OXIDATION AND SUZUKI CROSS-COUPLING REACTION FROM AZAHETEROARYLBORONIC ACIDS

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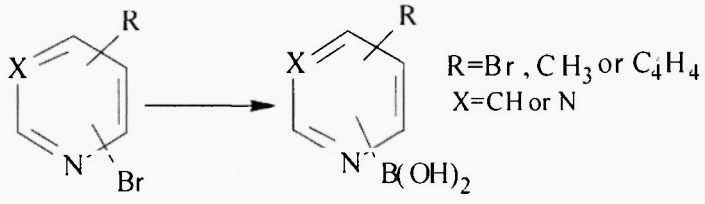
Abstract

New azaheteroarylboronic acids open the possibilities of the Suzuki cross-coupling reactions to build multi-purpose organometallic ligands with good yields (48%- 65%). The access to hydroxypyridines and hydroxypyrimidines is also described.

Introduction

Arylboronic acids and their esters have become a frequently utilized class of synthetic intermediates [1-3], and much attention has been paid to them in biology [4] and in the study of molecular recognition [5,6]. They have been used extensively in the synthesis of natural products, nucleoside analogues, liquid crystals, porphyrins and polymers [7]. In addition, arylboronic acids and esters have been used in boroneutrotherapy[4], as inhibitors of angiogenesis [8], as synthetic carriers of carbohydrates and ribonucleosides for selective membrane transport, chemosensors and receptors of mono and disaccharides [9]. They have recently been employed in the synthesis of achiral and chiral alcohols [10], of diaryl ethers [11], and are also currently used for palladium-catalyzed cross-coupling reactions with organic halides or triflates leading to the formation of carbon-carbon bonds (Suzuki reaction [12]). Owing to these applications, new methods to obtain arylboronic acids have always attracted attention. Few results, however, have been reported concerning azaheteroarylboronic acids. It is in this aim we have recently investigated routes that may lead to azaheteroarylboronic acids. We have proposed a transmetalation reaction between Grignard azine reagent and tris trimethylsilylborate under mild conditions leading to aza- and polyaza- heteroarylboronic acids **2**, as yet largely unknown, with good yields (70 to 75%) [13] (Scheme 1).



1 **2**

Scheme 1: Synthesis of azaheteroarylboronic acids **2** [13]

Thus, we have decided now to explore the properties of these new boronic acids into oxidation and Suzuki cross-coupling reactions. This paper describes the scope of these starting compounds for to access to hydroxyazaheterocycles and various polyazaheterocycles extensively used in catalytic synthesis.

Materials and methods

All reagents were of commercial quality and were used without purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 80 and Bruker 200 instruments; chemical shifts (δ) are reported in ppm.

General Procedure for Preparation of compounds 3

A dry 50 ml three-necked flask equipped with thermometer, reflux condenser, septum inlet, and magnetic stirring is flushed with nitrogen. The azaheteroarylboronic acid (10.0 ml of an appróximately 0.5*M* in THF solution) is placed in the flask by syringe. The flask is immersed in an ice bath, and the azaheteroarylboronic acid was oxidized by 2.0 ml of 3*M* NaOH, followed by 2.0 ml of 30% H_2O_2 at such a rate to keep the temperature at 0-5°C. After the addition, the reaction is stirred an additional 10 min at 40-50°C (warm water bath), then cooled to room temperature. The aqueous phase was saturated with solid K_2CO_3, the organic layer was separated and the aqueous layer was extracted with ether (2 x 5 ml). The combined organic extracts were dried over anhydrous $MgSO_4$

and evaporated in vacuo. The crude hydroxyazaheteroaryl was purified by flash chromatography (eluents ethyl acetate/hexane 1/3).

Spectral data of compounds isolated.

Compound 3a: ^{1}H NMR ($CDCl_3$) δ 7.10 (dd, H-5), 7.31-7.43 (m, H-3, H-4), 8.25 (dd, H-6), 11.77 (s, OH). ^{13}C NMR ($CDCl_3$) δ 122.69, 128.30, 138.56, 142.28, 150.28. Anal. calcd. for C_5H_5NO : C 63.15; H 5.30; N 14.82. Found: C 63.45 ; H 5.09 ; N 14.75.

Compound **3 b**: ^{1}H NMR ($CDCl_3$) δ 7.01 (dd, H-5), 7.62 (dd, H-4), 8.36 (dd, H-6), 8.53 (d, H-2), 11.87 (s, OH). ^{13}C NMR ($CDCl_3$) δ 115.94,124.67, 131.64, 141.24, 153.20. Anal. calcd. for C_5H_5NO : C 63.15; H 5.30; N 14.82. Found: C 63.32 ; H 5.42 ;N 14.73.

Compound **3 c**: ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 2H, H-4, H-6), 8.82 (s, H-2), 11.79 (s, OH). ^{13}C NMR ($CDCl_3$) δ 122.66, 123.78, 128.67, 132.24. Anal. calcd. for $C_4H_4N_2O$: C 50.00; H 4.20; N 29.15. Found: C 50.28 ; H 3.94 ;N 29.28.

Compound **3 d**: ^{1}H NMR ($CDCl_3$) δ 7.26, (dd, H-3), 7.38 (dd, H-5), 7.49 (ddd, H-4), 11.77 (s, OH). ^{13}C NMR ($CDCl_3$) δ 112.69, 128.33, 137.28, 142.30, 164.66. Anal. calcd. for C_5H_4BrNO : C 34.51; H 2.32; N 8.05. Found: C 34.63 ; H 2.64 ; N 8.18.

Compound **3 e**: ^{1}H NMR ($CDCl_3$) δ 6.93 (s, 1H, H-4), 7.50 (t, 1H, H-6), 7.65 (t, 1H, H-7), 8.10 (d, 1H, H-5), 8.20 (d, 1H, H-8), 8.82 (s, 1H, H-2), 11.75 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 126.95, 127.49, 128.69, 129.20, 134.40, 138.85, 147.88, 149.29, 150.24. Anal. calcd. for C_9H_7NO: C 74.47; H 4.86; N 9.65. Found: C 74.93; H 5.03 ; N 9.52

General Procedure for Cross-Coupling Reactions

A suspension of azaheteroaryl bromide (2.5 mmol, 1 equiv.), azaheteroarylboronic acid (2.86 mmol, 1.15 equiv.), sodium carbonate 2 M (2.7 ml, 5.3 mmol, 2.12 equiv.) in toluene (20 ml) and EtOH (2 ml) were stirred under an atmosphere of argon for 30 min. $Pd(PPh_3)_4$ (0.11 mmol, 0.045 equiv.) was then added and the mixture was heated at 110°C for 32 h. The toluene was removed in vacuo, the residue diluted with H_2O and extracted with CH_2Cl_2 (3x10 ml). The organic layers were dried over magnesium sulfate, concentrated in vacuo and purified by flash chromatography (eluent: methylene chloride/hexane 1/9).

Spectra data of compounds isolated

Compound **4**: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 4H, H-4, H-5), 7.65 (d, 2H, H-3), 7.90 (dd, 2H, H-6), ^{13}C NMR ($CDCl_3$) δ 151.60, 135.08, 134.96, 132.24, 118.74. Anal. calcd. for $C_{10}H_8N_2$: C 76.90; H 5.16; N 17.94. Found: C 77.17; H 5.34; N 17.84.

Compound **5**: ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 4H, H-4, H-5), 7.45 (d, 2H, H-2), 7.80 (dd, 2H, H-6), ^{13}C NMR ($CDCl_3$) δ 134.01, 133.26, 128.70, 128.62, 128.4. Anal. calcd. for $C_{10}H_8N_2$: C 76.90; H 5.16; N 17.94 Found: C 77.12 ; H 5.36 ; N 18.02.

Compound **6**: ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 4H, H-4, H-6), 7.74 (d, 2H, H-2), ^{13}C NMR ($CDCl_3$) δ 194.06, 193.70, 133.12, 129.54. Anal. calcd. For $C_8H_6N_4$: C 60.75; H 3.82; N 35.42 Found: C 60.52 ; H 4.06 ;N 35.38.

Compound **9**: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, H-2', H-2"), 7.67 (d, 2H, H-3, H-5), 7.60 (d, 2H, H-4', H-4"), 7.47 (s, 2H, H-6', H-6"), 7.43 (t, 1H, H-4), ^{13}C NMR ($CDCl_3$) δ 13.64, 129.15, 128.68, 128.40, 127.98, 127.50, 127.30, 127.18, 125.17. Anal. calcd. for $C_{13}H_9N_5$: C 66.37; H 3.86; N 29.77 Found: C 66.59 ; H 3.68 ; N 29.82

Compound **1 1**: ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H, H-2', H-2"), 7.68 (d, 2H, H-6', H-6"), 7.50 (dd, 2H, H-5', H-5"), 7.43 (dd, 2H, H-3, H-5), 7.32 (t, 1H, H-4), ^{13}C NMR ($CDCl_3$) δ 150.40, 148.01, 140.16, 134.67, 133.60, 132.03, 130.17, 128.46, 127.10, 119.18. Anal. calcd. for $C_{15}H_{11}N_3$: C 77.23; H 4.75; N 18.01 Found: C 77.54 ; H 4.63 ; N 17.96.

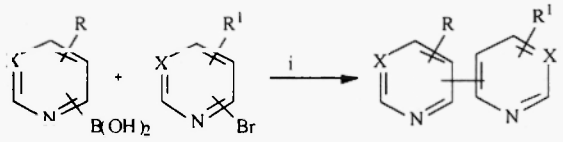
Table 1: Selected characteristics of hydroxy products 3a-3e

Entry n°	Hydroxy product X	R	place of OH		Yield(%
1	**3 a**	CH	H	-2	75
2	**3 b**	CH	H	-3	78
3	**3 c**	N	H	-5	85
4	**3 d**	CH	6-Br	-2	80
5	**3 e**	CH	C_4H_4	-3	90

Results and discussion

Reaction of oxidation

The oxidation of the C-$B(OH)_2$ bond is an elegant method to obtain alcohols [14]. More, many pharmaceutical products incorporate pyridine and pyrimidine units bearing an hydroxy group[15]. Recently, R-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) has been described as a powerful non-opiate analgesic [16]. An economical new synthesis has been proposed by Krow et al. [17].



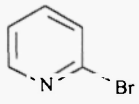
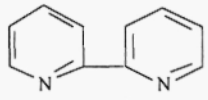
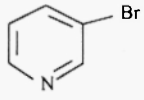
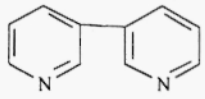
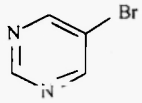
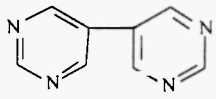
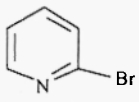
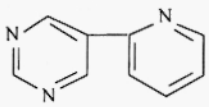
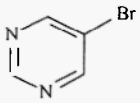
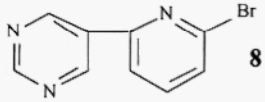
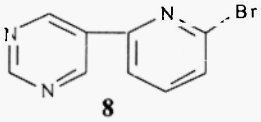
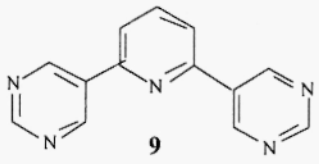
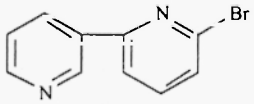
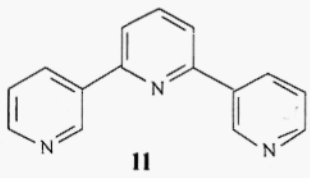
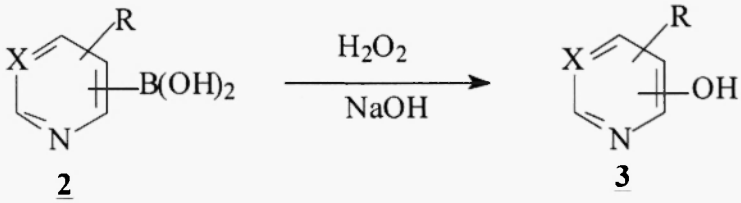
Boronic Acid $RB(OH)_2$	halide reagent	Suzuki compound	Yield* (%)	Rf
2-pyridyl **2a**		 **4**	56	0.39
3-pyridyl **2b**		 **5**	56	0.42
5-pyrimidyl **2e**		 **6**	65	0.48
5-pyrimidyl **2e**		 **7**	62	0.59
6-bromo-2-pyridyl **2d**		 **8**	52	0.61
5-pyrimidyl **2e**	 **8**	 **9**	48	0.90
3-pyridyl **2b**	 **10**	 **11**	52	0.86

Table 2: Selected Suzuki cross- coupling of boronic acids **2**

i)reaction conditions : boronic acid (1equiv.), halide reagent (1.15equiv.), Na_2CO_3 (2.12equiv.), $Pd(PPh_3)$ (0.045equiv.), toluene (20ml), EtOH (2ml), reflux during 32h ;

* yields of analytically pure compounds; solvent for elution: CH_2Cl_2/hexane 1/9

A brief survey of the oxidation parameters was perfomed by analogy with the classical conditions. The system H_2O_2/NaOH at pH 9 was found to be the best oxidant reagent. The corresponding alcohols were isolated with good yields (75 to 90%) (see Scheme 2 and Table 1).
It is worth noting that the oxidation in situ, at the end of the transmetalation, strongly reduced the yield of isolated alcohols because the presence of side-products.



2 3

Scheme 2: Synthesis of hydroxypyridines and hydroxypyrimidines

Suzuki cross-coupling reactions

This procedure, using arylboronic acids, has emerged as one of the most popular method to obtain biaryl compounds [12]. The absence of aza- and polyaza- heteroarylboronic acids had limited its application at cross-coupling aryl-aryl or aryl-azaheterocycles only. Subsequently at our results, the possibility to obtain polyazaheterocycles via symmetrical Suzuki cross-coupling offers a new opportunity according the scheme of the Table 2.
Among the multitude of process described, after several trials, we opted for one based on tetrakis (triphenylphosphine)palladium(0) in the presence of Na_2CO_3 in toluene under reflux. In these conditions, various di- or tri- symmetric or non–polyazaheterocycles have been isolated an the excellent yield as shown by the examples reported in Table 2. Importantly, this strategy has more general applications through the choice of various combinations of boronic acids and heteroarylhalides. By synthesizing these original boronic acids we bring a useful improvement to the usual aryl-aryl coupling reactions which do not have such a broad range of applications. Taking into account the good results obtained in monocoupling reactions, the work was extended to the synthesis of tricyclic skeletons. In a one-step reaction with boronic acid **2e** and 2,6-dibromopyridine, involving double coupling, we always obtained products **8** and **9** arising from competition between single and double coupling. In order to favor double coupling the conditions proposed here will have to be optimized. However, in a two-step reaction, using compound **8** as an intermediate, tricyclic structure **9** was formed with an overall yield of 48%. By the same way, terpyridine **11** is isolated by cross-coupling reaction between 3-pyridylboronic acid **2b** and intermediate compound **10** (52%). These examples illustrate the importance of azaheteroarylboronic acids in the Suzuki reaction permitting its extension to the building of polyazaheterocycles.

Conclusion

To conclude, we report preliminary results on a new and convenient route to synthesize hydroxypyridines and hydroxypyrimidines. In addition, the application of the Suzuki cross-coupling reaction proposed here should allow the synthesis of many diverse pyridine- and pyrimidine-containing molecules difficult to synthesize otherwise but which are useful in pharmacology and in the construction of multi-purpose organometallic ligands. Current efforts are focused on the synthesis of targeted molecules using this procedure.

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