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Synthesis of benzyloxycyanophenylboronic esters

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Abstract

The synthesis of six new benzyloxycyanoboronic esters: 2-benzyloxy-6-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**4a**), 4-benzyloxy-2-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**4b**), 4-benzyloxy-3-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**8a**), 2-benzyloxy-5-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**8b**), 3-benzyloxy-4-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**12a**), and 2-benzyloxy-5-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**12b**) is reported.

Keywords: benzyloxybenzonitriles; benzyloxycyanoboronic esters; palladium catalyzed cross-coupling.

Introduction

Boronic acids have been widely used in cross-coupling reactions for carbon-carbon bond formation (Suzuki, 1999; Littke et al., 2000). A typical preparation of arylboronic acids involves a reaction between an organoborate and an organometal (Li or Mg) species, usually prepared by magnesium insertion or lithium-halogen exchange of the corresponding aryl halides (Brown and Cole, 1983). This method has its limitations, however; first, it is difficult to apply it to substrates bearing functional groups not compatible with organolithium reagents such as esters and nitriles. Second, some aryllithium intermediates are intrinsically unstable, as is the case for several aromatic heterocycles (Gilman and Spatz, 1951). Alternately, arylboronic esters can be prepared from aryl halides or aryl triflates via a palladium-catalyzed cross-coupling reaction with tetraalkoxydiboron or dialkoxyhydroborane (Ishiyama et al., 1995; Murata et al., 2000). These methods tolerate a wide range of functional groups.

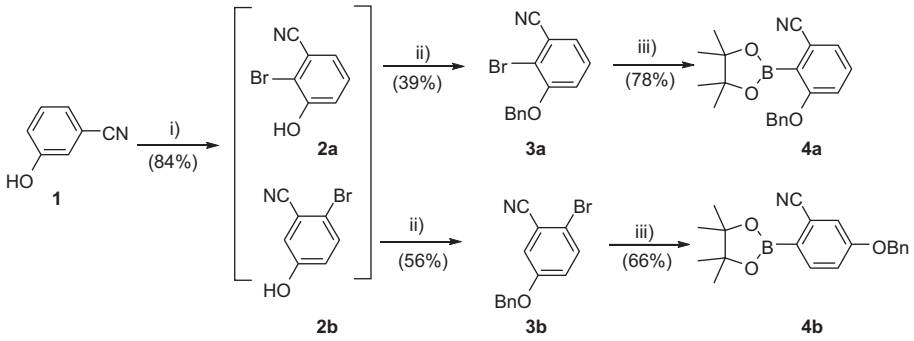
As part of an anti-infective drug discovery research program we needed to synthesize several different triaryl systems consisting of one or more hydroxy-substituted benzamidine groups. As these benzamidine-based triaryl systems are typically prepared by palladium-catalyzed Suzuki couplings with a substituted cyanophenylboronic acid, we required hydroxy-protected cyanophenols as precursors (Tidwell and Boykin, 2003). Following construction of the triaryl framework, the nitrile group can be converted to the amidine via reduction of an intermediate amidoxime (Kumar et al., 1996). Consequently, it seemed advantageous to use a hydroxy protecting group during the aryl couplings which could potentially be removed simultaneously during amidine formation. Therefore, we decided to explore the use of benzyl-protected boronic acid esters. A survey revealed that none of the benzyloxy cyanophenylboronic acid esters have been previously reported. This report describes the synthesis and characterization of six new isomeric benzyloxy cyanoboronic acid esters.

Results and discussion

We initiated this study by the synthesis of 2-benzyloxy-6-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**4a**) and 4-benzyloxy-2-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**4b**). As previously reported, bromination of 3-hydroxybenzonitrile (**1**) yields a mixture of 2-bromo-5-hydroxybenzonitrile (**2a**) and 2-bromo-3-hydroxybenzonitrile (**2b**) which could not be readily separated (Ismail et al., 2004). Alkylation of the mixture of phenols with benzyl bromide yields a mixture of the benzyloxy analogs **3a** and **3b**, which were more readily separated by column chromatography (Scheme 1) (Ismail et al., 2004).

Both **3a** and **3b** yielded NMR spectra that are similar and require assumptions for assignment (Ismail et al., 2004). It was deemed important to obtain unambiguous structural information for these compounds; therefore, we obtained an X-ray structure from crystals which were found to be that of **3b** (Figure 1) which was the structure assigned by NMR analysis. Table 1 contains the bond lengths and angles found for **3b**. The borylation of the bromo derivatives **3a** and **3b** using bis(pinacolato)diboran in presence of bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] and tricyclohexyl phosphine [PCy_3] as a ligand, KOAc as a base and dioxane as solvent provided 2-benzyloxy-6-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**4a**), and 4-benzyloxy-2-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**4b**), respectively.

Scheme 2 outlines the route used to prepare benzyloxy *m*-cyanophenylboronic esters: 4-benzyloxy-3-cyanophenyl-4,-4,5,5-tetramethyl-[1,3,2]dioxaborolane (**8a**) and 2-benzyloxy-5-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



Scheme 1: Reagents and Conditions. i) Br_2, HOAc
ii) benzyl bromide, K_2CO_3, Cs_2CO_3, MeCN
iii) bis(pinacolato)diboran, $Pd(dba)_2$, PCy_3, KOAc, dioxane

Scheme 1 Synthesis of benzyloxycyanophenylboronic esters **4a** and **4b.**

(**8b**) in three steps starting with the hydroxyl *m*-bromobenzaldehydes **5a,b**. Conventional alkylation of the hydroxyl-5-bromobenzaldehydes **5a,b** with benzyl bromide yields the corresponding benzyloxy compounds **6a,b**. The aldehyde group was converted into the cyano derivatives **7a,b** through the dehydration of the corresponding oximes using acetic anhydride. As before, the borylation of the bromo derivatives **7a,b** was achieved using bis(pinacolato)diboran in presence of $Pd(dba)_2$ and PCy_3 as a ligand, KOAc as a base and dioxane as solvent to provide phenylboronic acid esters (**8a,b**).

Finally, the synthesis of the *p*-cyanophenylboronic esters: 3-benzyloxy-4-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane (**12a**) and 2-benzyloxy-4-cyanophenyl-4,-4,5,5-tetramethyl-[1,3,2]dioxaborolane (**12b**) was achieved in three steps starting from the fluoro-4-bromobenzonitriles **9a,b** as outlined in Scheme 3. The key step in this approach employs displacement of fluoride under mild conditions using 2-(methylsulfonyl)ethoxide followed by elimination of vinylmethyl sulfone (Rodgers and Green, 2002; Ismail et al., 2004). It is worthy to note that in this process the yield obtained from the *o*-fluorobenzonitrile is higher than that for the *m*-fluorobenzonitrile. Conventional alkylation of the bromophenols **10a,b** with benzyl bromide yields the corresponding benzyloxy compounds **11a,b**. The borylation of the bromo derivative **11a,b** using bis(pinacolato)diboran in presence of $Pd(dba)_2$ and PCy_3 as a ligand, KOAc as a base and dioxane as solvent gave the target boronic acid esters **12a,b**.

Conclusion

We have described straightforward synthetic approaches for benzyloxy cyanoboronic acid esters: 2-benzyloxy-6-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**4a**),

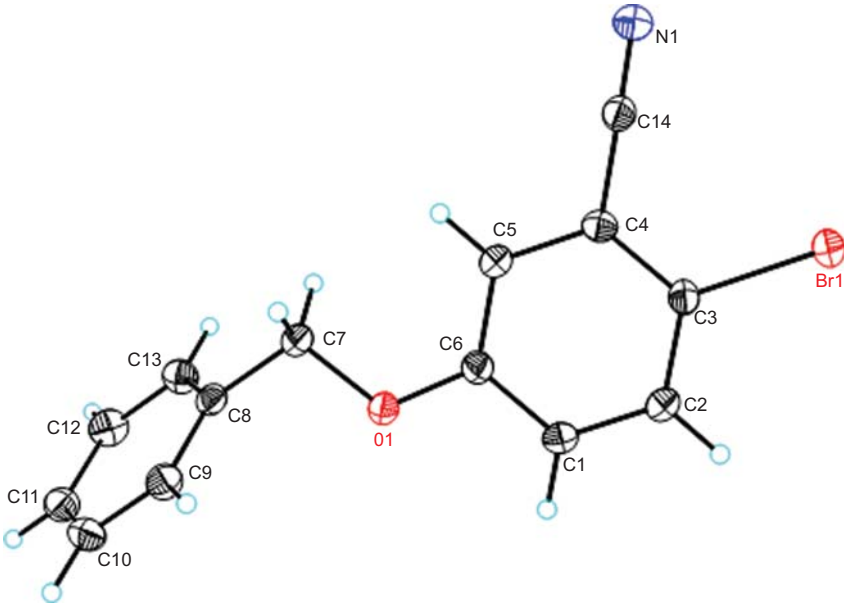


Figure 1 Crystal structure for **3b**.

Table 1 Bond lengths [Å] and angles [°] for **3b**.

Br(1)-C(3)	1.8900 (19)
C(1)-C(2)	1.379 (3)
C(1)-C(6)	1.396 (3)
C(1)-H(1A)	0.9500
C(2)-C(3)	1.393 (3)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.388 (3)
C(4)-C(5)	1.397 (3)
C(4)-C(14)	1.442 (3)
C(5)-C(6)	1.392 (3)
C(5)-H(5A)	0.9500
C(6)-O(1)	1.360 (2)
C(7)-O(1)	1.441 (2)
C(7)-C(8)	1.500 (3)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(13)	1.387 (3)
C(8)-C(9)	1.396 (3)
C(9)-C(10)	1.381 (3)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.390 (3)
C(10)-H(10A)	0.9500
C(11)-C(12)	1.383 (3)
C(11)-H(11A)	0.9500
C(12)-C(13)	1.387 (3)
C(12)-H(12A)	0.9500
C(13)-H(13A)	0.9500
C(14)-N(1)	1.145 (3)
C(2)-C(1)-C(6)	120.75 (18)
C(2)-C(1)-H(1A)	119.6
C(6)-C(1)-H(1A)	119.6
C(1)-C(2)-C(3)	119.80 (18)
C(1)-C(2)-H(2A)	120.1
C(3)-C(2)-H(2A)	120.1
C(4)-C(3)-C(2)	119.63 (18)
C(4)-C(3)-Br(1)	120.64 (15)
C(2)-C(3)-Br(1)	119.66 (15)
C(3)-C(4)-C(5)	120.91 (18)
C(3)-C(4)-C(14)	120.66 (18)
C(5)-C(4)-C(14)	118.44 (18)
C(6)-C(5)-C(4)	119.02 (18)
C(6)-C(5)-H(5A)	120.5
C(4)-C(5)-H(5A)	120.5
O(1)-C(6)-C(5)	124.37 (18)
O(1)-C(6)-C(1)	115.73 (17)
C(5)-C(6)-C(1)	119.89 (18)
O(1)-C(7)-C(8)	107.04 (15)
O(1)-C(7)-H(7A)	110.3
C(8)-C(7)-H(7A)	110.3
O(1)-C(7)-H(7B)	110.3
C(8)-C(7)-H(7B)	110.3
H(7A)-C(7)-H(7B)	108.6
C(13)-C(8)-C(9)	119.00 (18)
C(13)-C(8)-C(7)	120.53 (18)
C(9)-C(8)-C(7)	120.47 (18)
C(10)-C(9)-C(8)	120.40 (19)
C(10)-C(9)-H(9A)	119.8
C(8)-C(9)-H(9A)	119.8
C(9)-C(10)-C(11)	120.29 (19)
C(9)-C(10)-H(10A)	119.9
C(11)-C(10)-H(10A)	119.9
C(12)-C(11)-C(10)	119.53 (19)
C(12)-C(11)-H(11A)	120.2
C(10)-C(11)-H(11A)	120.2
C(11)-C(12)-C(13)	120.3 (2)
C(11)-C(12)-H(12A)	119.9
C(13)-C(12)-H(12A)	119.9
C(8)-C(13)-C(12)	120.52 (19)
C(8)-C(13)-H(13A)	119.7
C(12)-C(13)-H(13A)	119.7
N(1)-C(14)-C(4)	179.0 (2)
C(6)-O(1)-C(7)	117.42 (15)

4-benzyloxy-2-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (**4b**), 4-benzyloxy-3-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**8a**), 2-benzyloxy-5-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**8b**), 3-benzyloxy-4-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**12a**), and 2-benzyloxy-5-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane **(12b)** from readily available starting materials. The use of these analogs in the synthesis of triaryl hydroxybenzamidines will be reported in due course.

Experimental section

General

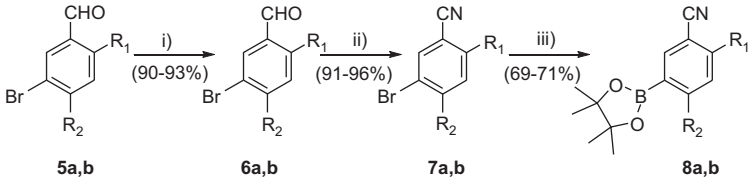
Melting points were recorded using a Thomas-Hoover (Uni-Melt) capillary melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60 F_{254} precoated aluminum sheets and detected under UV light. ^{1}H and ^{13}C NMR spectra were recorded employing a Bruker Avance 400 MHz spectrometer, and chemical shifts (δ) are in ppm relative to TMS as internal standard. Mass spectra were recorded on a VG analytical 70-SE spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA, USA) and are within ±0.4 of the theoretical values. All chemicals and solvents were purchased from Aldrich Chemical Co. or VWR.

Synthesis of hydroxy 2-bromobenzonitrile (2a,b)

To a solution of 3-hydroxybenzonitrile (8.33 g, 70 mmol) in acetic acid (80 ml) was dropwise added bromine (11.06 g). The reaction mixture was stirred overnight and treated with aqueous sodium thiosulfate to remove any remaining bromine. The excess solvent was removed under reduced pressure and diluted with water to yield (11.7 g, 84%) an inseparable white solid mixture (TLC very close R_f) of two products: 2-bromo-3-hydroxybenzonitrile (**2a**) and 2-bromo-5-hydroxybenzonitrile (**2b**). The mixture is pure enough to be used in the next step.

General procedures for synthesis of the benzyloxy bromobenzonitriles

Bromo hydroxybenzonitrile (3.96 g, 0.02 mol) was dissolved in (60 ml) MeCN. To this solution K_2CO_3 (8.28 g, 0.06 mol), Cs_2CO_3 (3.25 g, 0.01 mol) were added and the reaction mixture was heated at 40°C for 15 min. Benzyl bromide (3.40 g, 0.02 mol) was added and the reaction was heated at reflux for 3 h. Water (100 ml) was added and the reaction mixture was extracted with ethyl acetate, dried over sodium sulfate and concentrated. The crude mixture was purified by



No	R_1	R_2
5a	OH	H
5b	H	OH
6-8a	OBn	H
6-8b	H	OBn

Scheme 2: Reagents and Conditions. i) benzyl bromide, K_2CO_3, Cs_2CO_3, MeCN
ii) NH_2OH HCl, pyridine, acetic anhydride
iii) bis(pinacolato)diboran, $Pd(dba)_2$, PCy_3, KOAc, dioxane

Scheme 2 Synthesis of benzyloxycyanophenylboronic esters **8a** and **8b.**

flash column chromatography (20% EtOAc-hexanes). The synthesis, by various methods, and physical data of all the benzyloxy bromobenzonitriles, except **7b**, has been previously reported. Limited data for **7b** appears in a patent (Cooper et al., 2010).

3-Benzyloxy-2-bromobenzonitrile (3a)

The mixture of **2a** and **2b** was benzylated using the general procedure; afterwards, **3a** and **3b** were obtained pure by column chromatography. For compound **3a**, yield (6.56 g, 39%), mp 86–88°C (hexanes/ether), lit mp 93.5–94°C (Ismail et al., 2004). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54–7.46 (m, 5H, Ar-H), 7.49 (d, 1H, *J*=6.8 Hz, H-4), 7.41 (d, 1H, *J*=7.2 Hz, H-6), 7.15 (t, 1H, *J*=6.4, H-5), 5.17 (s, 2H, CH_2); ($CDCl_3$, 100 MHz) δ: 155.4 (C-3), 136.0 (C-1'), 129. 9 (C-5), 128.6 (C-3'), 128.2 (C-4'), 127.6 (C-2'), 126.5 (C-6), 117.3 (C-4), 115.8 (C-1), 115. 7 (CN), 114.4 (C-2), 70.7 (CH_2).

5-Benzyloxy-2-bromobenzonitrile (3b)

The mixture of **2a** and **2b** was benzylated using the general procedure; afterwards, **3a** and **3b** were obtained pure by column chromatography. For compound **3b**, yield (9.43 g, 56%), mp 103–102°C (hexanes/ether), lit mp 101.0–101.5°C (Ismail et al., 2004). ^{1}H NMR ($CDCl_3$, 400 MHz); δ: 7.53 (d, *J*=8.4 Hz, 1H, H-3), 7.63 (s, 1H, H-6), 7.45–7.33 (m, 5H), 7.38 (d, *J*=8.8 Hz, 1H, H-5), 5.15 (s, 2H); ($CDCl_3$, 100 MHz) δ: 157.7 (C-5), 137.0 (C-3), 134.2 (C-1'), 128.6 (C-3'), 128.2 (C-4'), 128.0 (C-2'), 126.5 (C-6), 122.5 (C-4), 120.5 (C-6), 117.1 (C-2), 115.0 (CN), 115.0 (C-1), 70.11 (CH_2).

2-Benzyloxy-5-bromobenzaldehyde (6a)

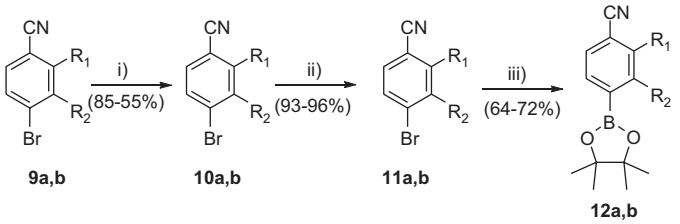
Using the general procedures for synthesis of the benzyloxy bromobenzonitrile; 5-bromo-2-hydroxybenzaldehyde (**5a**) (4.02 g, 0.02 mol) gave (5.42 g, 93%), mp 70–71°C, lit mp 67.5–69.5°C (Fresneda et al., 2001). ^{1}H NMR (DMSO-*d*6, 400 MHz) δ: 10.31 (s, 1H, CHO), 7.77 (dd, *J*=2.4, 8.8 Hz, 1H, H-4), 7.74 (d, *J*=2.4 Hz, 1H, H-6), 7.49 (d, *J*=7.6 Hz, 2H, Ar-H), 7.40 (t, *J*=7.6 Hz, 2H, Ar-H), 7.34 (d, *J*=7.2 Hz, 1H, Ar-H), 7.28 (d, *J*=8.8 Hz, 1H, H-3), 5.27 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d*6, 100 MHz) δ: 188.0 (CHO), 159.6 (C-2), 138.3 (C-4), 136.0 (C-1'), 129.2 (C-3'), 128.5 (C-4'), 128.1 (C-2'), 126.0 (C-1), 116.8 (C-3), 112.7 (C-5), 70.3 (CH_2).

4-Benzyloxy-3-bromobenzaldehyde (6b)

Using the general procedures for synthesis of the benzyloxy bromobenzonitrile; 3-bromo-4-hydroxybenzaldehyde (**5b**) (4.02 g, 0.02 mol) gave (5.24 g, 90%), mp 101–102°C, lit mp 97–98°C (Qin et al., 2008). ^{1}H NMR (DMSO-*d*6, 400 MHz); δ 9.87 (s, 1H, CHO), 8.13 (d, *J*=2.4 Hz, 1H, H-2), 7.93 (dd, *J*=8.4, 2.4 Hz, 1H, H-6), 7.39 (d, *J*=7.6 Hz, 2H, Ar-H), 7.29 (t, *J*=7.6 Hz, 2H, Ar-H), 7.18 (d, *J*=7.2 Hz, 1H, Ar-H), 7.10 (d, *J*=8.4 Hz, 1H, H-5), 5.25 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 188.3 (CHO), 159.6 (C-2), 138.3 (C-4), 136.0 (C-1'), 129.2 (C-3'), 128.5 (C-4'), 128.1 (C-2'), 126.0 (C-1), 116.8 (C-3), 112.7 (C-5), 70.2 (CH_2).

General method for synthesis of nitriles from aldehydes

A 5-ml pyridine solution of 0.7 g $NH_2OH{\cdot}HCl$ (6.95 g, 0.1 mol) was added to a stirred solution of **6a,b** (3.5 g, 0.012 mol) in (5 ml) pyridine and (5.5 ml) acetic anhydride and heated at reflux for 4 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted by ethyl acetate. The organic layer was dried (Na_2SO_4) and then concentrated to dryness under reduced pressure. The product was purified by column chromatography on silica gel using 10% EtOAc-hexanes.



No	R_1	R_2
9a	F	H
9b	H	F
10a	OH	H
10b	H	OH
11,12a	OBn	H
11,12b	H	OBn

Scheme 3: Reagents and Conditions. i) 2-(methylsulfonyl)ethanol, NaH, DMF
ii) benzyl bromide, K_2CO_3, Cs_2CO_3, MeCN
iii) bis(pinacolato)diboran, $Pd(dba)_2$, PCy_3, KOAc, dioxane

Scheme 3 Synthesis of benzyloxycyanophenylboronic esters **12a** and **12b.**

2-Benzyloxy-5-bromobenzonitrile (7a)

Yield (3.33 g, 96%), mp 79–80°C, lit mp 74–76°C (Zhang et al., 2010). ^{1}H NMR (DMSO-*d*6, 400 MHz); δ: 7.98 (d, *J*=2.4 Hz, 1H, H-6), 7.82 (dd, *J*=2.4, 8.8 Hz, 1H, H-4), 7.48 (d, *J*=7.4 Hz, 2H, Ar-H), 7.42 (t, *J*=7.6 Hz, 2H, Ar-H), 7.33 (d, *J*=7.2 Hz, 1H, Ar-H), 7.30 (d, *J*=8.8 Hz, 1H, H-3), 5.30 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 159.2 (C-2), 137.4 (C-4), 135.5 (C-1'), 135.4 (C-6), 128.4 (2×C-3'), 128.0 (C-4'), 127.3 (C-2'), 115.7 (C-3), 114.7 (CN), 111.8 (C-5), 102.9 (C-1), 70.4 (CH_2).

4-Benzyloxy-3-bromobenzonitrile (7b)

Yield (3.14 g, 91%), mp 98–100°C. ^{1}H NMR (DMSO-*d*6, 400 MHz); δ: 8.10 (s, 1H, H-2), 7.82 (d, *J*=8.4 Hz, 1H, H-6), 7.48 (d, *J*=6.8 Hz, 2H, H-2'), 7.41 (t, *J*=6.8 Hz, 2H, H-3'), 7.35 (d, *J*=6.8 Hz, 1H, H-5), 7.34 (d, *J*=6.8 Hz, 1H, H-4'), 5.32 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 158.0 (C-4), 136.2 (C-2), 135.5 (C-1'), 133.4 (C-6), 128.3 (C-3'), 127.9 (C-2'), 117.4 (C-5), 114.3 (CN), 111.6 (C-3), 104.4 (C-1), 70.3 (CH_2). Anal. calcd. for $C_{14}H_{10}BrNO$: C, 58.36; H, 3.50; N, 4.86. Found: C, 58.46; H, 3.49; N, 4.80.

Synthesis of hydroxy-4-bromobenzonitriles (10a,b)

To a stirred solution of 2-fluoro-4-bromobenzonitrile (2.0 g, 10 mmol) in 15 ml of anhydrous DMF was added 2-(methylsulfonyl) ethanol (1.86 g, 15 mmol) and the solution was cooled to 0°C. Sodium hydride (60% oil dispersion) (720 mg, 30 mmol) was added and the reaction mixture was allowed to warm to room temperature. The mixture was quenched with a 1-*N* HCl solution and extracted three times with ethyl acetate. The combined EtOAc was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography using 30% ethyl acetate in hexanes as the eluent.

4-Bromo-2-hydroxybenzonitrile (10a)

Yield (1.68 g, 85%), mp 165–166°C, lit mp 162.1–162.7°C (Ismail et al., 2004). ^{1}H NMR (DMSO-*d*6, 400 MHz); δ: 10.89 (s, 1H, OH); 7.57 (d, 1H, *J*=8.0 Hz, H-6), 7.18 (s, 1H, H-3), 7.13 (d, 1H, *J*=8.0 Hz, H). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 161.3 (C-2), 135.1 (C-6), 128.2 (C-4), 123.2 (C-5), 119.5 (C-3), 116.9 (CN), 98.9 (C-1).

4-Bromo-3-hydroxybenzonitrile (10b)

Yield (1.1 g, 55%), mp 158–160°C. ^{1}H NMR (DMSO-*d*6, 400 MHz); δ: 10.53 (s, 1H, OH), 7.6.1 (d, 1H, *J*=7.2 Hz, H-5), 7.23 (s, 1H, H-2), 7.04 (dd, 1H, *J*=1.6, 7.2 Hz, H-6). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 157.1 (C-3), 134.2 (C-5), 122.7 (C-6), 121.0 (C-2), 117.2 (CN), 114.8 (C-4), 112.6 (C-1).

2-Benzyloxy-4-bromobenzonitrile (11a)

Using the general procedures for synthesis of the benzyloxy bromobenzonitrile; 5-bromo-2-hydroxybenzonitrile (**10a**) (3.96 g, 0.02 mol) gave (5.35 g, 93%). mp 101–103°C, lit mp 105.3°C (Ismail et al., 2004). ^{1}H NMR (DMSO-*d*6, 400 MHz); δ: 7.43–7.37 (m, 5H, Ar-H), 7.33 (d, 1H, *J*=2.8 Hz, H-6), 7.18 (d, 1H, *J*=1.8 Hz, H-3), 7.15 (dd, 1H, *J*=8.0, 1.8 Hz, H-5), 5.17 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 160.7 (C-2), 135.0 (C-1'), 134.7 (C-6), 129.0 (C-3'), 128.9 (C-4), 128.6 (C-4'), 127.2 (C-2'), 124.7 (C-5), 116.8 (C-3), 101.6 (C-1), 115.8 (CN), 71.6 (CH_2).

3-Benzyloxy-4-bromobenzonitrile (11b)

Using the general procedures for synthesis of the benzyloxy bromobenzonitrile; 3-bromo-4-hydroxybenzonitrile (**10b**) (3.96 g, 0.02 mol) gave (5.53 g, 96%), mp 87–90°C, lit mp 113.5–114°C (Ismail et al., 2004). ^{1}H NMR (DMSO-*d*6, 400 MHz); δ: 7.51 (d, 1H, *J*=8.8 Hz, C-5), 7.34 (m, 5H, Ar-H), 7.19 (d, 1H, *J*=2.4 Hz, H-2), 7.05 (dd, 1H, *J*=8.8 Hz, H-6) 5.18 (s, 2H, CH_2). ^{13}C NMR (DMSO-*d*6, 100 MHz); δ: 157.9 (C-3), 135.6 (C-1'), 134.2 (C-5), 129.0 (C-3'), 128.7 (C-4'), 127.6 (C-2'), 121.8 (C-2), 120.1 (C-6), 117.2 (C-4), 116.4 (C-1), 116.1 (CN), 70.8 (CH_2).

General procedure for the synthesis of benzyloxycyanoboronic acid esters

To a degassed dioxane (30 ml) was added bis(dibenzylideneacetone) palladium (0.143 g, 0.25 mmol), and tricyclohexyl phosphine (0.168 g, 0.6 mmol) and the solution was allowed to stir for 30 min at 25°C. Aryl bromide (1.44 g, 5 mmol), KOAc (0.736 g, 7.5 mmol) and bis(pinacolato) diboran were added sequentially and the reaction mixture was vigorously stirred. The mixture was warmed to 90–100°C for 24 h under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (150 ml), then washed with water and passed through celite, dried (Na_2SO_4) and evaporated. The product was purified by column chromatography on silica gel using 30% EtOAc-hexanes as eluent.

2-Benzyloxy-6-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (4a)

Yield (1.3 g, 78%), mp 85–86°C. ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]; δ: 7.56 (m, 3H, H-3,4,5), 7.40 (d, *J*=7.2, 2H, H-2'), 7.38 (t, *J*=7.2 Hz, 2H, H-3'), 7.33 (d, *J*=7.6 Hz, 1H, H-4'), 5.17 (s, 2H, CH_2), 1.33 (s, 12H, 4 CH_3). ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]; δ: 162.9 (C-2), 137.7 (C-1'), 132.8 (C-4), 129.2 (C-3'), 128.8 (C-4'), 128.5 (C-2'), 125.2 (C-1), 125.6 (C-5), 119.3 (C-3), 117.3 (CN), 117.0 (C-6), 85.4 [2C-$(CH_3)_2$], 71.1 (CH_2), 25.1 (4 CH_3). Anal. calcd. for $C_{20}H_{22}BNO_3$: C, 71.66; H, 6.62; N, 4.18. Found: C, 71.39; H, 6.67; N, 4.17.

4-Benzyloxy-2-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (4b)

Yield (1.1 g, 66%), mp 105–106°C. ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]; δ: 7.82 (d, *J*=8.4 Hz, 1H, H-6), 7.50 (d, *J*=7.6, 2H, H-2'), 7.41 (d, *J*=8.0 Hz, 2H, H-3'), 7.40 (s, 1H, H-3), 7.36 (d, 1H, *J*=7.6 Hz, H-4'), 7.32 (dd, *J*=8.4, 2.4 Hz, H-5), 5.26 (s, 2H, CH_2), 1.35 (s, 12H, 4 CH_3). ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]; δ: 161.9 (C-4), 138.8 (C-1'), 137.4 (C-6), 129.5 (C-3'), 129.0 (C-4'), 128.7 (C-2'), 120.5 (C-3), 119.7 (C-5), 119.7 (C-2), 119.1 (CN), 85.2 [2C-$(CH_3)_2$], 71.0 (CH_2), 25.2 (4 CH_3). Anal. calcd. for $C_{20}H_{22}BNO_3$: C, 71.66; H, 6.62; N, 4.18. Found: C, 71.58; H, 6.63; N, 4.24.

4-Benzyloxy-3-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (8a)

Yield (1.18 g, 71%), mp 156–157°C. ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]; δ: 8.04 (d, *J*=1.6 Hz, 1H, H-2), 7.92 (dd, *J*=8.8, 1.6 Hz, 1H, C-6), 7.46 (dd, *J*=7.6 Hz, 2H, H-2'), 7.38 (dt, *J*=7.6, 1.6 Hz, 2H, H-3'), 7.33 (dd, *J*=7.6, 1.6 Hz, 1H, H-4'), 7.00 (dd, *J*=8.4, 1.6 Hz, 1H, H-5), 5.25 (s, 2H, CH_2), 1.38 (s, 12H, 4 CH_3). ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]; δ: 162.3 (C-4), 140.9 (C-2), 140.8 (C-6), 135.56 (C-1'), 128.8 (C-3'), 128.3 (C-4'), 127.1 (C-2'), 123.3 (C-1), 116.4 (CN), 112.2 (C-5), 102.3 (C-3), 84.3 [2C-$(CH_3)_2$], 70.6 (CH_2), 24.9 (4 CH_3).

Anal. calcd. for $C_{20}H_{22}BNO_3$: C, 71.66; H, 6.62; N, 4.18. Found: C, 71.60; H, 6.64; N, 4.23.

2-Benzyloxy-5-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (8b)

Yield (1.15 g, 69%), mp 109–110°C. ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]; δ: 7.93 (dd, *J*=8.8, 2.0 Hz, 1H, H-4), 7.85 (d, *J*=2.0 Hz, 1H, H-6), 7.59 (d, *J*=7.2 Hz, 2H, H-2'), 7.40 (t, *J*=7.6 Hz, 2H, H-3'), 7.33 (d, *J*=7.2 Hz, 1H, H-4'), 7.25 (d, *J*=8.8 Hz, 1H, H-3), 5.24 (s, 2H, CH_2), 1.30 (s, 12H, 4 CH_3). ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]; δ: 165.6 (C-2), 139.8 (C-6), 137.0 (C-4), 136.6 (C-1'), 128.2 (C-3'), 127.5 (C-4'), 126.6 (C-2'), 118.9 (CN), 113.1 (C-3), 102.9 (C-5), 83.7 [2C-$(CH_3)_2$], 69.2 (CH_2), 24.5 (4 CH_3). Anal. calcd. for $C_{20}H_{22}BNO_3$: C, 71.66; H, 6.62; N, 4.18. Found: C, 71.66; H, 6.67; N, 4.08.

3-Benzyloxy-4-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (12a)

Yield (1.0 g, 64%), mp 65–66°C. ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]; δ: 7.69 (d, *J*=8.0 Hz, 1H, H-5), 7.56 (d, 2H, *J*=8.0 Hz, C-6), 7.55 (s, 1H, H-2), 7.46 (dd, *J*=8.0, 3.6, 2H, H-2'), 7.42 (t, *J*=7.6 Hz, 2H, H-3'), 7.37 (d, *J*=7.2 Hz, 1H, H-4'), 5.32 (s, 2H, CH_2), 1.35 (s, 12H, 4 CH_3). ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]; δ: 160.6 (C-2), 137.3 (C-1), 134.0 (C-5), 129.5 (C-3'), 129.0 (C-4'), 128.4 (C-2'), 128.0 (C-6), 119.0 (C-2), 116.8 (CN), 105.4 (C-4), 85.4 [2C-$(CH_3)_2$], 71.3 (CH_2), 25.2 (4 CH_3). Anal. calcd. for $C_{20}H_{22}BNO_3$: C, 71.66; H, 6.62; N, 4.18. Found: C, 71.87; H, 6.64; N, 4.20.

2-Benzyloxy-4-cyanophenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (12b)

Yield (1.2 g, 72%), mp 102–103°C. ^{1}H NMR [$(CD_3)_2CO$, 400 MHz]; δ: 7.90 (d, *J*=8.4 Hz, 1H, C-6), 7.57 (d, *J*=7.2, 2H, H-2'), 7.50 (d, *J*=7.2 Hz, 2H, H-3'), 7.48 (d, *J*=2.4 Hz, 1H, H-3), 7.41 (d, *J*=8.4 Hz, 1H, H-5), 7.37 (d, *J*=7.2 Hz, 1H, H-4'), 5.34 (s, 2H, CH_2), 1.45 (s, 12H, 4 CH_3). ^{13}C NMR [$(CD_3)_2CO$, 100 MHz]; δ: 162.1 (C-2), 138.8 (C-1), 137.6 (C-5), 129.6 (C-3'), 129.1 (C-4'), 128.7 (C-2'), 120.7 (C-6), 119.9 (C-2), 119.8 (CN), 118.3 (C-4), 85.4 [2C-$(CH_3)_2$], 71.2 (CH_2), 25.3 (4 CH_3). Anal. calcd. for $C_{20}H_{22}BNO_3$: C, 71.66; H, 6.62; N, 4.18. Found: C, 71.93; H, 6.69; N, 4.26.

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References

Brown, H. C.; Cole, T. E. Organoboranes. 31. A simple preparation of boronic esters from organolithium reagents and selected trialkoxyboranes. *Organometallics* **1983**, *2*, 1316–1319.

Cooper, D. G.; Forges, I. T.; Garzya, V.; Johnson, D. J.; Stevenson, G. I.; Wyman, P. A. Compounds which have activity at M1 Receptor and their uses in Medicine. **2010**, US2010/0204272 A1.

Fresneda, P. M.; Molina, P. Bleda, J. A. Synthesis of the indole alkaloids meridianins from the tunicate *Aplidium meridianum*. *Tetrahedron* **2001**, *57*, 2355–2362.

Gilman, H.; Spatz, S. M. Pyridyllithium compounds. *J. Org. Chem.* **1951**, *16*, 1485–1494.

Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-catalyzed cross-coupling reaction of alkoxydiboron with haloarenes: a direct procedure for arylboronic esters. *J. Org. Chem.* **1995**, *60*, 7508–7510.

Ismail, M. A.; Anbazhagan, M.; Stephens, C. E.; Boykin, D. W. Synthesis of benzoxybromobenzonitriles. *Synth. Commun.* **2004**, *34*, 751–758.

Kumar, A.; Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. A versatile synthesis of amidines from nitriles via amidoximes. *Synth. Commun*. **1996**, *26*, 4351–4367.

Littke, A. F.; Dai, C.; Fu, G. C. Versatile catalysts for the Suzuki cross-coupling of arylboronic acids with aryl and vinyl halides and triflates under mild conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. Palladium-catalyzed borylation of aryl halides or triflates with dialkoxyborane: a novel and facile synthetic route to arylboronates. *J. Org. Chem.* **2000**, *65*, 164–168.

Qin, X. Q.; Chen, X.; Hughes, R. A.; Williams, S. J.; Woodman, O. L. Understanding the cardioprotective effects of flavonols: discovery of relaxant flavonols without antioxidant activity. *J. Med. Chem*. **2008**, *51*, 1874–1884.

Rodgers, J. F.; Green, D. M. Mild conversion of electron deficient aryl fluorides to phenols using 2-(methylsulfonyl)ethanol. *Tetrahedron Lett.* **2002**, *43*, 3585–3587.

Suzuki, A. Recent advances in the cross-coupling reactions of organoboron derivatives with organic electrophiles. *J. Organomet. Chem*. **1999**, *576*, 147–168.

Tidwell, R. R.; Boykin, D. W. Dicationic DNA minor groove binders as antimicrobial agents. In *Small Molecule DNA and RNA Binders: From Synthesis to Nucleic Acid Complexes*. Demeunynck, M.; Bailly, C.; Wilson, W. D., Eds. Wiley-VCH, New York, 2003; Vol. 2, pp. 416–460.

Zhang, P.; Zou, M. -F.; Rodriguez, A. L.; Conn, P. J.; Newman, A. H. Structure-activity relationships in a novel series of 7-substituted-arylquinolines and 5-substituted-aryl benzothiazoles at the metabotropic glutamate receptor subtype 5. *Bioorg. Med. Chem.* **2010**, *18*, 3026–3035.