JOC*Note*

Functionalized Pyridylboronic Acids and Their Suzuki Cross-Coupling Reactions To Yield Novel Heteroarylpyridines

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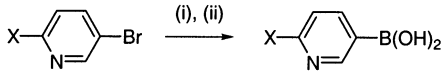
Abstract: 2-Bromo-5-pyridylboronic acid **2a**, 2-chloro-5-pyridylboronic acid **2b**, 2-methoxy-5-pyridylboronic acid **2c**, and 5-chloro-2-methoxy-4-pyridylboronic acid **4** have been synthesized and shown to undergo palladium-catalyzed cross-coupling reactions with heteroaryl bromides to yield novel heteroarylpyridine derivatives. The X-ray crystal structures of **2a** and **2b** have been obtained.

Metal-mediated catalytic cross-coupling reactions continue to be widely employed in the synthesis of biaryl and biheteroaryl systems that have contemporary pharmaceutical, agrochemical, materials, and supramolecular applications.[1] In this context, the Suzuki reaction,[2−4] which involves the palladium-catalyzed cross-coupling of aryl- or heteroarylboronic acids with aryl or heteroaryl halides (or triflates), has proved to be very versatile.[5−20] It is remarkable, therefore, that whereas halopyridines have often been employed in Suzuki reactions there are only isolated examples in the literature of pyridylboronic acids or pyridylboronic esters,[5−10,21] and no systematic study of their reactions has been reported. This is due, in part, to the difficulties in purification of the parent pyridylboronic acids.[21]

SCHEME 1[a]



1 a X = Br
b X = Cl
c X = OMe

2 a X = Br
b X = Cl
c X = OMe

[a] Reagents: (i) *n*-BuLi (1.0−1.1 equiv), −78 °C; triisopropyl borate (2.0−2.2 equiv), ether or THF, −78 °C; (ii) H_2O, 20 °C.

Our main objectives in this work were (i) to obtain shelf-stable pyridylboronic acids containing functional substituents that are suitable for subsequent transformations and (ii) to explore the scope of their reactions with a variety of brominated heterocycles under Suzuki cross-coupling conditions, and thereby to obtain new heteroaryl-substituted pyridine derivatives. Herein, we describe our results with 2-bromo-, 2-chloro-, and 2-methoxy-5-pyridylboronic acids **2a**−**c**, respectively, and 5-chloro-2-methoxy-4-pyridylboronic acid **4**. During the preparation of this manuscript, Rault et al.[10] reported similar syntheses of **2a** and **2b** and two cross-coupling reactions (with bromobenzene and 2-bromobenzonitrile, respectively) that are different from those reported herein.

We chose compounds **2a**−**c** and **4** as our initial targets because (i) suitable pyridyl precursors are commercially available and cheap, (ii) the halo and methoxy substituents would impart different electronic properties to the pyridine ring, and (iii) these substituents should be amenable to further synthetic modification after cross-coupling reactions had occurred. Lithium−halogen exchange reactions of compounds **1a**−**c** (*n*-BuLi at −78 °C)[22] followed by the standard procedure for introduction of a boronic acid group (triisopropyl borate, then aqueous workup)[2] afforded products **2a**−**c** in 79%, 61%, and 65% yields, respectively, as shelf-stable solids (Scheme 1). Lithiation of 5-chloro-2-methoxypyridine **3** (LDA at −78 °C)[23] and reaction with triisopropyl borate gave 5-chloro-2-methoxypyridyl-4-boronic acid **4** in 48% yield (Scheme 2). Compounds **2a**−**c** and **4** were isolated as shelf-stable solids. Crystal structures were determined for **2a** and **2b** by X-ray analysis (see the Supporting Information). These

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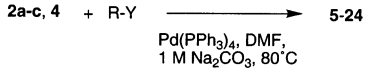
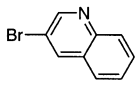
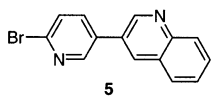
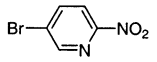
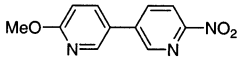
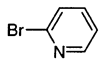
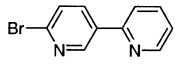
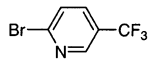
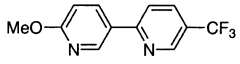
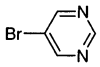
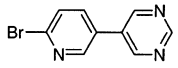
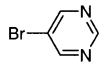
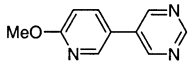
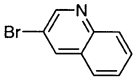
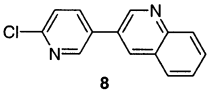
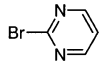
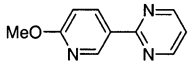
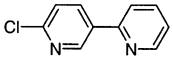
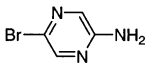
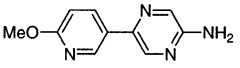
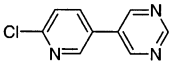
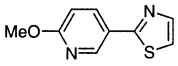
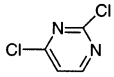
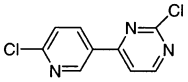
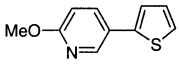
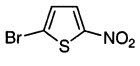
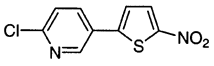
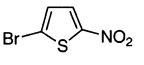
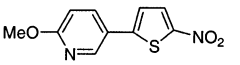
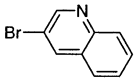
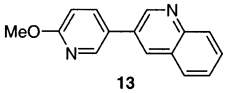
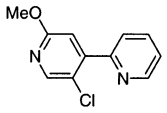
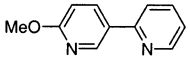
TABLE 1.



Entry	Boronic acid	R-Y	Product	Isolated yield (%)	Entry	Boronic acid	R-Y	Product	Isolated yield (%)
1	**2a**		 **5**	32	13	**2c**		 **17**	66
2	**2a**		 **6**	11	15	**2c**		 **18**	32
3	**2a**		 **7**	10	16	**2c**		 **19**	35
4	**2b**		 **8**	55	17	**2c**		 **20**	28
5	**2b**		 **9**	61	18	**2c**		 **21**	26
6	**2b**		 **10**	38	19	**2c**		 **22**	85
7	**2b**		 **11**	23	20	**2c**		 **23**	87
8	**2b**		 **12**	53	21	**2c**		 **24**	94
9	**2c**		 **13**	76	22	**4**		 **25**	35
10	**2c**		 **14**	50					
11	**2c**		**15**	58	23	**4**		**26**	28
12	**2c**		**16**	83					

SCHEME 2[a]

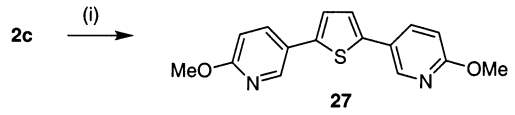
3 **4**

[a] Reagents: (i) LDA (1.2 sequiv), THF, −78 °C; (ii) triisopropyl borate, (2.0 equiv); (iii) H_2O, −78 → 20 °C.

are the first crystal structures to be reported for any heterocyclic boronic acids.

Coupling reactions of **2a**−**c** with a range of heteroaryl bromides were explored under standard conditions using sodium carbonate as base and tetrakis(triphenylphosphino)palladium as catalyst in DMF at 80 °C (Table 1). Compound **2a** consistently gave multicomponent product mixtures (TLC evidence) from which only low yields of bi(heteroaryl) products were isolated after column chromatography. For example, reaction with 3-bromoquinoline, 2-bromopyridine, and 5-bromopyrimidine gave products **5**−**7** in 10−32% yields (Table 1, entries 1−3). Analogous reactions with the boronic acid derivatives **2b** and **2c** were much cleaner and more efficient, providing

SCHEME 3[a]



27

[a] Reagents: (i) 2,5-dibromothiophene, $Pd(PPh_3)_4$, DMF, 1 M Na_2CO_3, 80 °C.

a means of attaching pyridyl, quinolyl, pyrimidyl, pyrazyl, thienyl, and thiazolyl substituents to the pyridine ring (Table 1, entries 4−6 and 8−21). It is notable that the more electron-deficient heterocycles (i.e., the bromopyrimidine and bromopyrazine derivatives) gave the lowest yields of coupled products (Table 1, entries 6 and 16−18). It has been reported that chloropyrimidines are good substrates for Suzuki couplings with phenylboronic acid derivatives.[15,18] Therefore, we treated pyridylboronic acid derivative **2b** with 2,4-dichloropyrimidine and obtained product **11** in 23% yield (Table 1, entry 7). The precedent is that the halogen at C4 will be more reactive than at C2,[15] as we have observed in this case.[24]

We have also established that 5-chloro-2-methoxy-4-pyridylboronic acid **4** similarly engages in cross-coupling reactions with 2-bromopyridine and 2-bromo-5-nitrothiophene to yield compounds **25** and **26**, respectively.

The data in Table 1 clearly show that pyridylboronic acids are versatile reagents for the synthesis of novel heteroarylpyridine derivatives. The suitability of reagent **2c** for ter(heteroaryl) synthesis was illustrated by its 2-fold reaction with 2,5-dibromothiophene, which gave **27** in 34% yield (Scheme 3). Linear oligo(heteroaryl) systems of this type are important materials for optoelectronic device applications.[25]

(24) The observed response in a NOESY spectrum between the proton at C5 of the pyrimidine with the protons at C2 and C4 of the pyridine ring confirmed this isomer structure; see the Supporting Information.

(25) Review: Mitsche, U.; Bauerle, P. *J. Mater. Chem*. **2000**, *10*, 1471.

In summary, this paper describes the synthesis of air-stable pyridylboronic acid derivatives and their reactions with heteroaryl bromides under Suzuki cross-coupling conditions to yield a range of heteroarylpyridine derivatives, generally in moderate or good yields.

Experimental Section

Representative Procedure for the Preparation of Pyridylboronic acids 2a−c and 4 As Exemplified by the Preparation of 2c. To a solution of 5-bromo-2-methoxypyridine (0.5 mL, 3.9 mmol) in anhydrous ether (10 mL) at −78 °C was added *n*-butyllithium (1.6 M in hexane, 2.5 mL, 4.0 mmol) dropwise. The reaction mixture was stirred for 1 h at −78 °C, and then triisopropyl borate (1.8 mL, 7.8 mmol) was added quickly. The reaction mixture was stirred at −78 °C for another 1 h, quenched with water, and allowed to warm to 20 °C with stirring overnight. The solvent was evaporated in vacuo, and the aqueous layer was taken to pH 10 (with 5% NaOH) and was washed with ether. The aqueous layer was then acidified to pH 4 (with 48% HBr) to precipitate compound **2c**.

Representative Procedure for the Cross-Coupling Reactions. The boronic acid, the halide, and tetrakis(triphenylphosphino)palladium (ca. 5 mol % relative to the boronic acid) were sequentially added to degassed DMF, and the mixture was stirred at 20 °C for 30−60 min. Degassed aqueous Na_2CO_3 solution was added, and the reaction mixture was heated under nitrogen at 80 °C until TLC monitoring showed that the reaction was complete (22−70 h). Solvent was removed in vacuo, ethyl acetate was added, and the organic layer was washed with brine, separated, and dried over $MgSO_4$. The product was purified by chromatography on a silica gel column.

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Supporting Information Available: Full characterization details for compounds **2a**−**c** and **4**−**27**; NOESY spectrum of compound **11**; tables of X-ray crystallographic data and ORTEP plots for compounds **2b** and **2c** and a discussion of their crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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