JOC*Note*

Versatile Synthesis of 3,5-Disubstituted 2-Fluoropyridines and 2-Pyridones

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Received December 18, 2002

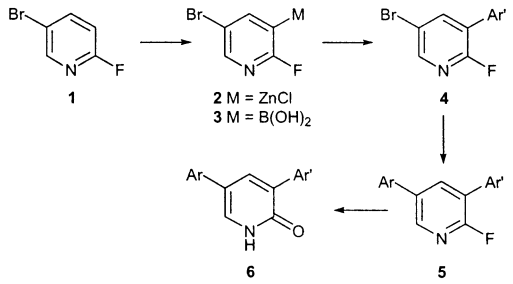
Abstract: 5-Bromo-2-fluoro-3-pyridylboronic acid (**3**) was prepared in high yield by *ortho*-lithiation of 5-bromo-2-fluoropyridine (**1**), followed by reaction with trimethylborate. Suzuki reaction of **3** with a range of aryl iodides gave 3-monosubstituted 5-bromo-2-fluoropyridines **4** in excellent yields. A second Suzuki reaction utilizing the bromo constituent of **4** with aryl and heteroaryl boronic acids provided 3,5-disubstituted 2-fluoropyridines **5**, which in turn could be converted to the corresponding 2-pyridones **6**.

The efficient synthesis of libraries of multiring aryl and heteroaryl small molecules is vitally important to both the pharmaceutical and agrochemical sectors in the search for biologically active compounds. In particular, the development of an efficient methodology toward the regiocontrolled preparation of highly substituted pyridines and pyridones represents a major challenge in heterocyclic chemistry.

A common strategy used to prepare substituted pyridines is directed *ortho*-lithiation (DoM) reactions, where a functional group attached to the pyridine ring is used to direct a regioselective deprotonation. This chemistry has developed significantly since the early pioneering work of Gribble,[1] and Quéguiner[2] has been prominent in the development and subsequent synthetic application of the *ortho*-lithiation and trapping of 2-, 3-, and 4-halopyridines.[3]

Recently, a number of groups have reported the directed lithiation and transmetalation of pyridines, combined with subsequent Pd(0)-mediated cross-coupling reactions to provide an entry to substituted pyridines. We utilized the regioselective C-4 deprotonation of 3-bromopyridine, followed by a Li/Zn transmetalation and Pd(0)-mediated Negishi coupling, to provide 3,4-disubstituted pyridines.[4a] 2-Bromopyridine provides an entry to 2,3- and 2,4-disubstituted pyridines,[4a] and 3,4-disubstituted and 3,4,5-trisubstituted pyridines are available by application of directed *ortho*-lithiation procedures to 4-bromopyridine.[4b] Rault and co-workers have described a series of other boronated halopyridines, including 2-halo-5-pyridyl, 2-, 4-, or 5-halo-3-pyridyl, and 2- or 3-halo-4-pyridyl boronic acids, which undergo efficient Suzuki coupling reactions.[5] Bryce has also reported the synthesis and Suzuki reactions of 2-halo(or 2-methoxy)-5-pyridyl boronic acids, and trisubstituted pyridines have been generated via 3-chloro-6-methoxy-4-pyridinyl boronic acid.[6]

SCHEME 1



We were interested in developing a flexible route toward more highly substituted and functionalized variants such as 3,5-diarylpyridin-2-ones. Previously, 3,5-diarylated pyridin-2-ones have been prepared using a nickel-catalyzed coupling of an arylmagnesium bromide with a 3,5-dihalopyridine, with the resulting symmetrical 3,5-diarylpyridine then converted to the corresponding 2-pyridone using a three-step oxidation/rearrangement/hydrolysis sequence.[7] We now describe an effective methodology that provides rapid, efficient, and regiocontrolled entry to unsymmetrical 3,5-disubstituted 2-pyridones. This is based on the regioselective metalation of 5-bromo-2-fluoropyridine and the subsequent chemoselective coupling reactions of 5-bromo-2-fluoropyridine-3-boronic acid **3**, as outlined in Scheme 1.

Our initial efforts focused on the synthesis of the 3-substituted 5-bromo-2-fluoropyridines **4** via the organozinc intermediate **2**. Commercially available 5-bromo-2-fluoropyridine (**1**) was treated with LDA at −78 °C to give the lithiated species **7**. Subsequent attempts to transmetalate **7** with zinc(II) chloride to provide **2**, followed by coupling to iodobenzene with $Pd(PPh_3)_4$ under standard Negishi conditions,[8] failed to provide the desired cross-coupled product (Scheme 2). *ortho*-Lithiation of

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(1) (a) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151−169. (b) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137−4140.

(2) (a) Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139−150. (b) Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Synop.* **1982**, 278−279. (c) Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *41*, 3433−3440. (d) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035−3042. (e) Mallet, M.; Quéguiner, G. *Tetrahedron* **1986**, *42*, 2253−2262. (f) Mallet, M.; Branger, G.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319−332. (g) Marsais, F.; Pineau, P.; Nivolliers, F.; Mallet, M.; Turck, A.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1992**, *57*, 565−573. (h) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832−7838.

(3) For reviews, see: Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−304. Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090.

(4) (a) Karig, G.; Spencer, J. A.; Gallagher, T. *Org. Lett.* **2001**, *3*, 835−838. (b) Karig, G.; Thasana, N.; Gallagher, T. *Synlett* **2002**, 808−810.

(5) (a) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369−4373. (b) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323−3328. (c) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885−2890.

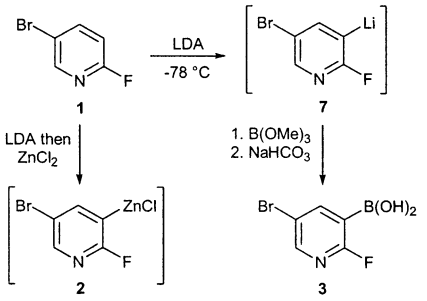
(6) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541−7543.

(7) Tagat, J. R.; McCombie, S. W.; Barton, B. E.; Jackson, J.; Shortall, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2143−2146.

(8) Negishi, E.; Luo, F. T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117−122.

10.1021/jo026864f CCC: $25.00
Published on Web 03/20/2003

SCHEME 2

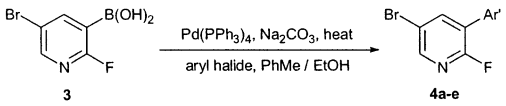


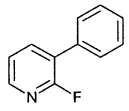
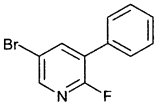
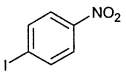
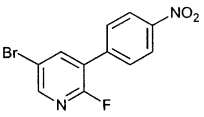
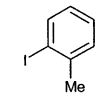
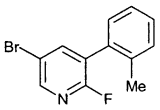
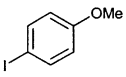
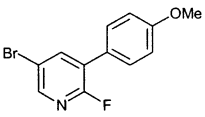
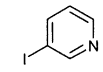
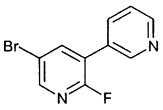
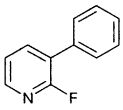
2-fluoropyridine with LDA is well-known,[2a,5b] and since the initial lithiation step to give **7** is successful (see below), it would appear that either Li/Zn transmetalation fails or the resulting aryl zinc reagent **2** is unreactive under the palladium cross-coupling conditions used.[9]

Proof of formation of **7** was obtained by generation of the 2,5-dihalopyridylboronic acid **3** (Scheme 2). Lithiation (LDA, −78 °C) of 5-bromo-2-fluoropyridine (**1**) followed by trapping with trimethylborate and hydrolytic workup gave boronic acid **3** in 80% yield. Boronic acid **3** is thermally stable, nonhygroscopic, and easily purified by recrystallization from ethyl acetate/hexane and represents a highly versatile heterocyclic building block.[10]

Suzuki coupling reactions of boronic acid **3** with a range of aryl iodides and bromides were explored under standard conditions (Na_2CO_3, $Pd(PPh_3)_4$, PhMe/EtOH, reflux) (Table 1). Several points arise from this study. An extended reaction time (6 h) led to coupling but also subsequent debromination to give **8** in 30% yield (Table 1, entry 1). This was overcome using shorter reaction times (2 h), which gave the desired coupled bromopyridines **4a**−**e** in high yields. It is also pertinent to note that no homocoupled products, resulting from **3** acting as both a boronic acid and an aryl bromide, were isolated from these reactions. Although reaction of the boronic acid with aryl iodides was expected to be faster than that with aryl bromides, a 1.1 equiv excess of boronic acid is used during these reactions. An attempt to couple boronic acid **3** with an aryl bromide (Table 1, entry 7) was not successful. A significant amount of bromobenzene remained after 2 h, and after 6 h, the debrominated product **8** was only isolated in 38% yield.[11] In summary, successful and high-yielding Suzuki cross-coupling of boronic acid **3** are best achieved using short reaction times with reactive aryl iodides as substrates.

TABLE 1



Entry	Aryl Halide	Reaction Time (h)	Product	Yield
1		6	 **8**	30%
2		2	 **4a**	71%
3		2	 **4b**	87%
4		2	 **4c**	79%
5		2	 **4d**	78%
6		2	 **4e**	72%
7		6	 **8**	38%

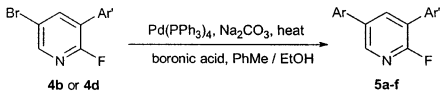
To explore the ability of 3-aryl-5-bromo-2-fluoropyridines **4** to undergo a second Suzuki coupling step to give 3,5-diaryl-2-fluoropyridines, two representative derivatives **4b** and **4d** were studied. Suzuki reaction of **4b** and **4d** with a series of aryl and heteroaryl boronic acids gave the corresponding 3,5-disubstiuted-2-fluoropyridines **5** in excellent yields (Table 2). All reactions were complete after only 2 h. This observation suggests that the presence of the boronic acid moiety of **3** exerts an influence on the reactivity of the 5-bromo component, which may explain why self-coupling of **3** to itself is also not detected. Reduction of the C−Br moiety (compare entries 1 and 2, Table 1) under these conditions occurs only after the initial Suzuki reaction is complete and the boronic acid component has been replaced. Once the first cross-coupling is completed, then the bromo residue (of **4**) is

(9) Unsuccessful Li−Zn exchange of the 3-lithiated species of 5-bromo-2-fluoropyridine **7** was expected, as similar results with the corresponding lithiated species of 2-fluoropyridine during the synthesis of fluoro analogues of UB-165 were observed. For a discussion of these results, see: Sutherland, A.; Gallagher, T.; Sharples, C. G. V.; Wonnacott, S. *J. Org. Chem*. **2003**, *68*, 2475−2478.

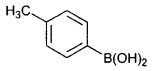
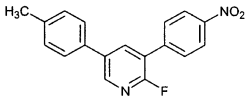
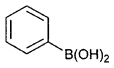
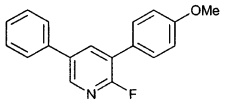
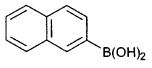
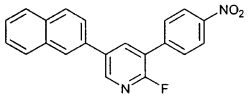
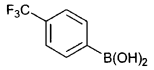
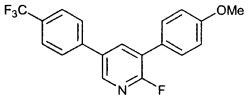
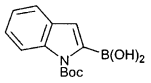
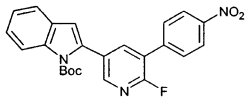
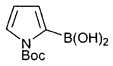
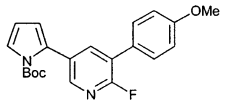
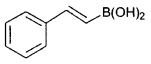
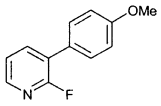
(10) For the synthesis of other dihalopyridyl boronic acids, see: Achad, S.; Guyot, M. Potier, P. *Tetrahedron Lett*. **1993**, *34*, 2127−2130. Mongin, F.; Trécourt, F.; Gervais, B.; Mongin, O.; Quéguiner G. *J. Org. Chem*. **2002**, *67*, 3272−3276. 2,6-Difluoropyridyl 3- and 4-boronic acids have been reported in the patent literature: Reiffenrath, V. Ger. Offen. 4218978, 1993. Boyd, F. L.; Gudmundsson, K.; Johns, B. A. WO 0278701, 2002. Alberti, M. J.; Baldwin, I. R.; Cheung, M.; Cockerill, S.; Flack, S.; Harris, P. A.; Jung, D. K.; Peckham, G.; Peel, M. R.; Stanford, J. B.; Stevens, K.; Veal, J. M. WO 0216359, 2002.

(11) Bryce and co-workers[6] examined the Suzuki reaction of a bromopyridyl boronic acid, and under extended reaction times (22−43 h) in DMF, only low yields (10−32%) of the coupled products were isolated.

TABLE 2



4b or **4d** → **5a-f**

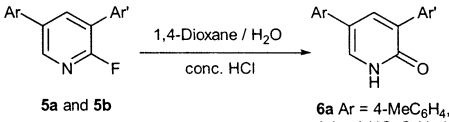
Entry	Boronic Acid	Aryl Bromide	Product	Yield
1		**4b**	 **5a**	85%
2		**4d**	 **5b**	89%
3		**4b**	 **5c**	85%
4		**4d**	 **5d**	70%
5		**4b**	 **5e**	58%
6		**4d**	 **5f**	75%
7		**4d**	 **9**	85%

activated. Attempts to couple a vinyl boronic acid (entry 7, Table 2) to **4d** failed, with only the debrominated derivative **9** being isolated.

The final step for the synthesis of 2-pyridiones **6** required hydrolysis of the 2-fluoropyridine of adducts **5**. Several multistep procedures have been reported for this conversion;[7,12] however, direct hydrolysis of 2-fluoropyridines **5a** and **5b** under acidic conditions (aqueous HCl, dioxane, reflux, 24 h)[13] provided the corresponding 2-pyridones **6a** and **6b**, respectively, in very high yields (Scheme 3).

In conclusion, we have described the synthesis of the synthetically versatile dihalopyridylboronic acid **3**, which has been applied to the chemoselective and stepwise synthesis of a range of 3,5-substituted 2-fluoropyridines

SCHEME 3



5a and **5b** → **6a** Ar = 4-MeC_6H_4, Ar' = 4-$NO_2C_6H_4$ (92%); **6b** Ar = C_6H_5, Ar' = 4-$MeOC_6H_4$ (88%)

5, which can then be readily converted to the corresponding 2-pyridones **6**. Appropriate reaction conditions for each step have been defined, and the efficiency of these processes makes this chemistry an attractive and, more importantly, a highly flexible entry to substituted pyridines and pyridones.

Experimental Section

5-Bromo-2-fluoro-3-pyridylboronic Acid (3). Butyllithium (13.7 mmol, 2.5 M in hexanes) was added dropwise to a solution of diisopropylamine (1.92 mL, 13.7 mmol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. After 20 min, this solution was added to 5-bromo-2-fluoropyridine (**3**) (2.0 g, 11.4 mmol) in THF (10 mL) at −78 °C under a nitrogen atmosphere. After 30 min, a solution of trimethylborate (2.31 mL, 13.7 mmol) in THF (5 mL) was added, and the reaction mixture was allowed to warm to room temperature over l h. After this time, saturated aqueous sodium hydrogen carbonate (10 mL) was added, the aqueous layer was separated, carefully acidified to pH 6−7 with 2 M hydrochloric acid (5 mL), and then extracted with ethyl acetate (3 × 10 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo, and the residue was recrystallized from ethyl acetate and hexane to give 5-bromo-2-fluoro-3-pyridylboronic acid (**3**) (1.86 g, 80%) as a colorless solid. Mp: 144−146 °C (ethyl acetate/hexane). IR (neat) ν (cm^{-1}): 3339, 1590, 1562. ^1H NMR (270 MHz, CD_3OD): δ 8.29 (1 H, dd, J = 2.7, 1.0 Hz, 6-H), 8.13 (1 H, dd, J = 7.3, 2.7 Hz, 4-H). ^{13}C NMR (100.5 MHz, CD_3OD): δ 164.4 (d, J = 238.2 Hz, C), 149.3 (d, J = 15.1 Hz, CH), 148.9 (d, J = 9.0 Hz, CH), 116.4 (d, J = 4.0 Hz, C). HRMS: calcd for $C_5H_5{}^{11}B^{79}BrFNO_2$ (MH^+), 219.9581; found, 219.9587.

General Procedure for the Preparation of 3-Substituted 5-Bromo-2-fluoropyridines 4 (Table 1). To a solution of aryl iodide (0.35 mmol) in toluene (8 mL) and ethanol (2 mL) containing $Pd(PPh_3)_4$ (20 mg, 0.017 mmol, 5 mol %) and 5-bromo-2-fluoro-3-pyridylboronic acid (**3**) (0.39 mmol) was added Na_2CO_3 (0.1 g, 0.96 mmol) in water (4 mL). The mixture was heated under reflux for 2 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (EtOAc/light petroleum) to give adducts **4** as either viscous oils or colorless solids. For recrystallization solvents and spectroscopic data for adducts **4**, see Supporting Information.

General Procedure for the Preparation of the 3,5-Disubstituted-2-fluoropyridines 5 (Table 2). To a solution of pyridyl bromide **4** (0.14 mmol) in toluene (8 mL) and ethanol (2 mL), containing $Pd(PPh_3)_4$ (16 mg, 0.014 mmol, 10 mol %), and the requisite boronic acid (0.21 mmol) was added sodium carbonate (0.1 g, 0.96 mmol) in water (4 mL). The reaction mixture was heated under reflux for 2 h, cooled to room temperature, diluted with water (20 mL), and extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated, and purification by flash column chromatography (EtOAc/light petroleum) gave adducts **5** as either viscous oils or colorless solids. For recrystallization solvents and spectroscopic data for adducts **5**, see Supporting Information.

General Procedure for the Preparation of the 3,5-Disubstituted 2-Pyridones 6. To a solution of the 3,5-disubstituted 2-fluoropyridine **5a** or **5b** in 1,4-dioxane (6 mL) and water (2 mL) was added concentrated hydrochloric acid (0.5 mL), and the reaction mixture was heated under reflux for 24

(12) Solomon, M. S.; Hopkins, P. B. *Tetrahedron Lett.* **1991**, *32*, 3297−3300.

(13) Bradlow, L.; Vanderwerf, C. A. *J. Org. Chem.* **1949**, *14*, 509−515.

h. The reaction mixture was cooled and concentrated, and the resulting residue was dissolved in water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo, and pyridones **6a** and **6b** were recrystallized from chloroform and hexane. Spectroscopic and characterization data for **6a** and **6b** are available in Supporting Information.

Acknowledgment. The authors thank the EPSRC and BBSRC (Biomolecular Sciences Project Grant 86/B11785) for financial support. Lancaster Synthesis, Ltd., is thanked for their gift of 5-bromo-2-fluoropyridine and for carrying out the large-scale preparation and supply of boronic acid **3**.

Supporting Information Available: Experimental, spectroscopic, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026864F