

## Regioselective Suzuki coupling on pyridinium *N*-(3,5-dibromoheteroar-2-yl)aminides

M. José Reyes, Rafael Castillo, M. Luisa Izquierdo and Julio Alvarez-Builla\*

*Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain*

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**Abstract**—A regioselective Suzuki–Miyaura cross-coupling reaction on 3',5'-dibromo pyridinium *N*-(2'-azinyl)aminides is reported. A series of 3'-aryl(or heteroaryl)-5'-bromo-pyridinium *N*-(2'-pirazinyl)aminides were obtained in good yields. Two isomeric 3',5'-diaryl pyridinium *N*-(2'-azinyl)aminides were also prepared.

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Functionalization of heterocycles through Suzuki–Miyaura palladium-catalyzed cross-coupling has been established as a standard method for the synthesis of biaryl and heterobiaryl systems.<sup>1</sup> Substituted pyridines and pyrazines are valuable intermediates in the pharmaceutical and flavour fields, so development of regioselective processes over both systems has an indubitable interest. In the past years, our research programme has been related with the synthetic utility of pyridinium *N*-(2'-azinyl)aminides **1**<sup>2</sup> (Fig. 1) as building blocks in the synthesis of azine derivatives,<sup>3</sup> and we recently reported preliminary results obtained in the cross-coupling reaction between arylboronic acids and pyridinium *N*-(5'-bromoheteroar-2'-yl)aminides **1a–c**<sup>4</sup> (Fig. 1).

The promising results obtained from ylides **1a,b** justified broadening of the process over other aminides, such as *N*-(3',5'-dibromopyrid-2'-yl)pyridinium aminide **1c**.<sup>3c</sup> On this substrate, a double Suzuki reaction was performed, and different 3,5-disubstituted azines were obtained.<sup>4</sup>

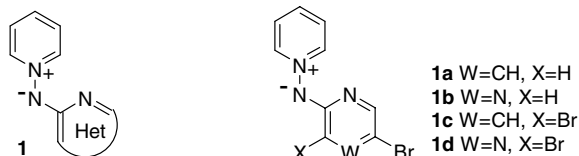


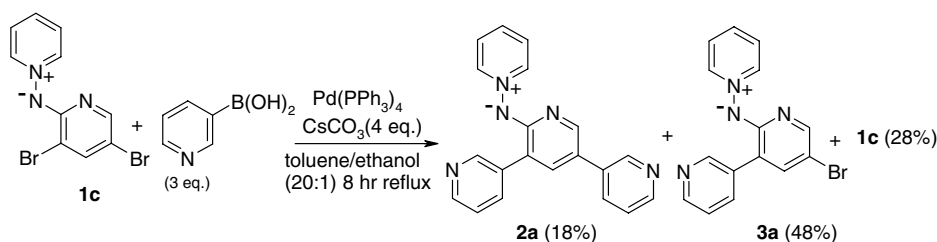
Figure 1.

\* Corresponding author. Fax: +34 91 885 46 86; e-mail: [julio.alvarez@uah.es](mailto:julio.alvarez@uah.es)

The same double coupling methodology on **1c**, employing 3-pyridylboronic acid (Scheme 1), produced a low yield (18%) of the expected bis-heteroaryl aminide **2a**, while the monosubstituted ylide **3a** appeared as the main reaction product (48%), in addition to 28% of starting material **1c** that was recovered. Neither the use of a large excess of 3-pyridylboronic acid and/or palladium catalyst, nor longer reaction times, improved the yields of compound **2a**.

The structure elucidation of **3a** was solved by comparison of its <sup>1</sup>H NMR spectra with those of related compounds. H6' of the 2-aminopyridine ring appears more shielded when a bromine atom is in position 5', than when an arene is placed in the same position.<sup>3b,4</sup> The following data were obtained for δH6' (CD<sub>3</sub>OD) in compounds **1c**, **2a** and **3a**: 7.74 ppm, 8.03 ppm and 7.71 ppm, respectively. This result pointed out a considerable degree of regioselectivity in the Suzuki process, when *N*-(3',5'-dibromo-2'-pyridin-2'-yl)pyridinium aminide **1c** was reacted with pyridyl-3-boronic acid.

Regioselectivity in palladium cross-coupling reactions of di-haloazines, having two identical halogen atoms in different positions of the ring, has not been often described in the literature.<sup>5a</sup> On uncharged systems, 2,5-dibromopyridine undergoes a regioselective palladium-catalyzed coupling with terminal acetylenes and arylzinc halides,<sup>5b</sup> and 2,5-dichloropyridine selectively reacts at 2-position with phenylboronic acid.<sup>5c,d</sup> Moreover, the synthesis of 2-aryl-6-chloronicotinamides via Suzuki coupling of 2,6-dichloronicotinamide with aryl boronic acids has also been described, and in this case, regioselectivity



Scheme 1.

was achieved by chelation of the palladium(0) species by the amide group.<sup>5c</sup> Furthermore, Thompson et al. obtained the 3,5-diheteroaryl product by Suzuki coupling of 3,5-dibromopyridin-2-ylamine and 2-methoxy-pyridin-3-yl boronic acid, but nothing appears in the letter concerning the presence of monocoupled products in the mixture.<sup>5f</sup> Regioselective Suzuki coupling has also been reported in certain dihaloazine and -diazine systems, but only when the reactivity differences between the two halogens was well defined.<sup>6</sup>

The above cited results encouraged us to perform new experiments to test the regioselectivity of the Suzuki reaction of *N*-(3',5'-dibromopyridin-2'-yl)pyridinium aminide **1c** and *N*-(3',5'-dibromopyrazin-2'-yl)pyridinium aminide **1d**. Table 1 shows the results obtained for parallel coupling tests on **1c** and **1d** with three different boronic acids, in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (5%), under slightly different conditions (A and B) (Scheme 2). In all cases the reaction mixtures, after 5 h reflux, were analyzed by HPLC/MS.<sup>7</sup>

The two aryl isomers **3** and **4** were detected together with the corresponding 3,5-disubstituted aminide **2** and a small quantity of starting material **1**. In all cases, a preference for substitution on position 3'- was observed (Scheme 2).

From these data, it appears that both the nature of the aminide substrate and the boronic acid used are the main factors influencing the degree of selectivity obtained. Aminide **1d** and, in this case, method B produced

the best results with phenyl boronic acid, with a higher yield and regioselectivity observed (Table 1, entries 5 and 6).

Although a model explaining the selectivity observed in mono coupling reaction towards one of the bromine groups in aminides **1** is not yet fully available, one important factor should be the increased stability of the palladium intermediate **5** (Fig. 2) with respect to its opposite regioisomer. However, comparing results between **1c** and **1d**, the regioselectivity is clearly higher in the pyrazine derivative, so the second ring nitrogen should have an additional influence. In a recent paper, Yang and Jiang<sup>8</sup> reported a similar selectivity for the Suzuki coupling on 2,5-dibromo-3-methoxy pyrazine, a non-charged substrate, which with one equivalent of phenylboronic acid, yielded the 2-phenyl derivative in a high yield.

In Table 2, the results obtained for the Suzuki coupling of *N*-(3',5'-dibromopyrazin-2'-yl)pyridinium aminide **1d** with aryl and heteroarylboronic acids, following method B are presented. In all cases a high degree of regioselectivity for the 3-position was observed, with both aryl and heteroarylboronic acids, and pyridinium *N*-(3'-aryl (or heteroaryl)-5'-bromopyrazin-2'-yl)aminides **3** were obtained in good yields.<sup>9</sup>

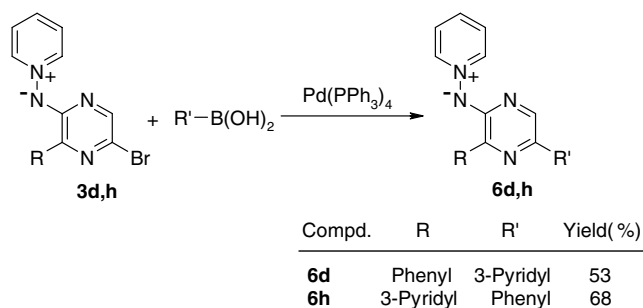
The availability of aminides **3** allowed the synthesis of two isomeric 3',5'-disubstituted *N*-pyrazin-2'-ylpyridinium aminides **6d,h** which were obtained when an additional Suzuki coupling was achieved on ylides **3d** and **3h**,

Table 1. Suzuki coupling of aminides **1c,d** and R-B(OH)<sub>2</sub>: a regioselectivity study

Entry	Aminide	Y	R	Method <sup>a</sup>	2b-d <sup>b</sup> Yield (%)	3b-d <sup>b</sup> Yield (%)	4b-d <sup>b</sup> Yield (%)	1c,d <sup>b</sup> Yield (%)
1	<b>1c</b>	CH	Ph	A	14	52	16	18
2	<b>1c</b>	CH	Ph	B	10	36	23	31
3	<b>1c</b>	CH	<i>p</i> -Tol.	A	22	36	27	15
4	<b>1c</b>	CH	<i>p</i> -Tol.	B	29	32	30	10
5	<b>1d</b>	N	Ph	A	8	61	26	5
6	<b>1d</b>	N	Ph	B	25	67	3	5

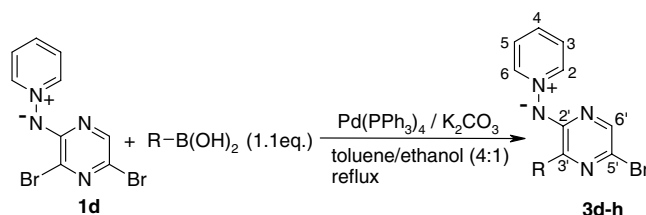
<sup>a</sup> Method A: Cs<sub>2</sub>CO<sub>3</sub> (4 equiv) as a base in toluene:ethanol (20:1). Method B: K<sub>2</sub>CO<sub>3</sub> (10 equiv) as a base in toluene:ethanol (4:1).

<sup>b</sup> Yields determined by HPLC/MS.<sup>7</sup>



Scheme 2.

employing 4-pyridyl- and phenylboronic acids, respectively<sup>10</sup> (Scheme 2). In this way, the method provides a straightforward strategy to obtain unsymmetrical 3',5'-disubstituted aminides **6**, and not only the symmetrical derivatives as has been described earlier.<sup>4</sup>

Table 2. Regioselective C–C coupling of aminide **1d** and boronic acids

Entry	Product	R	Reaction time (h)	Mp (°C)	Yield (%) <sup>a</sup>
1	<b>3d</b>		3	198–199	75
2	<b>3e</b>		4	200–202	50
3	<b>3f</b>		5	182–183	71
4	<b>3g</b>		1	190–192	65
5	<b>3h</b>		2	170–172	65
6	<b>3i</b>		4	229–231	77
7	<b>3j</b>		16	236–238	60
8	<b>3k</b>		12	163–165	84
9	<b>3l</b>		12	206–208	81

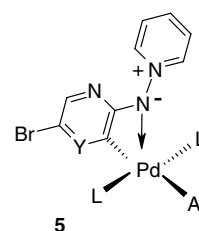
<sup>a</sup> Isolated yield. Method B, as described in Table 1, was used.

Figure 2.

In conclusion, a regioselective Suzuki–Miyaura cross-coupling process has been observed, on pyridinium *N*-(3',5'-dibromopyrazin-2'-yl)aminides similar to **1d**. Although less evident, the phenomenon appears also in their pyridine analogue. As a general methodology, the process can be useful to selectively functionalize the 3-position of the pyrazine ring. Two successive cross-coupling reactions over **1d** gave satisfactory yields in aminides **6** with a non-symmetrical substitution (Scheme 2)

that can undergo, as we have described earlier,<sup>3a,c</sup> either an N–N reduction to produce 3,5-disubstituted 2-aminopyrazines<sup>3a,c</sup> or a regioselective alkylation process at the exocyclic nitrogen followed by a similar N–N reduction, to yield 3,5-disubstituted *N*-alkyl-2-aminopyrazines.<sup>3d,f,g</sup> So, the whole approach might give access to useful pyrazine intermediates. Efforts in this direction are in progress in our laboratory.

### Acknowledgements

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- HPLC conditions*: Column, Luna C-18 (150 × 4.6 mm) from Jasco Analytica; Eluent, HCOOH (4% in H<sub>2</sub>O)(A), H<sub>2</sub>O(B) and CH<sub>3</sub>CN(C); Gradient, 93% B–4.5% B in 25 min, A = 2.5% *t* = 0–25 min; Flow, 1.0 mL/min;  $\lambda$ , 280, 284 and 210 nm. Experiments were performed on an Agilent 1100 HPLC/MS.
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- General procedure for monocoupling*: Pd(PPh<sub>3</sub>)<sub>4</sub> (57 mg, 5% mmol), boronic acid (1.1 mmol), aminide **1d** (330 mg, 1 mmol) and K<sub>2</sub>CO<sub>3</sub> (10 mmol) were stirred under argon and refluxed in a mixture of toluene:ethanol 4:1 (15 mL) until no starting material was detected by TLC. The mixture was filtered through celite and washed with acetonitrile. The filtrates were combined and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column using ethanol as eluent, and recrystallized from the appropriate solvent.  
*N*-(5'-Bromo-3'-phenylpyraz-2'-yl)pyridinium aminide (**3d**): Orange solid (245 mg, 75%), mp 198–199 °C (AcOEt), IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1484, 1404, 1372, 1239, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  (ppm) 8.71 (2H, dd, *J* = 7.0 and 1.3 Hz, H<sub>2</sub>(6)); 8.15 (1H, tt, *J* = 7.6 and 1.3 Hz, H<sub>4</sub>); 8.13 (2H, dd, *J* = 8.4 and 1.5 Hz, H<sub>2</sub>'(6'')); 7.87 (2H, dd, *J* = 7.6 and 7.0 Hz, H<sub>3</sub>(5)); 7.58 (1H, s, H<sub>6</sub>'); 7.44 (3H, m, H<sub>3</sub>'(5'') and H<sub>4</sub>''); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD):  $\delta$  156.4 (C<sub>2</sub>'), 142.3 (C<sub>2</sub>(6)), 141.9 (C<sub>3</sub>'), 140.0 (C<sub>6</sub>'), 137.3 (C<sub>1</sub>''), 134.1 (C<sub>4</sub>), 129.1 (C<sub>2</sub>'(6'')), 128.4 (C<sub>4</sub>''), 127.7 (C<sub>3</sub>'(5'')), 126.0 (C<sub>3</sub>(5)), 121.7 (C<sub>5</sub>'). Anal. Calcd for C<sub>15</sub>H<sub>11</sub>BrN<sub>4</sub>: C, 55.07; H, 3.39; N, 17.12. Found: C, 55.28; H, 3.60; N, 16.93.
- General procedure for compounds 6*: Pd(PPh<sub>3</sub>)<sub>4</sub> (57 mg, 5% mmol), boronic acid (1.5 mmol), aminide **3** (1 mmol) and K<sub>2</sub>CO<sub>3</sub> (10 mmol) were stirred and refluxed under argon, in a mixture of toluene:ethanol 4:1 (15 mL) until no starting material was detected by TLC. The mixture was filtered through celite and washed with acetonitrile. The filtrates were combined and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column using ethanol as eluent, and recrystallized from the appropriate solvent.  
*N*-[3'-Phenyl-5'-(3''-pyridyl)pyraz-2'-yl]pyridinium aminide (**6d**): Orange solid (173 mg, 53%), mp 173–176 °C (EtOH–AcOEt), IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>): 1554, 1501, 1468, 1401, 1368, 1303, 1252, 1142, 799, 754, 703, 664 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  (ppm) 9.06 (1H, d, *J* = 2.2 Hz, H<sub>2</sub>''); 8.71 (2H, dd, *J* = 6.8 y 1.3 Hz, H<sub>2</sub>(6)); 8.39 (1H, dd, *J* = 4.8 and 1.7 Hz, H<sub>6</sub>''); 8.30 (1H, ddd, *J* = 8.1, 2.2 and 1.7 Hz, H<sub>4</sub>''); 8.26 (2H, dd, *J* = 8.4 and 1.6 Hz, H<sub>2</sub>'(6'')); 8.13 (1H, tt, *J* = 7.5 y 1.3 Hz, H<sub>4</sub>); 8.06 (1H, s, H<sub>6</sub>'); 7.84 (2H, dd, *J* = 7.5 and 6.8 Hz, H<sub>3</sub>(5)); 7.44 (4H, m, H<sub>3</sub>'(5''), H<sub>4</sub>'' and H<sub>5</sub>''); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD):  $\delta$  159.3 (C<sub>2</sub>''), 147.4 (C<sub>6</sub>''), 146.0 (C<sub>2</sub>''), 145.6 (C<sub>2</sub>(6)), 142.4 (C<sub>3</sub>''), 139.7 (C<sub>1</sub>''), 139.4 (C<sub>4</sub>), 137.5 (C<sub>6</sub>'), 135.6 (C<sub>3</sub>'' or C<sub>5</sub>'), 134.8 (C<sub>3</sub>'' or C<sub>5</sub>'), 133.5 (C<sub>4</sub>''), 130.2 (C<sub>2</sub>'(6'')), 129.3 (C<sub>4</sub>''), 128.7 (C<sub>3</sub>'(5'')), 128.5 (C<sub>3</sub>(5)), 125.1 (C<sub>5</sub>''). Anal. Calcd for C<sub>20</sub>H<sub>15</sub>N<sub>5</sub>·1/2H<sub>2</sub>O: C, 71.84; H, 4.82; N, 20.94. Found: C, 71.80; H, 4.82; N, 20.63. MS (CI, *m/z*): 326 (57, M+1), 277 (20), 249 (100), 80 (43).