mm × 250 mm, No. 9413575). Boronic acids were obtained from Frontier Scientific and Combi-Blocks, Inc. Chemicals and solvents were bought from Aldrich or Acros and were used as received. Water used for HPLC studies was doubly distilled and further purified with a Milli-Q filtration system.

HPLC conditions for analytical studies (except A-iii, see synthesis section)
The stabilities and click reaction yields of different boronic acids were studied by HPLC (C8 RP analytical column, 260 nm). 20 μL of 50 μM boronic acid solution (diluted by methanol) was used for each injection. Elution condition: CH3CN-H2O, flow rate = 1.0 mL/min), 0-2 min (CH3CN 5 %), 2-18 min (CH3CN 5-95 %), 18-25 min (CH3CN 95-5 %), 25-30 min (CH3CN 95-5 %).

Stability studies
0.05 mmol boronic acid (1.0 equiv), 0.01 mmol TBTA ligand (0.2 equiv), and 0.02 mmol CuBr (0.4 equiv) were dissolved in a mixture of H2O/DMF/t-BuOH (0.2 mL/0.6 mL/0.2 mL) in a 3 mL vial [0.10 mmol CsF (2.0 equiv) was added only for the fluoride protected reactions]. The mixture was stirred at room temperature for 5 h. The solution was diluted by methanol (5 mL) and precipitate was filtered out. 5 μL of the reaction mixture (50 mM for each boronic acid) was diluted to 5 mL by methanol. 20 μL of the diluted reaction mixture was used for each injection to the analytical HPLC column. 20 μL of 50 μM pure boronic acid was used in HPLC studies for comparison. The ratio of the peak areas between the reaction mixture and pure boronic acid gives the degradation percentage.

Standard curve
After HPLC purification of triazole product (iii), 5-6 vials (20 mL) with different
concentrations (10-60 μM in methanol) of pure product (iii) were prepared. 20 μL product solution was used for each injection to HPLC. Standard curves were generated by plotting peak areas against concentrations. 5-6 data points were generated for each curve.

**Reaction yield studies**

5 μL of click reaction mixture (50 mM for each boronic acid starting material) was diluted to 5 mL by methanol. 20 μL of the diluted reaction mixture was used for each injection into HPLC. The peak area of the product (iii) was used for yield calculations using standard curves.

**Synthesis**

**General procedure for the model click reaction**

0.05 mmol azide (1.0 equiv), 0.05 mmol alkyne (1.0 equiv), 0.01 mmol TBTA ligand (0.2 equiv), and 0.02 mmol CuBr (0.4 equiv) were dissolved in a mixture of H2O/DMF/t-BuOH (0.2 mL/0.6 mL/0.2 mL) in a 3 mL vial. [0.10 mmol CsF (2.0 equiv) was added only for the fluoride protected click reactions] The mixture was stirred at room temperature for 5 h. The solution was diluted by methanol (5 mL) and precipitate was filtered out. The product was purified by HPLC (260 nm, Sil NP semi-preparation column for A-iii, C8 RP semi-preparation column for B-iii to I-iii).

**Tert-butyl 2-(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)acetate (A-iii).** HPLC elution condition: ethyl acetate-hexane, 0-2 min (hexane 90 %), 2-13 min (hexane 90-0 %), 13-13.5 min (hexane 0 %), 13.5-16 min (hexane 0-90 %), flow rate = 2 mL/min, RT = 11.5 min. This gave A-iii (79% without fluoride protection, 81% with fluoride protection) as a white solid. The same HPLC condition was used for the analytical studies of A-iii. 1H NMR (CDCl3) δ 7.93 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 5.13 (s, 2H), 1.53 (s, 9H); 13C NMR (CDCl3) δ 165.2, 147.2, 132.0, 129.5, 127.4, 122.1, 121.0, 84.1, 51.6, 28.0; MS (ESI+), m/z 340.1 (M+H)+.

**4-(1-(2-Tert-butoxy-2-oxoethyl)-1H-1,2,3-triazol-4-yl)phenylboronic acid (B-iii).** HPLC elution condition: isocratic flow of 30 % ACN in H2O, flow rate = 2 mL/min, RT = 9 min. This gave B-iii (57% without fluoride protection, 96% with fluoride protection) as a white solid. 1H NMR (CD3OD) δ 8.37 (s, 1H), 7.84 (m, 3H), 7.73 (s, 1H), 5.28 (s, 2H), 1.53 (s, 9H); 13C NMR (CD3OD) δ 167.5, 135.2, 128.5, 128.2, 128.1, 127.3, 125.6, 123.7, 116.8, 115.4, 84.5, 52.6, 28.2; MS (ESI-), m/z 302.2 (M-H)-, 316.1 (M-2H+CH3)-.

**4-((2-(4-(4-Bromophenyl)-1H-1,2,3-triazol-1-yl)acetamido)methyl)phenylboronic acid (C-iii).** HPLC elution condition: isocratic flow of 50 % ACN in H2O, flow rate = 3 mL/min, RT = 8 min. This gave C-iii (49 % without fluoride protection, 89% with fluoride protection) as a white solid. 1H NMR (DMSO-d6) δ 8.62 (d, J = 7.2 Hz, 1H),
8.01 (t, J = 7.2 Hz, 2H), 7.83 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 8.8 Hz, 2H), 7.26 (s, 2H), 5.24 (d, J = 7.6 Hz, 2H), 4.36 (s, 2H); 13C NMR (DMSO-d6) δ 165.6, 145.0, 134.1, 131.8, 129.9, 127.0, 126.3, 123.2, 120.7, 51.7; MS (ESI−), m/z 415.6 (M-H). 4-((4-(4-Bromophenyl)-1H-1,2,3-triazol-1-yl)methyl)phenylboronic acid (D-iii). HPLC elution condition: isocratic flow of 55 % ACN in H2O, flow rate = 3 mL/min, RT = 8 min. This gave D-iii (60 % without fluoride protection, 71 % with fluoride protection) as a white solid. 1H NMR (CD3OD) δ 8.37 (s, 1H), 7.75 (m, 3H), 7.59 (m, 3H), 7.36 (m, 2H), 5.67 (s, 2H); 13C NMR (CD3OD) δ 148.2, 133.2, 130.9, 128.5, 123.1, 122.6, 55.1; MS (ESI+), m/z 359.5 (M+H)+. 4-((2-(4-(4-Ethylphenyl)-1H-1,2,3-triazol-1-yl)acetamido)methyl)phenylboronic acid (E-iii). HPLC elution condition: isocratic flow of 50 % ACN in H2O, flow rate = 3 mL/min, RT = 7.5 min. This gave E-iii (79 % without fluoride protection, 94 % with fluoride protection) as a white solid. 1H NMR (CD3OD) δ 8.28 (s, 1H), 7.73 (m, 3H), 7.60 (s, 1H), 7.29 (m, 4H), 5.23 (s, 2H), 4.44 (s, 2H), 2.68 (m, J = 6.8 Hz, 2H), 1.27 (m, 3H); 13C NMR (CD3OD) δ 167.8, 146.0, 129.5, 129.1, 127.8, 126.8, 123.6, 53.3, 44.5, 29.7, 16.11; MS (ESI+), m/z 365.3 (M+H)+. 4-((2-(4-p-Tolyl-1H-1,2,3-triazol-1-yl)acetamido)methyl)phenylboronic acid (F-iii). HPLC elution condition: isocratic flow of 50 % ACN in H2O, flow rate = 3 mL/min, RT = 7 min. This gave F-iii (43% without fluoride protection, 77 % with fluoride protection) as a white solid. 1H NMR (CD3OD) δ 8.29 (s, 1H), 7.70 (d, J = 8.0 Hz, 3H), 7.58 (s, 1H), 7.26 (m, 4H), 5.23 (s, 2H), 4.58 (s, 1H), 4.43 (s, 2H), 2.37 (s, 3H); 13C NMR (CD3OD) δ 137.8, 129.2, 126.4, 125.3, 122.1, 51.8, 19.9; MS (ESI−), m/z 349.3 (M-H). 4-((2-(4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)acetamido)methyl)phenylboronic acid (G-iii). HPLC elution condition: isocratic flow of 40 % ACN in H2O, flow rate = 3 mL/min, RT = 8.5 min. This gave G-iii (47 % without fluoride protection, 83 % with fluoride protection) as a white solid. 1H NMR (CD3OD) δ 8.32 (s, 1H), 7.86 (t, J = 8.8 Hz, 2H), 7.72 (s, 1H), 7.59 (s, 1H), 7.29 (s, 2H), 7.18 (t, J = 8.8 Hz, 2H), 5.24 (s, 2H), 4.57 (s, 1H), 4.44 (s, 2H); 13C NMR (CD3OD) δ 127.4, 127.3, 126.4, 122.4, 115.5, 115.3, 51.8, 29.3; MS (ESI−), m/z 353.3 (M-H). 4-((2-(4-(4-Aminophenyl)-1H-1,2,3-triazol-1-yl)acetamido)methyl)phenylboronic acid (H-iii). HPLC elution condition: isocratic flow of 25 % ACN in H2O, flow rate = 3 mL/min, RT = 7.5 min. This gave H-iii (57 % without fluoride protection, 86 % with fluoride protection) as a white solid. 1H NMR (CD3OD) δ 8.16 (s, 1H), 7.60 (m, 4H), 7.30 (s, 2H), 7.30 (s, 2H), 5.23 (s, 2H), 4.45 (s, 2H); 13C NMR (CD3OD) δ 163.5, 133.5, 131.3, 129.3, 126.4, 121.0, 115.1, 51.8, 35.6; MS (ESI+), m/z 366.3.
(M+CH₃)⁺.

4-((2-(4-(4-Boroxophenyl)-1H-1,2,3-triazol-1-yl)acetamido)methyl)phenylboronic acid (I-iii). HPLC elution condition: isocratic flow of 25 % ACN in H₂O, flow rate = 3 mL/min, RT = 7.5 min. This gave I-iii (43 % without fluoride protection, 86 % with fluoride protection) as a white solid. ¹H NMR (CD₃OD) δ 8.38 (s, 1H), 7.84 (m, 3H), 7.73 (m, 2H), 7.62 (s, 1H), 7.33 (m, 2H), 5.27 (s, 2H), 4.60 (s, 1H), 4.47 (s, 2H); ¹³C NMR (CD₃OD) δ 167.8, 137.1, 135.6, 127.9, 125.8, 124.1, 53.3, 30.4; MS (ESI+), m/z 395.3 (M+CH₃)⁺, 409.4 (M-H+2CH₃)⁺, 409.4 (M-2H+2CH₃+Na)⁺.
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TIC: from Sample 3 (34c006) of Data34c.wiff (Turbo Spray)

Intensity, cps

+Q1: Exp 1, 14.076 to 14.987 min from Sample 3 (34c006) of Data34c.wiff (Turbo Spray), subtracted (8.579 to 13.200 min)

Intensity, cps

m/z, amu
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$M_r = 238.00$

$$\text{CH}_2\text{O}_4\text{H}_4$$
C:\shan\12-5-09 45(2) 000.dat, SPD-10AVvp Ch1-260nm
C:\mnt\12-30-08 00.dat, SPD-10AVvp Ch1-260nm