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

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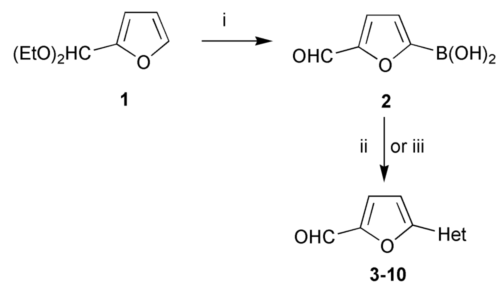
5-Formyl-2-furylboronic acid reacts cleanly with a range of heteroaryl bromides under Suzuki–Miyaura cross-coupling conditions to produce 2-formyl-5-heteroarylfuran derivatives. Subsequent Wittig olefination reactions afford π-conjugated alkene–pyridyl–furan derivatives.

Biaryl/heteroaryl derivatives are extremely important components of pharmaceutical and agrochemical compounds[1] 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 catalysts[5] 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 acid[9] and 5-formyl-2-thienylboronic acid[10] are known. Within the furan series, deboronation 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]

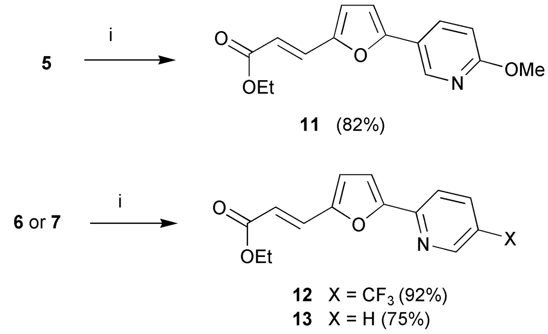
We now report that 5-formyl-2-furylboronic acid **2** can be readily obtained and purified, and we establish that it is a versatile reagent in the synthesis of a range of new π-extended furan derivatives.‡ The attraction of 2,5-disubstitution on the furan (as opposed to other isomers) is that π-conjugation 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 nBuLi, THF, trimethylborate, −78 to 25 °C, aqueous workup; ii Het–Br, $Pd(PPh_3)_4$, Na_2CO_3, DMF, 80 °C (conditions A); iii Het–Br, $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, 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 (ethoxycarbonylmethylene)-triphenylphosphorane under standard conditions[17] 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 Ph_3PCHCO_2Et, 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/b302767h/

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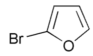
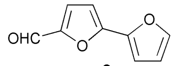
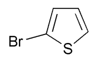
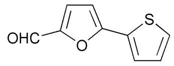
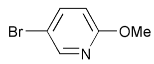
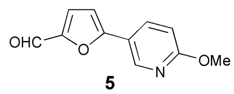
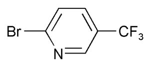
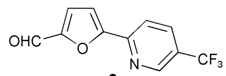
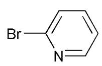
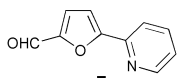
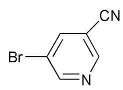
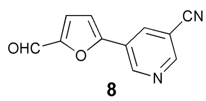
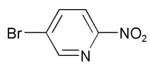
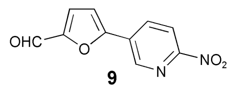
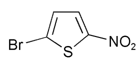
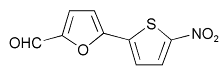
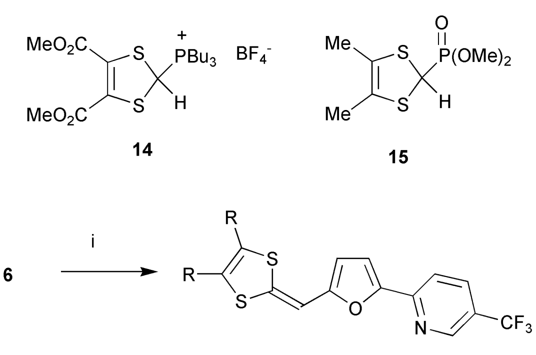
Table 1 Cross-coupling reactions of reagent **2**

Entry	Boronic acid	Br–Het	Product	Isolated yield (%) Conditions A	Isolated yield (%) Conditions B
1	**2**		 **3**	34	64
2	**2**		 **4**	30	61
3	**2**		 **5**	16	52
4	**2**		 **6**	24	31
5	**2**		 **7**	—	57
6	**2**		 **8**	—	15
7	**2**		 **9**	—	44
8	**2**		 **10**	—	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 cm^3) at −78 °C was added nBuLi (1.6 M in hexane, 2.2 cm^3, 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 cm^3) to afford **2** as a brown solid (428 mg, 52%), mp 150–151 °C; ^1H NMR (250 MHz, acetone-d_6) 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); ^{13}C NMR (100 MHz, acetone-d_6) δ 178.44, 155.97, 122.79, 121.63. Anal. calc. for $C_5H_5BO_2$: 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 cm^3) and the mixture was stirred at 20 °C for 30–60 min. Degassed aqueous base solution was added and the mixture was heated under N_2 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: $Pd(PPh_3)_4$, Na_2CO_3, DMF, 80 °C.

Conditions B: $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, 1,4-dioxane, 95 °C.

Acknowledgements

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Notes and references

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

1 Review: S. P. Stanforth, *Tetrahedron*, 1998, **54**, 263.
2 Review: Y. Shirota, *J. Mater. Chem.*, 2000, **10**, 1.
3 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) A. Suzuki, in *Metal-Catalyzed Cross-Coupling Reactions*, F. Diederich and P. J. Stang, eds., Wiley-VCH, Weinheim, Germany, 1998, ch. 2; . Aryl iodides, bromides and triflates are usually used; however, aryl chlorides (K-i. Gouda, E. Hagiwara, Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1996, **61**, 7232; R. B. Bedford, M. E. Blake, C. P. Butts and D. Holder, *Chem. Commun.*, 2003, 466) and even aryl fluorides (D. A. Widdowson and R. Wilhelm, *Chem. Commun.*, 2003, 578) can be used in certain circumstances.
4 For examples see (*a*) U. Lehmann, O. Henze and A. D. Schlüter, *Chem. Eur. J.*, 1999, **5**, 854; (*b*) A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 2885; (*c*) A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 3323; (*d*) A. Bouillon, J.-C. Lancelot, V. Collot, P. R. Bovy and S. Rault, *Tetrahedron*, 2002, **58**, 4368; (*e*) P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce and B. Tarbit, *J. Org. Chem.*, 2002, **67**, 7541; (*f*) W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, D. Cai, R. D. Larsen and P. J. Reider, *J. Org. Chem.*, 2002, **67**, 5394; (*g*) P. R. Parry, M. R. Bryce and B. Tarbit, *Synthesis*, 2003, in press.
5 (*a*) A. Zapf, A. Ehrentrant and M. Beller, *Angew. Chem., Int. Ed.*, 2000, **39**, 4153; (*b*) M. Feuerstein, D. Laurenti, C. Bougeant, H. Doucet and M. Santelli, *Chem. Commun.*, 2001, 325.
6 For examples of such π-extended systems obtained by different methodology see: (*a*) J. Roncali, *J. Mater. Chem.*, 1997, **7**, 2307; (*b*) C.-F. Lee, C.-Y. Liu, H.-C. Song, S.-J. Luo, J.-C. Tseng and H.-H. Tso and T.-Y. Luh, *Chem. Commun.*, 2002, 2824.
7 (*a*) S. Kotha and A. K. Ghosh, *Synlett*, 2002, 451; (*b*) D. Bouyssi, V. Gerusz and G. Balme, *Eur. J. Org. Chem.*, 2002, 2445.
8 N. D. Hone, S. G. Davies, N. J. Devereux, S. L. Taylor and A. D. Baxter, *Tetrahedron Lett.*, 1998, **39**, 897.
9 M. Cavazzini, A. Manfredi, F. Montanari, S. Quici and G. Pozzi, *Eur. J. Org. Chem.*, 2001, **24**, 4639.
10 K. Matsuka, M. Matsuo and M. Irie, *J. Org. Chem.*, 2001, **66**, 8799.
11 D. Florentin, M. C. Fournié-Zaluski, M. Callanquin and B. P. Rogers, *J. Heterocycl. Chem.*, 1976, **13**, 1265.
12 (*a*) S. Gronowitz and U. Michael, *Ark. Kemi.*, 1970, **32**, 283; (*b*) Y. Yang, *Synth. Commun.*, 1989, **19**, 1001.
13 S. M. Starling, D. S. Raslan and A. B. de Oliveira, *Synth. Commun.*, 1998, **28**, 1013.
14 S. F. Thames and H. C. Odom, Jr., *J. Heterocycl. Chem.*, 1966, 490.
15 R. A. Jones and P. U. Civcir, *Tetrahedron*, 1997, **53**, 11529.
16 P. Ribereau and G. Queguiner, *Can. J. Chem.*, 1983, **61**, 334.
17 G. Pandy, T. D. Bagul and A. K. Sahoo, *J. Org. Chem.*, 1998, **63**, 760.
18 M. Sato, N. C. Gonella and M. P. Cava, *J. Org. Chem.*, 1976, **41**, 882.
19 A. J. Moore and M. R. Bryce, *J. Chem. Soc., Perkin Trans. 1*, 1991, 157.
20 E. H. Elanddaloussi, P. Frère, J. Roncali, P. Richomme, M. Jubault and A. Gorgues, *Adv. Mater.*, 1995, **7**, 390.
21 (*a*) *Electronic Materials: The Oligomer Approach*, K. Müllen and G. Wegner, eds., Wiley-VCH, Weinheim, 1998; (*b*) J. M. Tour, *Acc. Chem. Res.*, 2000, **33**, 791.