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5-Pyrimidylboronic acid and 2-methoxy-5-pyrimidylboronic acid: new heteroarylpyrimidine derivatives *via* Suzuki cross-coupling reactions

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5-Pyrimidylboronic acid **2** and 2-methoxy-5-pyrimidylboronic acid **4** have been synthesised by lithium-halogen exchange reactions on 5-bromopyrimidine and 2-methoxy-5-bromopyrimidine, respectively, followed by reaction with triisopropylborate. Suzuki cross-coupling reactions of **2** and **4** with heteroaryl halides [Na_2CO_3, $Pd(PPh_3)_2Cl_2$, 1,4-dioxane, 95 °C] yield heteroarylpyrimidines (heteroaryl = thienyl, quinolyl and pyrimidyl). Two-fold reaction of **2** with 4,6-dichloropyrimidine **12** gave 4,6-bis(5-pyrimidyl)pyrimidine **8** (56% yield). Reaction of 4,6-dichloropyrimidine with 2-methoxy-5-pyridylboronic acid gave 4,6-bis(2-methoxy-5-pyridyl)pyrimidine **14** (84% yield). Conversion of **14** into 4,6-bis(2-chloro-5-pyridyl)pyrimidine **15** (63% yield) followed by two-fold Suzuki reaction with 4-*tert*-butylbenzeneboronic acid gave the penta-arylene derivative 4,6-bis[2-(4-*tert*-butyl)phenyl-5-pyridyl]pyrimidine **16** (16% yield). Analogous reaction of **12** with 2-methoxy-3-pyridylboronic acid **17** gave 4,6-bis(2-methoxy-3-pyridyl)-pyrimidine **18** (64% yield). The X-ray crystal structures of compound **2**·0.5H_2O and compound **18** are reported. The two hydroxyl H atoms in **2** have the usual *exo–endo* orientation. However, unlike most arylboronic acids, molecule **2** does not form a centrosymmetric hydrogen-bonded dimer. In molecule **18**, the pyridine rings form dihedral angles of 39.9° and 22.8° with the central pyrimidine ring.

Introduction

Aryl- and heteroaryl-pyrimidine derivatives have applications in many contemporary areas of chemistry, such as (i) ligands for coordination to metal ions;[1] (ii) components for molecular recognition studies involving hydrogen bonding and π–π interactions;[2] (iii) compounds with therapeutic and agrochemical properties;[3] and (iv) fluorophores and electron-transporting compounds in organic light-emitting devices.[4] The synthesis of many aryl- and heteroaryl-pyrimidine derivatives has been accomplished by cyclisation reactions of acyclic precursors,[4b,5] or by aryl lithium additions to pyrimidine.[6] There are some recent examples of halopyrimidines being used as partners with arylboronic acids in the palladium-catalysed Suzuki–Miyaura cross-coupling protocol[7] to yield aryl- and biaryl-pyrimidines.[4,8–10] However, the syntheses and reactions of the complementary pyrimidylboronic acids (or esters) have been largely ignored, although analytically-pure 2,4-dimethoxy-5-pyrimidylboronic acid was reported as early as 1964,[11] and Gronowitz *et al*. established that cross-coupling reactions of 2,4-di-*tert*-butoxy-5-pyrimidylboronic acid under Suzuki conditions yield 5-substituted uracils.[12] This remarkable neglect of pyrimidylboronic acid chemistry is in contrast to the recent surge of activity in the synthesis of new pyridylboronic acids.[10,13]

5-Pyrimidylboronic acid **2** has been synthesised from 5-bromopyrimidine **1** by maintaining a very low temperature during the lithium exchange reaction [*n*-BuLi, THF, $B(OBu)_3$, −100 °C, 52% yield] which would be problematic for scale-up.[14] It is well documented that the precise reaction conditions and the order of addition of reagents can be crucial for the successful preparation of certain heteroarylboronic acids,[15] and very recently a modified synthesis of **2** [*n*-BuLi, PhMe–THF, $B(O\textit{i}\text{-Pr})_3$, −70 °C, 76% yield] using an "*in situ* quench" procedure was reported by Li *et al*.[13e]

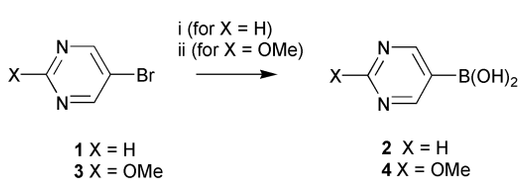
In the course of our studies on heterobiaryl systems[10,13i] and pyrimidine-containing oligoarylene systems,[4c] we needed a reliable route to 5-pyrimidylboronic acid **2**. Herein we report efficient syntheses of compound **2** and 2-methoxy-5-pyrimidylboronic acid **4**, and describe their cross-coupling reactions with heteroaryl halides under Suzuki conditions to afford new heteroarylpyrimidines. As a complementary approach to di(pyridyl)pyrimidines we also report new reactions of 2-methoxy-5-pyridylboronic acid and 2-methoxy-3-pyridylboronic acid with 4,6-dichloropyrimidine.

Results and discussion

Synthesis

In our hands, both literature routes to compound **2**[13e,14] repeatedly gave impure product (as established by ^{1}H NMR spectra) in <30% yield, and attempted scale-up to prepare *ca*. 10 g batches led to more impurities.[16] However, we have now found that using THF alone as the solvent at −70 °C and simply modifying the workup procedure cleanly and reproducibly gives product **2** in 45% yield for 1–10 g batches (Scheme 1). Conducting the lithiation at −50 °C leads to a slight reduction in yield (35–40%) but the purity of the product is maintained. Compound **2** obtained by this route is air-stable and analytically-pure as a hemi-hydrate: its X-ray crystal structure is reported below.

Extending our studies to the lithiation of 5-bromo-2-methoxypyrimidine **3**, we obtained 2-methoxy-5-pyrimidylboronic acid



1 X = H
3 X = OMe

2 X = H
4 X = OMe

Scheme 1 *Reagents and conditions:* i *n*-BuLi, triisopropylborate, THF, −78 °C, then H_2O. ii *n*-BuLi, triisopropylborate, toluene–THF, −70 °C, then H_2O.

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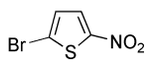
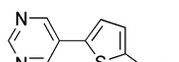
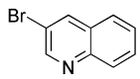
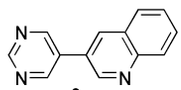
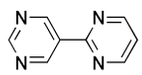
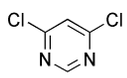
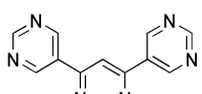
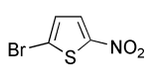
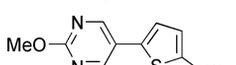
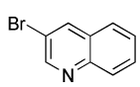
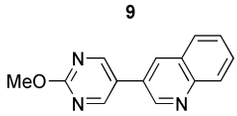
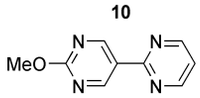
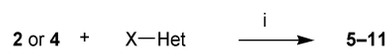
Table 1 Cross-coupling reactions

Entry	Boronic Acid	X–Het	Product	Isolated yield of pure product (%)
1	**2**		 **5**	87
2	**2**		 **6**	18(30[a])
3	**2**		 **7**	9 (X = Br) 34 (X = Cl)
4	**2**		 **8**	56
5	**4**		 **9**	73
6	**4**		 **10**	83
7	**4**		 **11**	4 (X = Br) 50 (X = Cl)

[a] Estimated yield of product (>90% pure) contaminated with catalyst residues.

4 (also air-stable and analytically-pure as a hemi-hydrate) in an optimised yield of 61% [*n*-BuLi, PhMe–THF, $B(O\textit{i}\text{-}Pr)_3$, −70 °C] again using the "*in situ* quench" procedure (Scheme 1).

To examine the suitability of reagent **2** in cross-coupling reactions it was treated with a range of heteroaryl halides which were selected for the different electronic characteristics of the heterocycle (*viz*. thienyl, quinolyl, pyrimidyl) in the presence of sodium carbonate as base and bis(triphenylphosphino)-palladium dichloride as catalyst in 1,4-dioxane at 95 °C to yield 5-heteroarylpyrimidines (Scheme 2 and Table 1). The reactions of **2** were efficient with 2-bromo-5-nitrothiophene (87% yield; entry 1) and with 4,6-dichloropyrimidine; the latter affording the novel bis(pyrimidyl)pyrimidine system **8** by a two-fold reaction (56% yield; entry 4). However, yields were low when 3-bromoquinoline and 2-bromopyrimidine were used (entries 2 and 3, respectively). The yield of product **6** was considerably reduced in the final stages of purification due to difficulties in removing all the residues of the catalyst by chromatography and recrystallisation. The low yield of product **7** is consistent with our earlier observations that reactions of pyridylboronic acids with 2-bromopyrimidine are low-yielding.[10] Using 2-chloropyrimidine instead of 2-bromopyrimidine increased the yield of **7** to 34%.

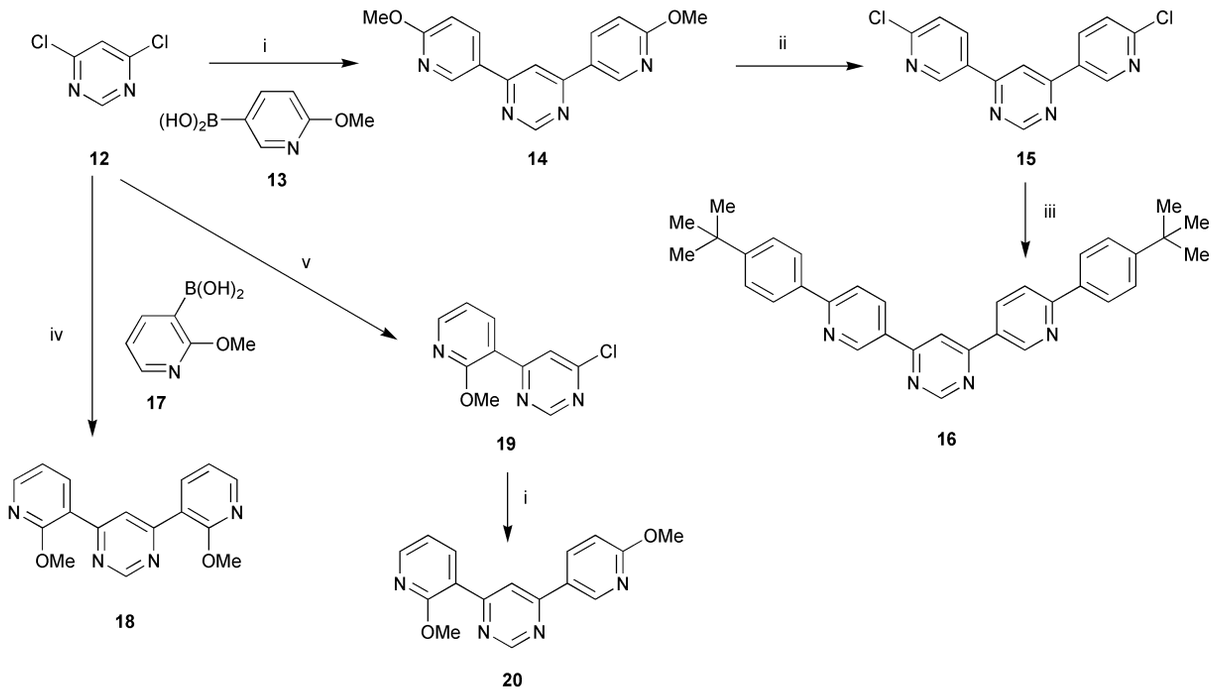


Scheme 2 *Reagents and conditions:* i $Pd(PPh_3)_2Cl_2$, Na_2CO_3, 1,4-dioxane, 95 °C.

Analogous reactions of reagent **4** with 2-bromo-5-nitrothiophene, 3-bromoquinoline, 2-bromopyrimidine and 2-chloropyrimidine gave products **9**–**11** in 73, 83, 4 and 50% yields, respectively (entries 5–7; Table 1). Again, the reaction with 2-bromopyrimidine was very low yielding, but for the pyrimidylquinoline derivative **10** (unlike analogue **6**) purification was straightforward and the product was obtained in high yield.

As a complementary approach to di(pyridyl)pyrimidines, 4,6-dichloropyrimidine **12** was treated with 2-methoxy-5-pyridylboronic acid **13**[10] (2.3 equiv.) under standard conditions, and product **14** was obtained in 84% yield. The same reaction using 4,6-diiodopyrimidine instead of **12** gave product **14** in 82% yield. This result agrees with earlier observations (and entries 3, 4 and 7; Table 1) that π-deficient heteroaryl chlorides are good substrates for Suzuki reactions[8,9,17] and do not require the use of more specialised catalysts which are needed for analogous couplings of chlorobenzene and the more challenging electron rich aryl chlorides.[7d,18] Conversion of **14** into the dichloro analogue **15** proceeded readily (63% yield) upon heating with phosphoryl chloride in DMF.[19] The good yield for this two-fold reaction is consistent with the known trend that electron withdrawing substituents (in this case the pyrimidine ring) facilitate this transformation.[19b] Compound **15** was then used in a further two-fold cross-coupling reaction with 4-*tert*-butylbenzeneboronic acid to give the angular penta-arylene system **16** (16% yield).

The analogous reaction of **12** with 2-methoxy-3-pyridylboronic acid **17**[13i] gave the di(pyridyl)pyrimidine derivative **18** in 64% yield, the X-ray crystal structure of which is reported below. If this reaction was quenched before it had gone to completion the mono-coupled derivative **19** (20% yield) was isolated alongside the di-coupled compound **18** (41% yield). A subsequent reaction of **19** with the pyridylboronic acid **13** afforded the di(pyridyl)pyrimidine derivative **20** in remarkably high yield (97%) (Scheme 3). This sequence clearly demonstrates that compound **19** is a valuable building block for the synthesis of unsymmetrically substituted 4,6-di(heteroaryl)pyrimidines, which should be suitable for further elaboration, by analogy with the conversion of the symmetrical compound **14** into **16**.



Scheme 3 *Reagents and conditions:* i reagent **13**, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, 1,4-dioxane, 95 °C. ii $POCl_3$, *N,N,*-dimethylformamide, 110 °C; iii 4-(*tert*-butyl)phenylboronic acid, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, 1,4-dioxane, 95 °C; iv reagent **17**, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, 1,4-dioxane, 95 °C; v as for iv with workup before the reaction has gone to completion.

Conjugated oligoarylene systems such as **16**, containing electron-deficient pyridine and pyrimidine moieties in the backbone, are prime candidates as electron-transporting/hole blocking compounds for organic light-emitting device applications.[4b,20]

X-Ray crystal structures of compounds 2 and 18

Compound **2** crystallised as a hemihydrate, with molecule **2** in a general position and a water molecule on a crystallographic twofold axis (Fig. 1). The boron atom has planar-trigonal geometry and both hydroxyl H atoms lie in the same plane within experimental error. Thus the molecule deviates from being entirely planar, by a small twist τ = 6.4° around the C(5)–B bond. Similar conformations are adopted by 5-chloro- and 5-bromopyridylboronic acids (τ = 4.0 and 10.9°, respectively),[10] $PhB(OH)_2$ (τ = 6.6 and 21.4° in two independent molecules)[21] and *p*-tolylboronic acid (τ = 4 and 22° in two independent molecules).[22] The C(5)–B bond in **2** [1.583(2) Å] is marginally longer than in 5-chloro- and 5-bromopyridylboronic acids [1.573(2) Å in both] and $PhB(OH)_2$ [1.565(3) Å after libration correction].

The two hydroxyl H atoms in **2** have the usual *exo–endo* orientation. However, unlike most of its analogues, molecule **2** does not form a centrosymmetric hydrogen-bonded dimer in the crystal of **2**·0.5H_2O (resembling those of carbon acids), but a more complex pattern instead (Fig. 2).

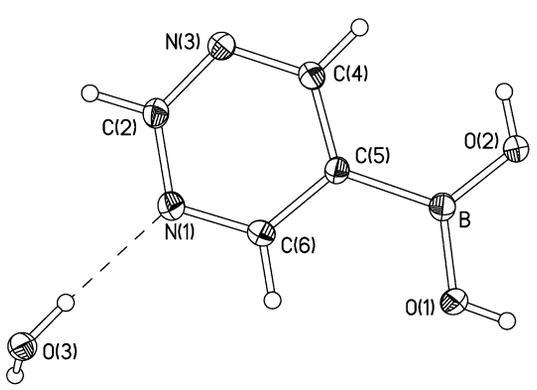


Fig. 1 X-Ray structure of **2**·0.5H_2O, showing 50% displacement ellipsoids.

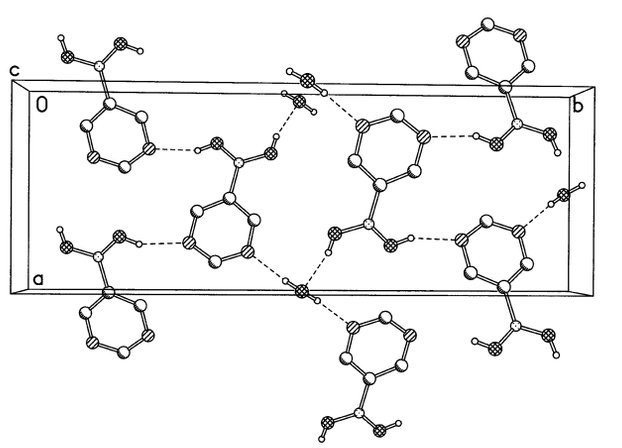


Fig. 2 Hydrogen bonds in **2**·0.5H_2O (pyrimidine H atoms are omitted).

In molecule **18** (Fig. 3), pyridine rings *i* and *ii* form dihedral angles of 39.9° and 22.8°, respectively, with the central pyrimidine ring. The methoxy substituents are almost coplanar with the corresponding pyridine rings, the twists around the C(12)–O(1) and C(22)–O(2) bonds amounting to 3.2° and 3.9°, respectively. The intramolecular distances H(5) ··· O(1) 2.49(3) Å and

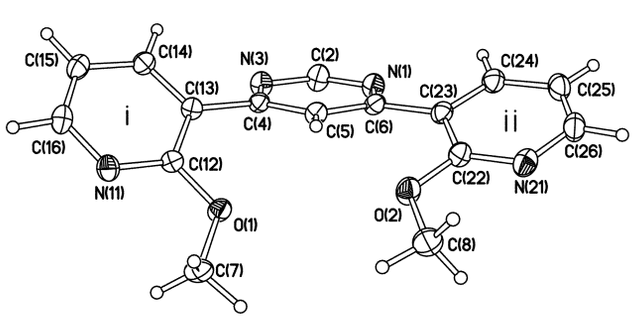


Fig. 3 X-Ray structure of **18**.

especially H(5) ··· O(2) 2.29(3) Å are shorter than the sum of Van der Waals' radii (2.68 Å),[23] indicating electrostatic attraction. Indeed, the opposite orientation of the methoxypyridyl rings (with the methoxy groups *cis* to the pyrimidine nitrogens) would involve no shortened intramolecular contacts, but would be less favourable because of the proximity between negatively charged O and N atoms.

Conclusions

This work paves the way for further studies on pyrimidylboronic acids which are greatly under-developed reagents in pyrimidine chemistry. These compounds and the methodology described herein offer an attractive and flexible approach to new highly-functionalised pyrimidines. We have established precise conditions for the syntheses of 5-pyrimidylboronic acid **2** and 2-methoxy-5-pyrimidylboronic acid **4**, and described their use in the synthesis of novel heteroarylpyrimidines. As a complementary and efficient route to 4,6-di(pyridyl)pyrimidine derivatives, we have described the reactions of 2-methoxy-5-pyridylboronic acid **13** and 2-methoxy-3-pyridylboronic acid **17** with 4,6-dichloropyrimidine. Subsequent transformations of 4,6-bis(2-methoxy-5-pyridyl)pyrimidine **14** have afforded the penta-arylene system **16**.

Experimental

General details are the same as those reported previously.[10]

5-Pyrimidylboronic acid (2)

To a solution of 5-bromopyrimidine (5.50 g, 34 mmol) and triisopropylborate (13.0 g, 69 mmol) in anhydrous THF (70 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 22.0 cm^3, 35 mmol) dropwise. The reaction mixture was stirred for 4 h at −78 °C then quenched with H_2O (10 cm^3) and allowed to warm to 20 °C with stirring overnight. The solvent was evaporated *in vacuo* and the aqueous layer was taken to pH 10 with 5% NaOH and was then washed with diethyl ether. The aqueous layer was then acidified to pH 4 with 48% aq HBr to precipitate compound **2** as a white solid (1.90 g, 45%); mp >320 °C; ^{1}H NMR (DMSO-d_6) δ 9.36 (s, 1 H), 9.17 (s, 2 H), 8.81 (s, 2 H, OH); ^{13}C NMR (DMSO-d_6) δ 161.84, 159.31. Anal. calc. for $C_4H_5BN_2O_2\cdot 0.5H_2O$: C, 36.15; H, 4.55; N, 21.08. Found: C, 36.47; H, 4.50, N, 20.80%. Crystals for X-ray analysis were grown from ethanol–water.

2-Methoxy-5-pyrimidylboronic acid (4)

A mixture of triisopropylborate (2.8 cm^3, 12 mmol) and 5-bromo-2-methoxypyrimidine[24] (1.73 g, 10 mmol) dissolved in toluene (16 cm^3) and THF (4 cm^3) under a nitrogen atmosphere was cooled to −70 °C. *n*-Butyllithium (7.5 cm^3, 12 mmol, 1.6 M in hexanes) was added dropwise *via* a syringe pump over 1 h, and the mixture was stirred for 6 h while the temperature was held at −70 °C. The reaction mixture was then allowed to warm to −20 °C before HCl solution (2 M, 10 cm^3) was added. When the mixture reached room temperature, the layers were separated. The aqueous layer was acidified to pH 4 with 48% aq. HBr to precipitate compound **4** as a white solid (939 mg, 61%); mp 159–161 °C. ^{1}H NMR (DMSO-d_6) δ 8.82 (s, 2 H), 8.42 (s, 2 H, OH), 3.92 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.01, 164.99 (2C), 54.41. Anal. calc. for $C_5H_7BN_2O\cdot 0.5H_2O$: C, 36.86; H, 4.95; N, 17.19. Found: C, 36.57; H, 4.49; N, 17.04%.

General procedure for the cross-coupling reactions

Reactions were carried out under argon. Unless stated otherwise, the boronic acid (1.7 mmol), the halide (1.5 mmol), the catalyst [$Pd(PPh_3)_2Cl_2$] (5 mol% relative to the boronic acid) and degassed 1,4-dioxane (10 cm^3) were stirred at room temperature for *ca.* 30 min. Degassed aqueous Na_2CO_3 solution (4 cm^3) was added and the mixture was stirred for 65 h at 95 °C. The solvent was evaporated *in vacuo*, ethyl acetate (50 cm^3) was added and the mixture was stirred for 0.5 h. The reaction was washed with brine (50 cm^3) and the organic layer was separated, dried ($MgSO_4$) and purified using column chromatography on silica gel.

5-(5-Nitrothien-2-yl)pyrimidine (5)

5-Pyrimidylboronic acid **2**, 2-bromo-5-nitrothiophene, $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 in dioxane; eluent EtOAc–hexane 1 : 2 (v/v) gave compound **5** as a brown solid (87% yield), mp 152–154 °C; ^{1}H NMR ($CDCl_3$) δ 9.24 (s, 1 H), 8.99 (s, 2 H), 7.96 (d, 1 H, J = 3.7 Hz), 7.36 (d, 1 H, J = 3.7 Hz); ^{13}C NMR ($CDCl_3$) δ 159.14, 154.00 (2C), 152.53, 143.16, 129.47, 126.84, 124.62; *m*/*z* (EI) 207 (M^+, 100%). Anal. calc. for $C_8H_5N_3O_2S$: C, 46.37; H, 2.43; N, 20.28. Found: C, 46.20; H, 2.61; N, 20.44%.

3-(Pyrimidin-5-yl)quinoline (6)

5-Pyrimidylboronic acid **2**, 3-bromoquinoline, $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 in dioxane; eluent EtOAc–hexane 1 : 4 (v/v) gave compound **6** (*ca.* 30% yield; >90% purity as judged by ^{1}H NMR). Recrystallisation from toluene–hexane gave compound **6** as a white solid (18% yield) mp 143–144 °C. ^{1}H NMR ($CDCl_3$) δ 9.33 (s, 1 H), 9.17 (s, 1 H), 9.13 (s, 2 H), 8.39 (s, 1 H), 8.21 (d, 1 H, J = 8.3 Hz), 7.96 (d, 1 H, J = 8.3 Hz), 7.84 (m, 1 H), 7.68 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 158.17, 155.18 (2C), 148.47, 148.06, 134.04, 131.67, 130.60, 129.49, 128.13, 127.75, 127.66, 127.25; *m*/*z* (EI) 207 (M^+, 100%). Anal. calc. for $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.09; H, 4.33; N, 20.06%.

2-(Pyrimidin-5-yl)pyrimidine (7)[25]

5-Pyrimidylboronic acid **2**, 2-bromopyrimidine, $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 in dioxane; eluent EtOAc–hexane 1 : 2 (v/v) and then recrystallisation from chloroform gave compound **7** as a white solid (9% yield) mp 206–208 °C. ^{1}H NMR ($CDCl_3$) δ 9.72 (s, 2 H), 9.33 (s, 1 H), 8.87 (d, 2 H, J = 4.8 Hz), 7.33 (t, 1 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 161.01, 159.85, 157.59 (2C), 156.62 (2C), 130.82, 120.48; *m*/*z* (EI) 158 (M^+, 100%); HRMS (EI) (M^+) (calcd. $C_8H_6N_4$) 158.05920 (158.05925). The analogous reaction of 2-chloropyrimidine gave **7** in 34% yield.

4,6-Bis(5-pyrimidyl)pyrimidine (8)

5-Pyrimidylboronic acid **2** (200 mg, 1.61 mmol), 4,6-dichloropyrimidine (106 mg, 0.71 mmol), $Pd(PPh_3)_2Cl_2$ (57 mg, 0.08 mmol) and Na_2CO_3 (2 cm^3) in dioxane (5 cm^3); eluent EtOAc–hexane, 1 : 2 (v/v) gave compound **8** as a white solid (94 mg, 56%) mp 248–250 °C. ^{1}H NMR (DMSO-d_6) δ 9.69 (s, 4 H), 9.49 (s, 1 H), 9.41 (s, 2 H), 9.01 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 160.88, 160.74, 160.08, 156.53, 130.25, 114.91; *m*/*z* (EI) 236 (M^+, 100%); HRMS (EI) (M^+) (calcd. $C_{12}H_8N_6$) 236.08032 (236.08104).

2-Methoxy-5-(5-nitrothien-2-yl)pyrimidine (9)

2-Methoxy-5-pyrimidylboronic acid **4**, 2-bromo-5-nitrothiophene, $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 in dioxane; eluent EtOAc–hexane 1 : 2 (v/v) gave compound **9** as a yellow solid (73% yield) mp 169–170 °C. ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 2 H), 7.93 (d, 1 H, J = 4.3 Hz), 7.22 (d, 1 H, J = 4.3 Hz), 4.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.05, 156.80, 151.24, 144.17, 129.60, 123.12, 120.80, 55.58; *m*/*z* (EI): 237 (M^+, 100%). Anal. calc. for $C_9H_7N_3O_3S$: C, 45.57; H, 2.97; N, 17.71. Found: C, 45.98; H, 3.34; N, 17.23%.

3-(2-Methoxypyrimidin-5-yl)quinoline (10)

2-Methoxy-5-pyrimidylboronic acid **4**, 3-bromoquinoline, $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 (3 cm^3) in dioxane; eluent EtOAc–

hexane, 1 : 1 (v/v) gave compound **10** as a white solid (83% yield) mp 181–182 °C. ^{1}H NMR ($CDCl_3$) δ 9.09 (d, 1 H, J = 2.3 Hz), 8.86 (s, 2 H), 8.27 (d, 1 H, J = 2.3 Hz), 8.14 (d, 1 H, J = 8.3 Hz), 7.89 (d, 1 H, J = 8.3 Hz), 7.77 (m, 1 H), 7.62 (m, 1 H), 4.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.50, 157.65 (2C), 148.56, 147.69, 133.03, 130.08, 129.42, 127.95, 127.77, 127.55, 127.46, 125.42, 55.27; *m*/*z* (EI) = 237 (M^+, 100%). Anal. calc. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.36; H, 4.82; N, 17.69%.

2-Methoxy-5-(2-pyrimidyl)pyrimidine (11)

2-Methoxy-5-pyrimidylboronic acid **4**, 2-bromopyrimidine, $Pd(PPh_3)_2Cl_2$ and Na_2CO_3 in dioxane; eluent EtOAc–petroleum ether, 1 : 2 (v/v) gave compound **11** as a white solid (4% yield) mp 149–150 °C. ^{1}H NMR ($CDCl_3$) δ 9.48 (s, 2 H), 8.78 (d, 2 H, J = 4.8 Hz), 7.22 (t, 1 H, J = 4.8 Hz), 4.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.70, 161.34, 159.57, 157.39, 125.14, 119.65, 55.33; *m*/*z* (EI) = 188 (M^+, 98%), 173 (100%). Anal. calc. for $C_9H_8N_4O$: C, 57.44; H, 4.28; N, 29.77. Found: C, 57.77; H, 4.56; N, 29.88%. The analogous reaction of 2-chloropyrimidine gave **11** in 50% yield.

4,6-Bis(2-methoxy-5-pyridyl)pyrimidine (14)

2-Methoxy-5-pyridylboronic acid **13**[10] (1.032 g, 6.79 mmol), 4,6-dichloropyrimidine **12** (461 mg, 3.00 mmol), $Pd(PPh_3)_2Cl_2$ (238 mg, 0.34 mmol) and Na_2CO_3 (8 cm^3) in dioxane (10 cm^3); eluent EtOAc–hexane, 1 : 5 (v/v) gave compound **14** as a white solid (740 mg, 84%) mp 149–150 °C. ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1 H), 8.88 (s, 2 H), 8.30 (d, 2 H, J = 8.7 Hz), 7.89 (s, 1 H), 6.84 (d, 2 H, J = 8.7 Hz), 3.99 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 165.91, 162.30, 159.27, 146.51 (2 C), 137.25 (2 C), 126.02, 111.27 (2 C), 110.63, 53.90 (2 C); *m*/*z* (EI) = 294 (M^+, 100%). Anal. calcd for $C_{16}H_{14}N_4O_4$: C, 65.30; H, 4.80; N, 19.04. Found: C, 65.48; H, 4.90; N, 18.74%.

The same reaction using 4,6-diiodopyrimidine (prepared in 81% yield from **12**)[26] gave **14** in 82% yield.

4,6-Bis(2-chloro-5-pyridyl)pyrimidine (15)

Phosphoryl chloride (782 mg, 5.10 mmol) was added dropwise to a stirred solution of compound **14** (150 mg, 0.51 mmol) in dry DMF (10 cm^3) at 0 °C. Stirring was continued for 1 h then the mixture was heated at 110 °C for 19 h, then cooled to 0 °C and quenched with saturated sodium acetate solution (25 cm^3). The mixture was extracted with EtOAc (4 × 50 cm^3). The organic layer was then washed with water (3 × 100 cm^3) and was dried over $MgSO_4$. The residue was chromatographed through a silica gel column, eluent EtOAc–hexane 1 : 2 (v/v) to give compound **15** as a white solid (98 mg, 63%) mp 233–234 °C. ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1 H), 9.13 (s, 2 H), 8.45 (d, 2 H, J = 8.3 Hz), 8.09 (s, 1 H), 7.53 (d, 2 H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 161.78, 159.72, 154.23, 148.51, 137.37, 131.19, 124.77, 112.34; *m*/*z* (EI) = 302 (M^+, 100%). Anal. calc. for $C_{14}H_8Cl_2N_4$: C, 55.47; H, 2.66; N, 18.48. Found: C, 55.27; H, 2.93; N, 18.50.

4,6-Bis[2-(4-*tert*-butyl)phenyl-5-pyridyl]pyrimidine (16)

4-(*tert*-Butyl)phenylboronic acid (154 mg, 0.87 mmol), compound **15** (116 mg, 0.38 mmol), $Pd(PPh_3)_2Cl_2$ (30 mg, 0.04 mmol) and Na_2CO_3 (3 cm^3) in dioxane (10 cm^3) were reacted according to the general procedure. Elution with EtOAc–hexane 1 : 10 (v/v) gave compound **16** as a white solid (30 mg, 16%) mp 274–276 °C. ^{1}H NMR ($CDCl_3$) δ 9.42 (s, 2 H), 9.37 (s, 1 H), 8.53 (d, 2 H, J = 8.3 Hz), 8.19 (s, 1 H), 8.05 (d, 4 H, J = 8.6 Hz), 7.90 (d, 2 H, J = 8.3 Hz), 7.55 (d, 4 H, J = 8.3 Hz), 1.38 (s, 18 H); ^{13}C NMR ($CDCl_3$) δ 162.56, 159.61, 159.49, 153.12, 148.43, 135.61, 135.39, 130.35, 126.91, 125.91, 120.18, 112.13, 34.81, 31.27; *m*/*z* (EI) = 498 (M^+, 100%). Anal. calc. for $C_{34}H_{34}N_4$: C, 81.89; H, 6.87; N, 11.24. Found: C, 57.00; H, 6.18; N, 17.29%.

4,6-Bis(2-methoxy-3-pyridyl)pyrimidine (18)

2-Methoxy-3-pyridylboronic acid **17**[13*i*] (200 mg, 1.32 mmol), 4,6-dichloropyrimidine **12** (87 mg, 0.58 mmol), $Pd(PPh_3)_2Cl_2$ (46 mg, 0.07 mmol) and Na_2CO_3 (2 cm^3) in dioxane (5 cm^3) were reacted according to the general procedure. Eluent EtOAc–hexane 1 : 5 (v/v) gave compound **18** as a white solid (110 mg, 64%) mp 115–116 °C. ^{1}H NMR ($CDCl_3$) δ 9.31 (s, 1 H), 8.83 (s, 1 H), 8.48 (m, 2 H), 8.30 (m, 2 H), 7.09 (m, 2 H), 4.11 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.70, 161.09, 158.55, 148.71, 139.69, 121.09, 120.69, 117.51, 53.72; *m*/*z* (EI) = 294 (M^+, 100%). Anal. calc. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.37; H, 4.90; N, 18.71%. Crystals for X-ray analysis were grown from ethanol.

4-Chloro-6-(2-methoxy-3-pyridyl)pyrimidine (19)

Following the procedure above for the preparation of **18** [using **12** (870 mg, 5.81 mmol), **17** (2.00 g, 13.18 mmol), $Pd(PPh_3)_2Cl_2$ (460 mg, 0.66 mmol), dioxane (15 cm^3) and Na_2CO_3 solution (6 cm^3)] and quenching the reaction before it had gone to completion (as judged by TLC monitoring) gave compound **19** as the first product eluted, followed by compound **18** (706 mg, 41% yield). Compound **19**, a white solid (260 mg, 20%) mp 97–98 °C. ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1 H), 8.57 (m, 1 H), 8.25 (m, 1 H), 8.19 (m, 1 H), 7.10 (m, 1 H), 4.17 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.20, 162.01, 159.20, 150.00, 140.64, 122.01, 119.55, 118.03, 117.02, 54.22; *m*/*z* (EI) = 221 (M^+, 100%). Anal. calc. for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.28; H, 3.63; N, 19.04%. [For analytically-pure samples of **19** additional unassigned peaks of low intensity were always present in the ^{1}H NMR spectra: δ 8.18 (m), 7.60 (m), 6.96 (m)].

4-(2-Methoxy-5-pyridyl)-6-(2-methoxy-3-pyridyl)pyrimidine (20)

2-Methoxy-5-pyridylboronic acid **13** (109 mg, 0.72 mmol), compound **19** (140 mg, 0.63 mmol), $Pd(PPh_3)_2Cl_2$ (25 mg, 0.04 mmol) and Na_2CO_3 solution (3 cm^3) in dioxane (10 cm^3) were reacted according to the general procedure. Eluent EtOAc–hexane 1 : 10 (v/v) gave compound **20** as a white solid (180 mg, 97%) mp 125–126 °C. ^{1}H NMR ($CDCl_3$) δ 9.25 (s, 1 H), 8.91 (s, 1 H), 8.51 (d, 1 H, J = 7.6 Hz), 8.45 (s, 1 H), 8.36 (d, 1 H, J = 8.7 Hz), 8.29 (m, 1 H), 7.08 (m, 1 H), 6.88 (d, 1 H, J = 8.7 Hz), 4.09 (s, 3 H), 4.01 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.84, 161.86, 161.65, 161.28, 158.87, 148.86, 146.56, 139.63, 137.45, 126.37, 120.21, 117.54, 115.92, 111.31, 53.86; *m*/*z* (EI) = 294 (M^+, 100%). Anal. calc. for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.49; N, 19.04. Found: C, 65.55; H, 4.53; N, 19.38%.

Crystallographic studies

X-Ray diffraction experiments (Table 2) were carried out on a SMART 3-circle diffractometer with a 6K CCD area detector, using graphite-monochromated Mo–K_α radiation (λ = 0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structures were solved by direct methods and refined by full-matrix least squares against F^2 of all data, using SHELXTL software.[27] Full crystallographic data, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference numbers 224163 and 224164. See http://www.rsc.org/suppdata/ob/b3/b314624n/ for crystallographic data in.cif or other electronic format.

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Table 2 Crystal data

Compound	**2**	**18**
Formula	$C_4H_5BN_2O_2 \cdot 0.5H_2O$	$C_{16}H_{14}N_4O_2$
Formula weight	132.92	294.31
T/K	120	120
Symmetry	Orthorhombic	Monoclinic
Space group	$P2_12_12$ (# 18)	$P2_1$ (# 4)
a/Å	7.6474(7)	9.1245(11)
b/Å	21.062(5)	3.7622(7)
c/Å	3.6345(2)	20.595(6)
β/°	90	95.806(4)
V/Å^3	585.4(2)	703.4(3)
Z	4	2
μ/mm^{-1}	0.12	0.10
Refls collected	7717	10016
Unique refls	1039	2337
R_{int}	0.039	0.069
Refls $F^2>2\sigma(F^2)$	936	1881
$R[F^2>2\sigma(F^2)]$	0.032	0.040
w$R(F^2)$, all data	0.084	0.104

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