

5-Formyl-2-furylboronic acid as a versatile bifunctional reagent for the synthesis of π -extended heteroarylfuran systems †

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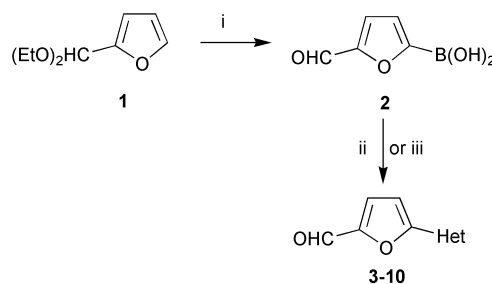
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5-Formyl-2-furylboronic acid reacts cleanly with a range of heteroaryl bromides under Suzuki–Miyaura cross-coupling conditions to produce 2-formyl-5-heteroarylfuran derivatives. Subsequent Wittig olefination reactions afford π -conjugated alkene–pyridyl–furan derivatives.

Biaryl/heteroaryl derivatives are extremely important components of pharmaceutical and agrochemical compounds¹ and optoelectronic materials.² For their synthesis, the Suzuki–Miyaura protocol for palladium-catalysed cross-coupling of aryl- or heteroarylboronic acids with aryl- or heteroaryl halides is particularly versatile,³ and there has been a recent upsurge of interest in the development of new heteroarylboronic acids (especially pyridyl derivatives)⁴ and new catalysts⁵ for this purpose.

A reagent possessing both boronic acid and aldehyde functionalities should offer considerable scope for the synthesis of π -extended biaryl/heteroaryl systems.⁶ Remarkably, very few such bifunctional reagents are known, and for those which are known their use in sequential Suzuki and Wittig reactions has not been reported. 4-Formylphenylboronic acid,⁷ 3-formylphenylboronic acid,⁸ 3-formyl-4-methoxyphenylboronic acid⁹ and 5-formyl-2-thienylboronic acid¹⁰ are known. Within the furan series, deboration of formylfurylboronic acids is a common problem;¹¹ however, 2-formyl-3-furylboronic acid has been well characterised.¹² A recent report claimed the preparation of crude 5-formyl-2-furylboronic acid **2**, although no spectroscopic or analytical data were presented to support this structure.¹³

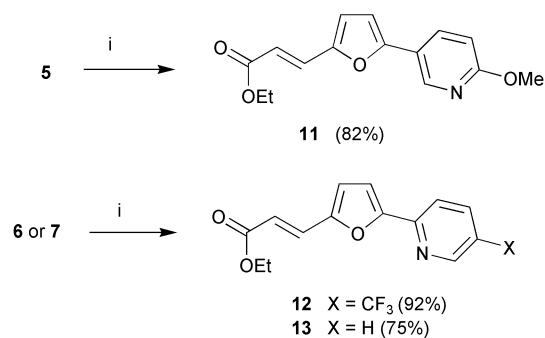
We now report that 5-formyl-2-furylboronic acid **2** can be readily obtained and purified, and we establish that it is a versatile reagent in the synthesis of a range of new π -extended furan derivatives. ‡ The attraction of 2,5-disubstitution on the furan (as opposed to other isomers) is that π -conjugation through the system will be maximised (see below). Lithiation of acetal **1**¹⁴ using *n*-butyllithium followed by reaction with trimethylborate and aqueous workup concomitantly introduced the boronic acid group and liberated the aldehyde group to afford compound **2** in 52% yield after purification (Scheme 1). Cross-coupling reactions of **2** with a range of heteroaryl bromides were explored under standard conditions, using either tetrakis(triphenylphosphine)palladium as catalyst and sodium carbonate as base in DMF at 80 °C (conditions A) or bis(triphenylphosphine)palladium dichloride and caesium carbonate in 1,4-dioxane at 95 °C (conditions B). As shown in Table 1 for entries 1–4, conditions B consistently gave higher yields of the desired products **3–6**, so conditions A were not used for the other examples (entries 5–8). These results establish that cross-coupling of **2** occurs with both electron-rich heterocyclic partners (furyl and thienyl: entries 1, 2 and 8) and electron-deficient



Scheme 1 i *n*BuLi, THF, trimethylborate, –78 to 25 °C, aqueous workup; ii Het–Br, Pd(PPh₃)₄, Na₂CO₃, DMF, 80 °C (conditions A); iii Het–Br, Pd(PPh₃)₂Cl₂, Cs₂CO₃, 1,4-dioxane, 95 °C (conditions B).

pyridyl derivatives. It is notable that electron-withdrawing substituents on the pyridyl ring (entries 4, 6 and 7) resulted in lower yields. This is consistent with previous reactions of pyridylboronic acids with halogenated heterocycles.^{4e} We note that entries 3–7 represent a new route to pyridylfuran derivatives which hitherto have been obtained *via* the Paal reaction of intermediate pyridyl-1,4-diketones,¹⁵ or *via* a Hantzsch-type reaction from pyridinoylacetates.¹⁶

Extension of the π -system of **5–7** was readily achieved by Wittig olefination using (ethoxycarbonylmethyl)triphenylphosphorane under standard conditions¹⁷ to afford π -conjugated alkene–pyridyl–furan derivatives **11–13** in high yields (Scheme 2). To illustrate further the scope of these reactions, the more elaborate Wittig and Horner–Wadsworth–Emmons reagents **14**¹⁸ and **15**¹⁹ respectively, were employed. Deprotonation of **14** and **15** with *n*-butyllithium followed by reaction with compound **6** gave products **16** and **17** in 51 and 11% yields, respectively (Scheme 3). The low yield of the latter reaction was due to the presence of many unidentified byproducts (TLC evidence) and the known instability of reagent **15**.¹⁹


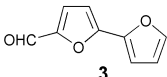

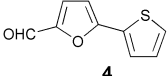
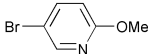
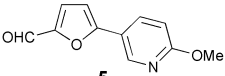
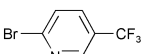
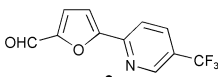

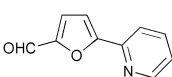
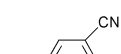
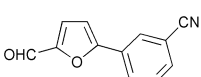
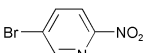
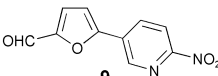
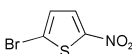
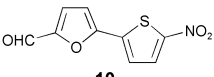


Scheme 2 i Ph₃PCHCO₂Et, MeCN, reflux.

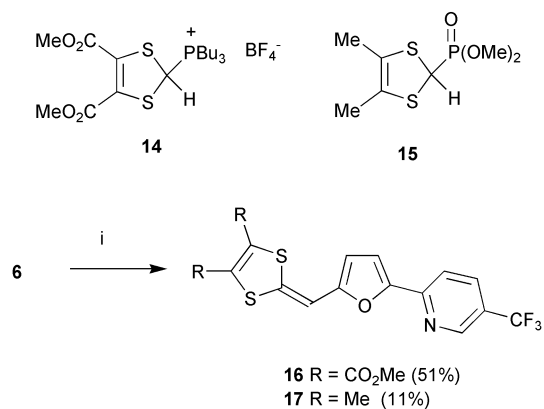
The UV-Vis absorption spectra of compounds **16** and **17** established that effective intramolecular charge-transfer arises from combining an electron-donating 1,3-dithiol-2-ylidene moiety and an electron-deficient pyridyl unit at opposing

† Electronic supplementary information (ESI) available: synthesis and characterisation data for **3–17**. See <http://www.rsc.org/suppdata/ob/b3/3302767h/>

Table 1 Cross-coupling reactions of reagent **2**

Entry	Boronic acid	Br-Het	Product	Isolated yield (%)	
				Conditions A	Conditions B
1	2			34	64
2	2			30	61
3	2			16	52
4	2			24	31
5	2			—	57
6	2			—	15
7	2			—	44
8	2			—	54

Conditions A: tetrakis(triphenylphosphine)palladium as catalyst and sodium carbonate as base in DMF at 80 °C; Conditions B: bis(triphenylphosphine)palladium dichloride and caesium carbonate in 1,4-dioxane at 95 °C.


Scheme 3 i) **14** or **15**, nBuLi, THF, -78 °C, then reflux.

termini of the conjugated π -system. There is a red shift in the lowest energy absorption band in dichloromethane solution in the sequence **6** (λ_{max} 329 nm), **16** (λ_{max} 403 nm) and **17** (λ_{max} 430 nm) which is consistent with enhanced electron donating ability of the dimethyl-1,3-dithiole unit in **17** compared with its dimethoxycarbonyl analogue **16**.²⁰

In summary, we have demonstrated a new route to π -extended heteroarylfuran systems by exploiting the rare combination of functional groups in compound **2**. Further extension of this sequential Suzuki–Miyaura and Wittig methodology will be applicable to other 2-heteroarylfuran derivatives and derived π -extended systems of particular relevance to conjugated molecular wires of well-defined conjugation lengths.^{6,21}

Experimental

5-Formyl-2-furylboronic acid (**2**)

To a solution of **1** (1.0 g, 5.9 mmol) in anhydrous THF (20 cm³) at -78 °C was added nBuLi (1.6 M in hexane, 2.2 cm³, 3.5 mmol) dropwise. The reaction mixture was stirred for 5 h at -78 °C then TMB (815 mg, 9.6 mmol) was added dropwise and the reaction mixture was allowed to warm to 25 °C with stirring overnight. The organic solvent was evaporated *in vacuo* and the remaining aqueous layer was taken to pH 10 (with 5% NaOH) and washed with ether. The aqueous layer was then carefully acidified to pH 4 (with 48% HBr) to precipitate a product which was filtered then washed with ether (10 cm³) to afford **2** as a brown solid (428 mg, 52%), mp 150–151 °C; ¹H NMR (250 MHz, acetone-d₆) δ 9.70 (1H, s, CHO), 7.92 (2H, s, OH), 7.40 (1H, d, J = 3.5 Hz), 7.19 (1H, d, J = 3.5 Hz); ¹³C NMR (100 MHz, acetone-d₆) δ 178.44, 155.97, 122.79, 121.63. Anal. calc. for C₅H₅BO₂: C, 42.93; H, 3.60. Found: C, 42.72; H, 3.70%.

General procedure for the cross-coupling reactions

The boronic acid **2**, the halide, and the catalyst (5 mol% relative to **2**) were added sequentially to degassed solvent (10 cm³) and the mixture was stirred at 20 °C for 30–60 min. Degassed aqueous base solution was added and the mixture was heated under N₂ until TLC monitoring showed that the reaction was complete. Solvent was evaporated *in vacuo* and ethyl acetate was added. Then the organic layer was purified by column chromatography on silica gel.

Conditions A: Pd(PPh₃)₄, Na₂CO₃, DMF, 80 °C.

Conditions B: Pd(PPh₃)₂Cl₂, Cs₂CO₃, 1,4-dioxane, 95 °C.

Acknowledgements

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‡ All new compounds gave satisfactory spectroscopic and analytical data. Detailed characterisation is given in the ESI.

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