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Polyhalogenoheterocyclic compounds Part 54: [1] Suzuki reactions of 2,4,6-tribromo-3,5-difluoropyridine

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In commemoration of the centenary of the birth of Professor Ivan Ludvigovich Knunyants.

Abstract

Palladium catalysed Suzuki cross-coupling reactions between 2,4,6-tribromo-3,5-difluoropyridine and a short series of aromatic boronic acid derivatives gave 4-bromo-3,5-difluoro-2,6-diphenylpyridine derivatives arising from displacement of bromine atoms attached to positions *ortho* to ring nitrogen or the corresponding triaryl systems depending on the reaction conditions. Consequently, the use of polybromofluoropyridine scaffolds for the synthesis of polyfunctional heteroaromatic derivatives is expanded further.

Keywords: Heterocycle; Heterocyclic scaffold; Pyridine; Fluoropyridine; Suzuki; Palladium catalysis

1. Introduction

Polybromofluoropyridine derivatives are, potentially, very valuable scaffolds for the synthesis of multifunctional pyridine derivatives [2,3] because not only are nucleophilic substitution reactions possible, involving either replacement of fluorine or bromine depending upon the nature of the nucleophile, but also, for example, palladium catalysed processes involving activation of a carbon–bromine bond [1,2]. We have developed effective methodology for the synthesis of various polybromofluoroheteroaromatic systems [2] and are exploring the use of these novel scaffolds for a variety of synthetic applications in both the medicinal chemistry and materials arenas. A surprisingly high proportion of commercially important pharmaceutical and plant protection products are based upon a small heterocyclic ring core scaffold [4–7] and, consequently, efficient methodology for the synthesis of polyfunctional heterocyclic systems is an important research goal [8,9].

The palladium catalysed Suzuki cross-coupling reaction is a versatile method for the synthesis of biaryl and hetero-aryl derivatives [10] and the wide range of commercially available boronic acids, the relatively low toxicity of the by-products formed and the possibility to work under aqueous conditions has been widely exploited in all aspects of synthetic organic chemistry.

In this paper, we describe representative Suzuki cross-coupling reactions between a short series of aromatic boronic acid derivatives and 2,4,6-tribromo-3,5-difluoropyridine **1** and demonstrate how this readily accessible system can be used as a building block for the synthesis of polyfunctional fluoroaryl-pyridine derivatives.

2. Results and discussion

Electron rich arene boronic acids are prone to deboronation under the reaction conditions [$Pd(PPh_3)_4$, Cs_2CO_3/H_2O, toluene] first reported by Suzuki for the synthesis of biaryl derivatives but, subsequently, Gronowitz demonstrated that such deboronations can be suppressed by using glycol dimethyl ether (DME) as the solvent. Consequently, we have used refined Gronowitz conditions [11,12] [$Pd(PPh_3)_4$,

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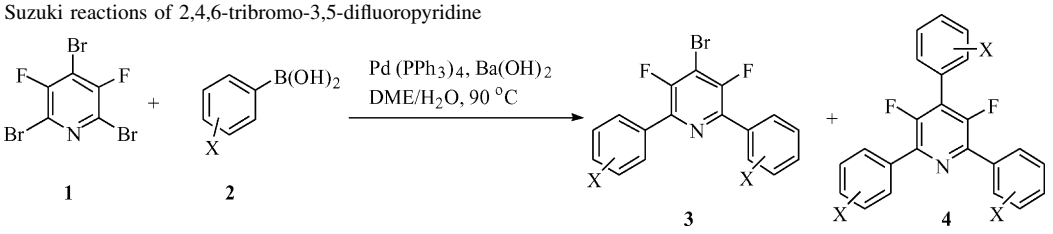
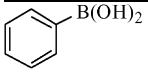
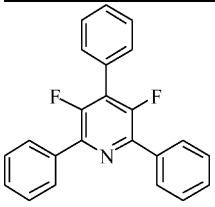
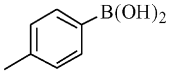
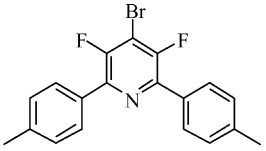
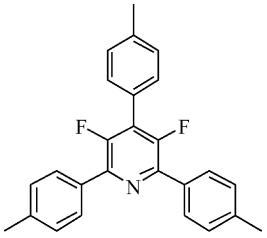
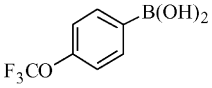
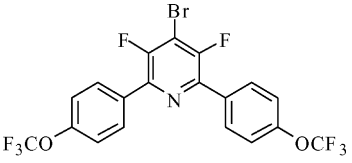
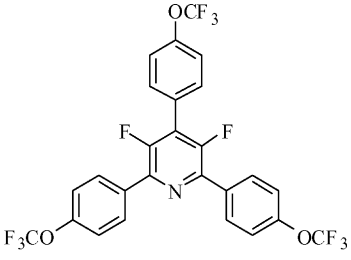
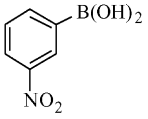
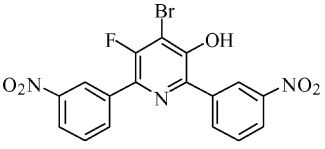
$Ba(OH)_2/H_2O$, DME] for Suzuki coupling reactions between a short range of boronic acids **2** and 2,4,6-tribromo-3,5-difluoropyridine **1** and the results are collated in Table 1. Using one equivalent of boronic acid generally afforded a mixture of diphenyl **3** and triphenylated **4** pyridine derivatives with complete conversion of the starting material whereas an excess of boronic acid led to good yields of the corresponding triphenyldifluoropyridine systems **4**. All products were isolated and fully characterised and, in addition, the diphenyl derivative **3b** was characterised by X-ray crystallography (Fig. 1). The phenyl group at C(6) is almost coplanar to the pyridine ring (dihedral angle 8.8°) whilst the phenyl group at C(2) is disordered equally between two orientations (A and B), which are inclined to the pyridine ring by similar, opposite angles (29.4° and 26.8°). Molecules related by the *b* translation form a π–π stack with an interplanar separation of ca. 3.6 Å and have the same orientation of the disordered ring, whereas molecules related by the inversion—*x*1–*y*–*z*, must have different orientations (i.e. A versus B), to avoid impossibly short intermolecular contacts.

Table 1
Suzuki reactions of 2,4,6-tribromo-3,5-difluoropyridine



Boronic acid **2**	**3**, Yield %	**4**, Yield%
 **2a**, 3 equiv.	–	 **4a**, 43
 **2b**, 1.2 equiv.	 **3b**, 32	 **4b**, 21
2b, 3 equiv.  **2c**, 0.8 equiv	–  **3c**, 22	**4b**, 52  **4c**, 8
2c, 3 equiv.  **2d**, 1.2 equiv.	–  **3d**, 54%	**4c**, 80 –

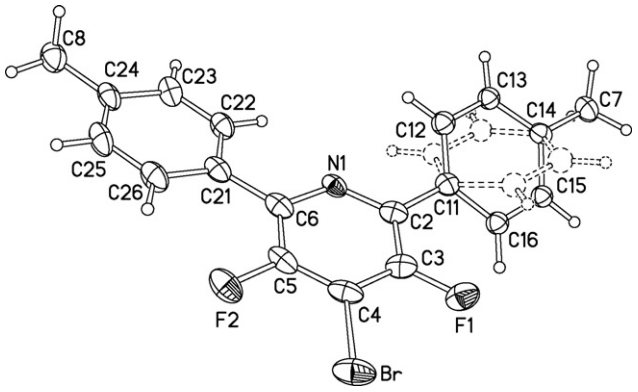
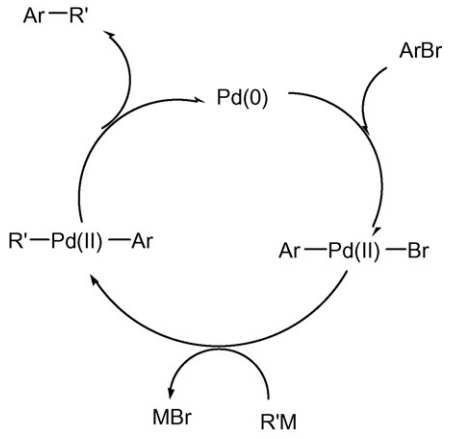


Fig. 1. X-ray molecular structure of **3b**, showing 50% thermal ellipsoids and the alternative orientations of the disordered phenyl group (A solid; B dashed).

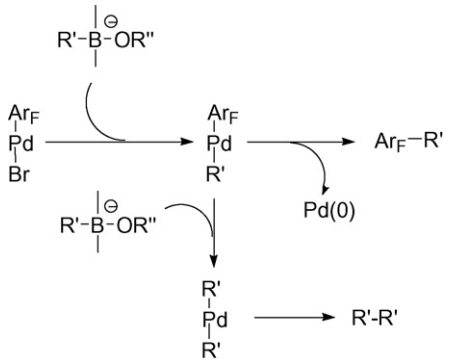


Scheme 1. General mechanism of the Suzuki coupling.

Coupling with 3-nitrobenzene boronic acid **2d** afforded unexpected results since when both equimolar and excess amounts of the nucleophile were used we observed the exclusive formation of **3d**. We suggest that **3d** is formed because the introduction of the strongly electron withdrawing group at the 2 and 6 positions activates the pyridine ring towards nucleophilic substitution and attack at the carbon–fluorine bond by free hydroxide ion present in solution occurs.

The generally accepted mechanism for Suzuki cross-coupling processes [10] involves slow oxidative addition of the aryl halides to Pd(0) complexes to give a stable trans σ-Pd(II) complex with retention of configuration (Scheme 1).

In the first stage, the palladium species acts as a nucleophile and reaction with an electron deficient polyhalogenated heterocycle is, therefore, a favoured process because such systems are especially prone to nucleophilic aromatic substitution reactions. Also, insertion of the palladium



Scheme 2.

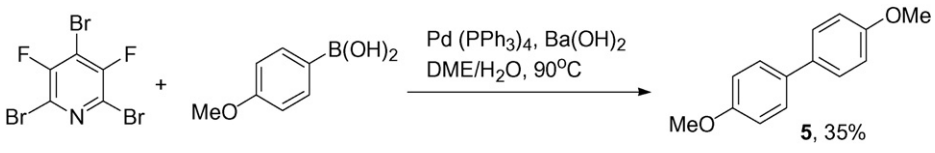
nucleophile occurs at the weaker and softer carbon–bromine bond rather than at the stronger carbon–fluorine bond. However, attack occurs unusually at positions that are *ortho* to ring nitrogen. Although most other nucleophiles attack preferentially at the 4- rather than the 2-position in polyhalogentated pyridines, these insertion reactions present a further example where transition metal induced reactions give a different outcome for displacement of either fluorine or bromine in heteroaromatic systems, suggesting some involvement of charge on nitrogen in the transition state [13,14]. The transmetalation step has been proposed to proceed by an enhancement of the nucleophilicity of the organic group on the boron atom by quaternization of the boron with the base to afford the ate complex (Scheme 2). Reductive elimination occurs from the *cis* RPd(II)R′complex to afford the coupled product.

When coupling with 4-methoxybenzeneboronic acid **2e** was performed (Scheme 3), the dimerised product 1-methoxy-4-(4-methoxyphenyl)benzene **5** was obtained indicating a change in mechanism. In this case, the stronger *p*-methoxy aryl nucleophile displaces the electron withdrawing polybromofluoropyridyl group leading to the coupled product as an effective competing process (Scheme 2).

In summary, bis-aryl- and tri-aryl-pyridine derivatives may be synthesised by Suzuki cross-coupling processes using polybromofluoropyridine as polyfunctional substrates.

3. Experimental

All starting materials were obtained commercially. All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a spectrometer operating at 500 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on either a VG 7070E spectrometer coupled with



Scheme 3.

a Hewlett Packard 5890 series II gas chromatograph. Accurate mass measurements were performed by the EPSRC Mass Spectrometry Service, Swansea, UK. Elemental analyses were obtained on an Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions was monitored by ^{19}F NMR Column chromatography was carried out on silica gel. 2,4,6-Tribromo-3,5-difluoropyridine was prepared following the literature procedure [2].

3.1. Suzuki reactions of 2,4,6-tribromo-3, 5-difluoropyridine *1*

3.1.1. General procedure

2,4,6-Tribromo-3,5-difluoropyridine **1**, monoglyme, tetrakistriphenylphosphine palladium (6%), boronic acid **2** and barium hydroxide and water were heated together with stirring. After completion of the reaction, the crude mixture was filtered through celite. Water was added and the aqueous solution was extracted into dichloromethane (3 × 30 mL), dried ($MgSO_4$) and evaporated. Purification was achieved by column chromatography on silica gel, sublimation or recrystallisation.

3.1.2. Reaction with benzeneboronic acid *2a*

1 (1 g, 2.84 mmol), monoglyme (5 mL), Pd catalyst (6%, 119.7 mg), benzeneboronic acid **2a** (1.04 g, 8.52 mmol), $Ba(OH)_2$ (2.82 g, 17.1 mmol) and water (2 mL), after heating at 90 °C for 48 h and column chromatography on silica gel using dichloromethane-hexane (1:1) as the eluent, gave 3,5-difluoro-2,4,6-triphenylpyridine **4a** (0.42 g, 43%) as a white solid; m.p. 135–137 °C (found: 343.117393. $C_{23}H_{15}F_2N$ requires 343.117256); δ_H 7.48–7.95 (m, ArH); δ_F −126.4 (s); *m/z* (EI^+) 343 ($[M]^+$, 100%), 267 (17).

3.1.3. Reactions with p-tolylboronic acid *2b*

1 (1 g, 2.84 mmol), monoglyme (5 mL), Pd catalyst (6%, 197 mg), *p*-tolylboronic acid, **2b** (0.48 g, 3.55 mmol), $Ba(OH)_2$ (1.17 g, 7.10 mmol) and water (2 mL), after heating at 90 °C for 24 h and column chromatography on silica gel using dichloromethane-hexane (3:1) as the eluent, gave 4-bromo-3,5-difluoro-2,6-bis(4-methylphenyl)-pyridine **3b** (32%, 0.35 g) as a white solid; m.p. 150–151.2 °C (from chloroform) (found C, 60.8; H, 3.8; N, 3.7. $C_{19}H_{14}BrF_2N$ requires C, 60.9; H, 3.7; N, 3.7%); δ_H 2.56 (3H, s, CH_3), 7.22 and 7.81 (4H, AA'XX', J_{AX} 8.0, ArH); δ_F −117.5 (s); δ_C 21.2 (s, CH_3), 109.7 (t, $^2J_{CF}$ 23.2, C–Br), 128.8 (m, ArH), 129.5 (s, ArH), 131.9 (d, $^3J_{CF}$ 7.0, *C*–C=N), 139.8 (s, *C*–CH_3), 141.9 (m, C=N), 153.1 (d, $^1J_{CF}$ 271.5, CF); *m/z* (EI^+) 375 ($[M]^+$, 100%), 373 ($[M]^+$, 98%); and, 3,5-difluoro-2,4,6-tris-(4-methylphenyl)pyridine **4b** (0.23 g, 21%), as a white solid; m.p. 152–154 °C (found C, 80.7; H, 5.5; N, 3.6. $C_{26}H_{21}F_2N$ requires C, 81.0; H, 5.5; N, 3.6%); δ_H 2.43 (6H, s, CH_3), 2.45 (3H, s, CH_3), 7.25 and 7.50 (4H, AA'XX', J_{AX} 8.0, ArH), 7.30 and 7.95 (8H, AA'XX', J_{AX} 8.0, ArH); δ_F −127.0 (s); δ_C 21.3 (s, CH_3), 21.4 (s, CH_3), 125.0 (s, ArH), 127.4 (t, $^3J_{CF}$ 23.2, C-4), 128.9 (s, ArH), 129.0 (s, ArH), 129.4 (C–CH_3), 129.5 (s, C–CH_3), 130.2 (m, ArH), 132.9 (t, $^3J_{CF}$ 3.4, C4–*C*), 139.1 (s, N=C–*C*), 141.7 (m, N=C), 152.7 (d, $^1J_{CF}$ 264.7, CF); *m/z* (EI^+) 385 ($[M]^+$, 100%), 193 (7).

By a similar procedure, **1** (0.3 g, 0.855 mmol), monoglyme (5 mL), Pd catalyst (6%, 59.3 mg), **2b** (0.34 g, 256 mmol), $Ba(OH)_2$ (0.36 g, 2.2 mmol) and water (2 mL), after heating at 90 °C for 18 h and column chromatography on silica gel using dichloromethane–hexane (2:1) as the eluent, gave **4b** (52%, 0.17 g), as a white solid; spectral data as above.

3.1.4. Reactions with 4-trifluoromethoxybenzeneboronic acid *2c*

1 (1 g, 2.84 mmol), monoglyme (5 mL), Pd catalyst (6%, 155 mg), 4-trifluoromethoxybenzeneboronic acid **2c** (0.47 g, 2.27 mmol), $Ba(OH)_2$ (1.19 g, 4.54 mmol) and water (2 mL), after heating at 90 °C for 48 h and column chromatography on silica gel with hexanes as the eluent, gave 2-bromo-3,5-difluoro-4,6-bis(4-trifluoromethoxyphenyl)-pyridine **3c** (22%, 0.32 g) as a white solid; b.p. > 300 °C (found: $[MH]^+$, 513.9689. $C_{19}H_8BrF_8NO_2$ requires: $[MH]^+$, 513.9693); δ_H 7.33 and 8.03 (AA'XX', J_{AX} 8.0, ArH); δ_F −58.1 (3F, s, CF_3), −115.5 (1F, s, ArF); δ_C 110.0 (m, C–Br), 120.3 (q, $^1J_{CF}$ 257.8, CF_3), 120.8 (s, ArH), 130.3 (m, ArH), 132.6 (s, N=C–*C*), 140.5 (m, N=C), 150.1 (C–O), 153.5 (d, $^1J_{CF}$ 267.5, CF); *m/z* (EI^+) 515 ($[M]^+$, 16%), 513 ($[M]^+$, 26%), 418 (12), 247 (29), 150 (75), 69 (100); and 3,5-difluoro-2,4,6-tris(4-trifluoromethoxyphenyl)pyridine **4c** (0.13 g, 8%) as a thick orange oil; b.p. 209–211 °C (found: C, 52.2; H, 2.2; N, 2.1. $C_{26}H_{12}F_{11}NO_3$ requires: C, 52.4; H, 2.0; N, 2.3%); δ_H 7.52 and 8.51 (8H, AA'XX', J_{AX} 8.0, ArH), 7.60 and 7.83 (4H, AA'XX', J_{AX} 8.1, ArH); δ_F −58.8 (3F, s, CF_3), −126.1 (1F, s, CF); *m/z* (EI^+) 595 ($[M]^+$, 27%), 321 (100), 253 (29), 225 (38).

By a similar procedure, **1** (0.15 g, 0.43 mmol), monoglyme (5 mL), Pd catalyst (6%, 30.14 mg), **2c** (0.27 g, 1.31 mmol), $Ba(OH)_2$ (0.144 g, 0.86 mmol) and water (2 mL), after heating at 90 °C for 48 h and column chromatography on silica gel with ethyl acetate-petroleum ether 40–60 °C (1:10) as the eluent, gave **4c** (80%, 0.21 g) as a thick orange oil; spectral data as above.

3.1.5. Reaction with 3-nitrobenzeneboronic acid *2d*

1 (0.8 g, 2.28 mmol), monoglyme (5 mL), Pd catalyst (6%, 158.5 mg), 3-nitrobenzeneboronic acid **2d** (0.48 g, 2.85 mmol), $Ba(OH)_2$ (0.76 g, 4.56 mmol) and water (2 mL), after heating at 90 °C for 48 h and column chromatography on silica gel with petroleum ether-ethyl acetate (1:1) as the eluent, gave 4-bromo-5-fluoro-2,6-bis(3-nitrophenyl)pyridine-3-ol **3d** (0.53 g, 54%) as a white solid; m.p. 145.1–145.8 °C (found: $[M + H]^+$, 432.9708. $C_{17}H_9BrFN_3O_5$ requires: $[M + H]^+$, 432.9709); δ_H 7.72 (1 H, t, $^3J_{HH}$ 8.0, H-δ5′), 7.73 (1H, t, $^3J_{HH}$ 8.0, H-5), 8.33 (2 H, m, H-4,4′), 8.40 (1 H, d, $^3J_{HH}$ 7.5, H-6), 8.48 (1 H, d, $^3J_{HH}$ 7.0, H-6′), 8.90 (1 H, s, H-2), 9.02 (1 H, s, H-2′); δ_F −114.3 (s); *m/z* (EI^+) 435 ($[M]^+$, 95%), 433 ($[M]^+$, 100%), 389 (12), 341 (21), 233 (17).

3.1.6. Reaction with 4-methoxybenzeneboronic acid

1 (0.18 g, 0.52 mmol), monoglyme (5 mL), Pd catalyst (6%, 35.5 mg), 4-methoxybenzeneboronic acid (1.56 mmol, 0.24 g),

$Ba(OH)_2$ (0.17 g, 104 mmol) and water (2 mL), after heating at 90 °C for 48 h, recrystallisation from dichloromethane followed by chromatography on silica gel with dichloromethane-hexane (2:1) as the eluent, gave 1-methoxy-4-(4-methoxyphenyl)benzene (0.12 g, 35%); ($_H$ 3.80 (3 H, s, OCH_3), 6.90 (2H, m, ArH), 7.80 (2H, m, ArH); δ_C 55.4 (s, OCH_3), 113.8 (s, C-3), 135.5 (s, C-2), 137.7 (C-4), 163.4 (C–O); as compared to an authentic sample (Aldrich).

3.2. X-ray crystallography of **3b**

The X-ray diffraction experiment was carried out on a Bruker 3-circle diffractometer with a SMART 1K CCD area detector, using graphite-monochromated Mo Kα radiation ($\bar{\lambda}$ = 0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structure was solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL software (version 6.14, Bruker AXS, Madison WI, USA, 2003). *Crystal data*: $C_{19}H_{14}BrF_2N$, M = 374.22, T = 110 K, monoclinic, space group *I*2/*a* (no. 15, non-standard setting), a = 22.695(3), b = 4.7838(6), c = 28.562(4) Å, β = 95.78(3)°, V = 3085.3(7) Å^3, Z = 8, D_c = 1.611 g cm^{-3}, μ = 2.68 mm^{-1}, crystal size 0.50 × 0.13 mm × 0.04 mm, 10176 reflections with $2\theta \leq 55°$ measured by narrow-frame ω scans and corrected for absorption by numerical integration (transmission factors 0.6252 to 0.9074, R_{int} = 0.073 before and 0.043 after correction), final $R(F)$ = 0.047 on 2404 data with $I \geq 2\sigma(I)$, w$R(F^2)$ = 0.121 on all 3554 unique data.[1]

Acknowledgement

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[1] CCDC 634126 contains the supplementary crystallographic data for this paper. These data can be viewed free of charge via http://www.ccdc.cam.ac.uk/cont/retrieving.html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.