Facile amidinations of 2-aminophenylboronic acid promoted by boronate ester formation

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General Experimental Methods:
Acetonitrile was distilled prior to use. All chemicals were purchased as reagent grade and used without further purification with the exception that 2-aminophenylboronic acid 1 (Alfa Aesar) was recrystallised from MeOH/H₂O before use. ¹H and ¹³C NMR spectra were obtained using a Bruker spectrometer (400 MHz). Signals are reported in terms of their chemical shift (δ in ppm) relative to DMSO (¹H, 2.50 and ¹³C, 39.5) and J coupling constants are in hertz (Hz). For ¹H spectra, multiplicities, integration, intensity, coupling constants and assignment values are reported. Multiplicities are indicated using standard notation; singlet (s), doublet (d), doublet of doubles (dd), triplet (t) and multiplet (m). Mass spectral analysis (MS) was performed using a Bruker Esquire 3000 electrospray ionisation mass spectrometer. IUPAC names are derived from structures where B-N interactions are treated as dative bonds (non-covalent) for all compounds.

General Method A for amidination of 2-aminophenylboronic acid (1):
To a neat solution of nitrile (2 mL), salicylic acid (10 mg, 0.072 mmol) and 1 as free base (9.9 mg, 0.072 mmol) were added and stirred at 343 K for 2 hours under argon, monitoring via TLC (DCM:MeOH, 10:1, Rf 0.28 for 5). The reaction mixture was then allowed to crystallise out of solution to give the desired amidine product as crystalline solid in most cases. The yields listed for compounds 5-7 below are isolated yields using this method.

General Method B for amidination of 2-aminophenylboronic acid (1):
2-aminophenylboronic acid 1 (9.9 mg, 0.072 mmol) was dissolved in dry CHCl₃ (4 ml) in a glass round bottom by stirring under argon. Salicylic acid (10 mg, 0.072 mmol) was added and left to stir for 1 hour during which time a white precipitate formed. The sample was filtered to collect 17.5 mg a white solid. ESMS +ve ion mode (MeOH): m/z observed 261.6, calculated [M+Na⁺] 262.06, Boron Isotopes: ¹⁰B 22% and ¹¹B 78%.
This sample was left under high vacuum for 24 hours before it was dissolved in nitrile under argon and heated at 303 K for 4 hours. Percent conversion was estimated by NMR integration of the amidine NH proton peaks relative to the total aromatic proton peaks (including both 1 and product) in DMSO-d₆ solvent.
Catechol and salicylate esters of (2-acetimidamidophenyl)boronic acid:
Yield 33% and 68% (respectively). Clear crystalline solids.

Catechol ester:

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\text{1H NMR (400 MHz, DMSO): } \delta 2.30 (s, 3H, CH\textsubscript{3}), 6.50 (m, 4H, ArH), 6.99 (m, 2H, ArH), 7.30 (m, 2H, ArH), 9.19 (s, 1H, NH), 11.04 (s, 1H, C=NH) \text{ ppm. ESMS (m/z) } [\text{M-H}^+] \text{ observed 250.5, calculated } [\text{C}_{14}\text{H}_{12}\text{BN}_{2}\text{O}_{2}-\text{H}_{2}\text{O}] \text{ 251.07. Boron isotopes: } ^{10}\text{B} 23.6\% \text{ and } ^{11}\text{B} 76.4\%.
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Crystal data for C\textsubscript{14}H\textsubscript{13}BN\textsubscript{2}O\textsubscript{2}-H\textsubscript{2}O (1118th21): M = 270.1, monoclinic, space group P2\textsubscript{1}/c, a = 7.0763(5), b = 9.3343(7), c = 20.5929(14) Å, β = 92.821(7)°, U = 1358.6(2) Å\textsuperscript{3}, Z = 4, D\textsubscript{c} = 1.32 g cm\textsuperscript{-3}, μ = 0.092 mm\textsuperscript{-1}, Crystal size: 0.47 x 0.37 x 0.34 mm. T\textsubscript{min/max} = 0.97, 1.00. 8052 reflections collected, 3760 unique (R\text{int} = 0.025), R = 0.054 [2877 reflections with I > 2s(I)], wR\text{F}^2 = 0.185 (all data). CCDC#1848684. IUPAC name: N-(2-(benzo[d][1,3,2]dioxaborol-2-yl)phenyl)acetimidamide.

Salicylate ester (5):

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\text{1H NMR (400 MHz, DMSO): } \delta: 2.33 (s, 3H, CH\textsubscript{3}), 6.76 (dd, J = 8.2, 1.0 Hz, 1H, ArH), 6.86 (td, J = 7.5, 1.1 Hz, 1H, ArH), 7.08 (m, 2H, ArH), 7.29 (t, J = 7.4 Hz, 2H), 7.40 (ddd, J = 8.3, 7.2, 1.8 Hz, 1H), 7.78 (dd, J = 7.7, 1.8 Hz, 1H), 9.38 (s, 1H, NH), 11.16 (s, 1H, C=NH) \text{ ppm.}
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Crystal data for C\textsubscript{15}H\textsubscript{13}BN\textsubscript{2}O\textsubscript{3} (1110th19): M = 280.1, monoclinic, space group P2\textsubscript{1}/c, a = 11.2723(8), b = 11.6971(6), c = 10.6896(6) Å, β = 101.099(6)°, U = 1383.1(2) Å\textsuperscript{3}, Z = 4, D\textsubscript{c} = 1.34 g cm\textsuperscript{-3}, μ = 0.094 mm\textsuperscript{-1}, Crystal size: 0.35 x 0.25 x 0.15 mm. T\textsubscript{min/max} = 0.99, 1.00. 6482 reflections collected, 3718 unique (R\text{int} = 0.027), R = 0.058 [2422 reflections with I > 2s(I)], wR\text{F}^2 = 0.174 (all data). CCDC#1848682. IUPAC name: N-(2-(4-oxo-4H-benzo[d][1,3,2]dioxaborinin-2-yl)phenyl)acetimidamide.
Proton- and C13-NMR of catechol ester of (2-acetimidamidophenyl)boronic acid:
Proton NMR of salicylate ester of (2-acetimidamidophenyl)boronic acid (5):

Salicylate ester of (2-(2-methoxyacetimidamido)phenyl)boronic acid (6):

Yield 60%. Clear crystalline solid; $^1$H NMR (400 MHZ, DMSO): $\delta$ 2.51 (s, 3H, CH$_3$) 2.83 (t, $J = 6.2$ Hz, 2H, CH$_2$), 3.71 (t, $J = 6.2$ Hz, 2H, CH$_2$), 6.76 (dd, $J = 8.2$, 1.0 Hz, 1H, ArH), 6.86 (td, $J = 7.5$, 1.1 Hz, 1H, ArH), 7.10 (m, 2H, ArH), 7.28 (dd, $J = 7.5$, 1.4 Hz, 2H, ArH), 7.40 (ddd, $J = 8.3$, 7.2, 1.9 Hz, 1H, ArH), 7.78 (dd, $J = 7.8$, 1.8 Hz, 1H, ArH), 9.40 (s, 1H, NH), 11.17 (s, 1H, C=NH) ppm. $^{13}$C NMR (100 MHz, DMSO solution): $\delta$ 34.0, 58.4, 69.5, 115.3, 116.4, 118.7, 118.9, 125.1, 128.3, 129.8, 131.8, 135.0, 137.8, 159.8, 160.2, 163.6 ppm. ESMS ($m/z$) [M+Na$^+$] observed 346.5, calculated [C$_{17}$H$_{17}$BN$_2$O$_4$Na$^+$] 347.1. Boron isotopes $^{10}$B 20.7% and $^{11}$B 79.3%.

Crystal data for C$_{17}$H$_{17}$BN$_2$O$_4$ (1122h23): M = 324.13 monoclinic, space group P2$_1$/c, $a = 14.4042(11)$, $b = 9.165(5)$, $c = 13.2350(9)$ Å, $\beta = 113.504(8)\degree$, $U = 1602.2(2)$ Å$^3$, $Z = 4$, $D_c = 1.34$ g cm$^{-3}$, $\mu = 0.095$ mm$^{-1}$, Crystal size: 0.52 x 0.27 x 0.22 mm. $T_{\min}/T_{\max} = 0.98$, 1.00. 10442 reflections collected, 4470 unique ($R_{int} = 0.029$) $R = 0.049$ [3341 reflections with $I > 2s(I)$], $wR_F^2 = 0.152$ (all data). CCDC#1848685. IUPAC name: 2-methoxy-N-(2-(4-oxo-4H-benzo[d][1,3,2]dioxaborinin-2-yl)phenyl)acetimidamide.
Proton- and C13-NMR of 6:
Salicylate ester of (2-(2-bromoacetimidamido)phenyl)boronic acid (7): Yield 95%. Clear crystalline solid; $^1$H NMR (400 MHz, DMSO solution): $\delta$ 4.42 (s, 2H, CH$_2$), 6.75 (d, $J = 8.2$ Hz, 1H, CH), 6.86 (t, $J = 7.4$ Hz, 1H, ArH), 7.08 (td, $J = 7.0$, 1.6 Hz, 1H, ArH), 7.30 (m, 3H, ArH), 7.39 (m, 2H, ArH), 7.77 (dd, $J = 7.7$, 1.9 Hz, 1H, ArH), 9.08 (s, 1H, NH), 11.04 (s, 1H, C=NH) ppm. $^{13}$C NMR (100 MHz, DMSO solution): $\delta$: 59.8, 116.2, 117.7, 118.9, 125.6, 128.3, 129.9, 131.8, 135.2, 137.8, 156.8, 160.2, 161.4, 163.6 ppm. HRMS ($m/z$) [M+H$^+$] observed 359.0198/361.0178, calculated [C$_{15}$H$_{13}$BBrN$_2$O$_3^+$] 359.0203/361.0182. IUPAC name: 2-bromo-N-(2-(4-oxo-4H-benzo[d][1,3,2]dioxaborinin-2-yl)phenyl) acetimidamide.

Proton- and DEPT C13-NMR of 7:
(E)-5H-dibenzo[c,h][1,5,7,2,10]oxadiazadiborecine-5,7(12H)-dial (10):
A solution of 1 (117.7 mg, 0.8 mmol), catechol (85.9 mg, 0.8 mmol) and 3-phenyl-2-propynenitrile (100.0 mg, 0.8 mmol) in DMF (4 mL) was heated at 338 K for 5 hours. At this time no product had been produced via TLC (DCM:MeOH, 10:1) so the reaction mixture was increased to 383 K for 2 hours and monitored via TLC (DCM:MeOH, 10:1, R_f = 0.08) indicating the formation of a single product. The reaction mixture was concentrated in vacuo to yield 10 as a white solid.

^H NMR (400 MHz, DMSO solution): δ 2.57 (s, 1H, CH), 7.05 (m, 1H, ArH), 7.11 (td, J = 7.2, 1.2 Hz, 1H, ArH), 7.20 (ddt, J = 11.4, 7.4, 1.3 Hz, 2H, ArH), 7.47 (td, J = 7.6, 1.6 Hz, 1H, ArH), 7.56 (m, 1H, ArH), 7.60 (d, J = 8.7 Hz, 1H, ArH), 7.70 (dd, J = 7.3, 1.6 Hz, 1H, ArH), 8.42 (s, 1H, NH) ppm. ^1C NMR (100 MHz, DMSO solution): δ 115.6, 118.2, 124.7, 125.1, 126.8, 131.4, 132.8, 134.0, 137.2, 145.9, 147.8 ppm.

This material was dissolved in MeOH and cooled to produce flat disk-like crystals of 15 (~20 mg, 9%) that were suitable for analysis by X-ray crystallographic techniques.

ESMS (m/z) [M-H]^+ observed 292.4, calculated [C_{15}H_{16}B_{2}N_{2}O_{3}] 292.92.

Crystal data for C_{15}H_{16}B_{2}N_{2}O_{3} (1113th20): M = 293.9, monoclinic, space group P2_1/c, a = 11.3834(13), b = 10.8026(9), c = 12.7677(10) Å, β = 103.589(10), U = 1526.1(3) Å³, Z = 4, D_x = 1.33 g cm⁻³, μ = 0.087 mm⁻¹, Crystal size: 0.24 x 0.19 x 0.10 mm. T_min/max = 0.11, 1.00. 6288 reflections collected, 4066 unique (Rint = 0.064), R = 0.081 [2170 reflections with I > 2σ(I)], wR_F² = 0.217 (all data). CCDC#1848683. IUPAC name: (E)-5,7-dimethoxy-7,12-dihydro-5H-dibenzo[c,h][1,5,7,2,10]oxadiazadiborecine.
Proton- and C13-NMR spectra of 10: