Palladium (0)-Catalysed Arylations using Pyrrole and Indole 2-Boronic Acids

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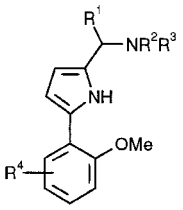
Abstract: A versatile synthesis of 2-arylpyrroles and 2-arylindoles is described based on the use of either *N*-(Boc) pyrrole-2-boronic acid or *N*-(Boc) indole-2-boronic acid as components for Suzuki coupling.

We have described the design of a series of 2,5-disubstituted pyrroles **1** as selective dopamine D_3 receptor antagonists, the synthesis of which required 2-arylpyrroles **2** as key intermediates.[1] Initial approaches to **2** involved reaction of the appropriate benzoyl chloride **3** with Grignard reagent **4** and subsequent treatment with ammonium acetate in a modification of a known procedure.[2] This method is, however, incompatible with the presence of acidic protons or basic nitrogens in **2**, and each desired substitution pattern requires repetition of a lengthy reaction sequence. An alternative strategy based on palladium-catalysed aryl cross-coupling methodology offered promise as a shorter, direct and more flexible route and here we describe the successful implementation of this approach.



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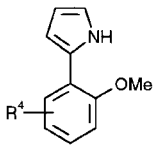

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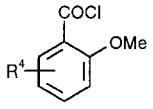

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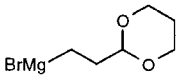

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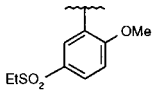
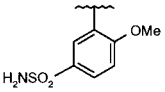
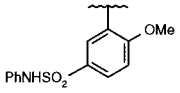
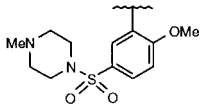
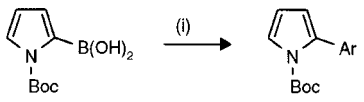
The few literature examples of palladium-catalysed cross coupling involving metallated pyrroles have mainly described the use of magnesium, zinc and tin species.[3,4,5] The use of *N*-(triisopropylsilyl)pyrrole-3-boronic acid as a Suzuki coupling substrate has been reported,[5] and more recently, the coupling of *N*-(Boc) pyrrole-2-boronic acid[6] **5** to a pyrrole-2-triflate has been described.[7] The use of *N*-(phenylsulfonyl) pyrrole-2-boronic acid in Suzuki couplings has also been reported. However, the synthesis of this boronic acid starting material proceeds in only 7.5% yield.[8]

The wide availability of aryl halides, together with the reported stability of **5** suggested a general methodology for the synthesis of 2-arylpyrroles. The *N*-Boc pyrrole **5** can be readily prepared on a 20 g scale according to the procedure of Martina *et al.*[6] and the cross coupling reactions of **5** with a range of aryl halides were carried out using the Gronowitz conditions.[9] A mixture of the appropriate aryl iodide or bromide (ArX), *tetrakis*-(triphenylphosphine)palladium(0) (5 mol%) and **5** (1.4 equivalents) in 1,2-dimethoxyethane, with an excess of aqueous sodium carbonate as base, was heated at reflux for 0.5-18 h to give the corresponding *N*-Boc aryl pyrroles **6**[10] (**Scheme 1**). The results of the study are summarised in Table 1.

Table 1. Synthesis of the *N*-(Boc) 2-arylpyrroles **6**

Entry	Ar	X	Yield %[a]
1	Ph	I	55
2	Ph	Br	16
3	4-MeC$_6$H$_4$	Br	15
4	4-ClC$_6$H$_4$	Br	34
5	1-naphthyl	Br	34
6	2-thienyl	Br	35
7	3-pyridyl	Br	72
8		Br	98
9		Br	83
10		Br	63
11		Br	70

[a]Isolated pure product following SiO_2 chromatography

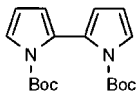


5 **6**

Scheme 1. *Reagents:* (i) ArX, $Pd(PPh_3)_4$, Na_2CO_3, H_2O, DME, reflux (see Table 1)

For the simple monosubstituted and unsubstituted aryl halides (entries 1-7), a trend was observed towards greater reactivity with increased electron deficiency of the Ar group. In the case of Ar = Ph, iodobenzene (entry 1) gave a cleaner reaction than bromobenzene (entry 2).

In all instances the major competing side reactions were deboronation of **5** to give *N*-(Boc) pyrrole and production of the homodimer **7**.[11] The 2-methoxy substituted halides (entries 8-11) gave particularly high yields, possibly due to participation by the 2-methoxy group in the coordination of the intermediate arylpalladium species, and this methodology proved to be compatible with the presence of acidic NH residues (entries 9 and 10) and with the presence of a basic nitrogen centre (entry 11). Removal of the Boc group could be effected in high yield in each case by treatment of **6** with an excess of sodium methoxide in methanol at room temperature.



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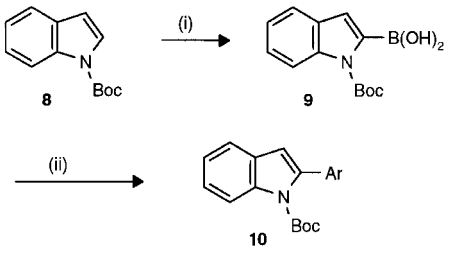
The encouraging results obtained with **5** as a cross-coupling substrate prompted the investigation of similar methodology applied to indole (Scheme 2). Deprotonation of *N*-(Boc) indole **8** with 1-lithio-2,2,6,6-tetramethylpiperidine (LiTMP) in THF followed by addition of triisopropyl borate and acidic work-up then gave the desired boronic acid **9**. Coupling with aryl halides was carried out in the manner described above to give the *N*-Boc 2-aryl indoles **10**, and the results of this aspect of the study are shown in Table 2.

Table 2. Synthesis of the *N*-Boc 2-arylindoles **10**

Entry	Ar	X	Yield %
1	Ph	I	52
2	4-MeC$_6$H4	Br	0
3	4-ClC$_6$H4	Br	26[a]
4	2-thienyl	Br	0
5	3-pyridyl	Br	66

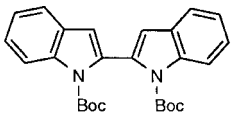
[a] Yield of deprotected 2-arylindole **12**



Scheme 2. *Reagents*: (i) 1. LiTMP, THF, -78 °C. 2. B(O^{i}Pr)$_3$. 3. H$^+$, H_2O (65 % overall yield); (ii) ArX, Pd(PPh$_3$)$_4$, Na_2CO_3, H_2O, DME, reflux (see Table 2)

In general, the Suzuki coupling yields obtained with **9** were lower than in the corresponding examples in the pyrrole series. In all cases, a significant amount of a by-product was obtained which was assigned as the 2,2´-dimer **11** on the basis of MS, IR and NMR data.[12] In the case of electron rich aryl bromides (entries 2 and 4) no desired product was observed but iodobenzene (entry 1) and 3-bromopyridine (entry 5) each gave a respectable yield of the corresponding *N*-Boc 2-aryl indole **10**. With 1-bromo-4-chlorobenzene (entry 3), *in situ* cleavage of the Boc group occurred, giving 2-(4-chlorophenyl)indole **12**. The lower reactivity of **9** relative to **5** may be due to greater steric hindrance of the *N*-Boc group in the indole series. This may arise because the presence of a hydrogen atom in the indole 7-position prevents the Boc group of **9** adopting a conformation where the bulky *t*-butyl group points away from the reacting C(2) site. This hypothesis is supported by data obtained with cross-couplings of (2-indolyl)stannanes,[13] where the Boc indole derivative gave lower yields than the corresponding SEM protected indole.

In conclusion, both the pyrrole and indole boronic acids, **5** and **9** respectively, can function as substrates for the Suzuki coupling reaction and in the pyrrole series, particularly high yields have been obtained for aryl halides bearing an *ortho*-methoxy group. In contrast with other



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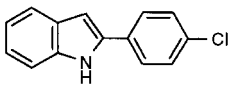

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methods, which require the use of potentially toxic and comparatively unstable stannane intermediates,[13] or *in situ* generation of an organometallic species,[3,4,14] the methodology described here uses boronic acid intermediates which are highly stable, relatively non-toxic, and easily prepared.

References and Notes

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10. All compounds gave satisfactory physiochemical data. A representative procedure is as follows: To a stirred solution of 2-bromo-5-ethylsulfonyl anisole (1.0 g, 3.6 mmol), *N*-(Boc) pyrrole-2-boronic acid **5** (1.06 g, 5.0 mmol) and *tetrakis*-(triphenylphosphine)palladium (0) (0.21 g, 0.18 mmol) in 1,2-dimethoxyethane (100 ml) at room temperature under argon was added a solution of sodium carbonate (1.6 g, 15 mmol) in water (8 ml). The mixture was heated at reflux for 4 h, cooled, then partitioned between water (300 ml) and dichloromethane (4 x 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. Chromatography with gradient elution using 10 - 50% ethyl acetate in hexane gave *N*-(Boc) 2-(5-ethylsulfonyl-2-methoxy)phenyl-1H-pyrrole (1.28 g, 98%) as a colourless solid, m.p. 135 - 139 °C (Found C, 59.39; H, 6.42; N, 3.83. $C_{18}H_{23}NO_5S$ requires C, 59.16; H, 6.34; N, 3.83%); ν_{max}/cm^{-1} 1743 (C=O), 1315, 1130 (S=O); δ_H (250 MHz; $CDCl_3$) 1.30 (3 H, t, *J* = 7 Hz), 1.37 (9 H, s), 3.13 (2 H, q, *J* = 7 Hz), 3.85 (3 H, s), 6.23 (1 H, m), 6.27 (1 H, m), 6.99 (1 H, d, *J* = 9 Hz), 7.38 (1 H, m), 7.79 (1 H, d, *J* = 2 Hz), 7.88 (1 H, dd, *J* = 9, 2 Hz).
11. Data for **7**: ν_{max}/cm^{-1} 1732; m/z (CI) 333 (MH$^+$, 80%), 277 (25), 233 (90), 177 (95), 133 (100); δ_H (400 MHz; $CDCl_3$) 1.37 (18 H, s), 6.17 (4 H, d, *J* = 3 Hz), 7.37 (2 H, t, *J* = 3 Hz).

12 Data for **11**: ν_{max}/cm^{-1} 1729 (C=O); Found M^+ 432.2049. $C_{26}H_{28}N_2O_4$ requires 432.2051; δ_H (300 MHz, $CDCl_3$) 1.24 (18 H, s), 6.65 (2 H, s), 7.25 (2 H, dt, *J* = 8, 1 Hz), 7.35 (2 H, dt, *J* = 8, 1 Hz), 7.57 (2 H, d, *J* = 8 Hz), 8.31 (2H, d, *J* = 8 Hz).

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