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Tetrahedron Letters 45 (2004) 8713–8715

Tetrahedron Letters

Suzuki reaction on pyridinium *N*-(5-bromoheteroar-2-yl)aminides

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Received 19 July 2004; revised 20 September 2004; accepted 21 September 2004

Abstract—The reactivity of substituted pyridinium *N*-(2′-azinyl)aminides in Suzuki–Miyaura cross-coupling reaction is reported. The reaction proceeds in good yield employing Cs_2CO_3 as base, and producing substitution on the negatively charged moiety.

The palladium-catalyzed cross-coupling has become one of the most widely used methods for the formation of sp^2–sp^2 carbon–carbon bonds.[1] As compared with other related procedures, Suzuki reaction has emerged as a powerful tool for the cross-coupling of aryl bromides, iodides and triflates with arylboronic acids.[2] Functional group compatibility, good yields and low toxicity of both reagents and intermediates have been reasons for the widespread use of the Suzuki reaction either on small or large scale. The process has provided an efficient pathway towards the synthesis of new heterobiaryls[3] and in the search for biologically active compounds.[4]

For several years, we dedicated part of our research programme to the heteroaryl-stabilized cycloiminium ylides **1**, as building blocks for the synthesis of heterocyclic derivatives[5] and, more recently, to the synthetic utility of pyridinium *N*-(2′-azinyl)aminides **2** (Fig. 1).[6] Due to their peculiar structure, these compounds show a clearly defined reactivity. The negatively charged 2-aminoazine fragment reacts efficiently with electrophiles such halogens, quinones and diazonium salts under mild conditions.[6b–e] In addition, the regioselective *N*-exoalkylation of heteroaryl-stabilized aminides, followed by the reduction of the N–N bond allowed us to prepare 2-alkylaminoazines,[6f] and *N*-(2-pyridyl) substituted polyamines.[6g]

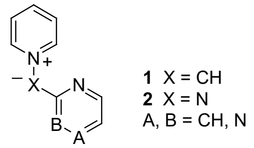
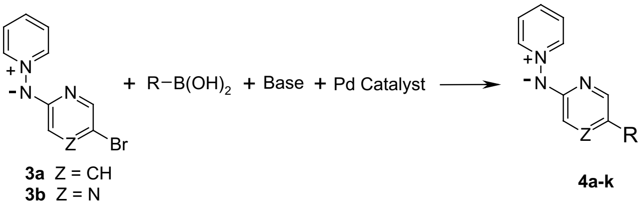


Figure 1.

The palladium-catalyzed cross-coupling processes have received little attention in charged heteroaromatic species and, to our knowledge, only a few examples have been reported.[7,8] For that reason, we considered testing the Suzuki reaction on a series of pyridinium haloazin-2-ylaminides.[6c,9] Keeping in mind that the use of chloro derivatives and 'electron-rich' systems (as the azine ring of our aminides **2**) may hinder the coupling process, our initial efforts have focused on the reaction of the more reactive bromo derivatives **3**[6c] (Scheme 1) with several boronic acids.

As there is a large number of variables to be considered in a Suzuki reaction, like palladium source, ligand, additive, solvent, temperature, etc.; a standard methodology was initially tested ($PhB(OH)_2$ 1.1 equiv; $Pd(PPh_3)_4$ 2%; K_2CO_3 1.25 equiv; toluene–ethanol 20:1; reflux one day). The first experiment performed over **3a** showed evidence of reaction, producing **4a** in a 50% yield. The use of a stronger base such as K^tBuO produced a lower yield (25%), while Cs_2CO_3 gave the best result (86%). On optimizing the method, we established that coupling



Scheme 1.

Keywords: Suzuki; Pyridinium-*N*-aminides.

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0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.09.136

between **3a** and phenylboronic acid takes place efficiently in the presence of 5% $Pd(PPh_3)_4$ with 2 equiv of Cs_2CO_3 (Table 1, entry 1).[10] Using this method, a wide set of Suzuki reactions proceeded, as shown in Table 1, in good yield using the aminide **3a**.

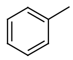
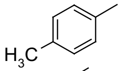
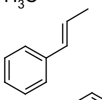
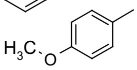
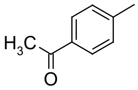
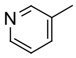
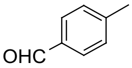
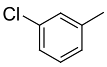
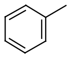
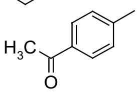
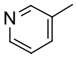
A similar behaviour was observed using the same reaction conditions with pyridinium *N*-(bromopyrazin-2′-yl)aminide **3b**[6c] and several arylboronic acids (entries 9–11, Table 1). Substitution of the diazine ring, which is more electron deficient than pyridine, required longer reaction times, giving compounds **4i–k** in moderate yields.

These results encouraged us to try other ylides, as the dibromoaminide **5**,[6d] which undergoes a double Suzuki process (Scheme 2), yielding diarylated ylides **6**.

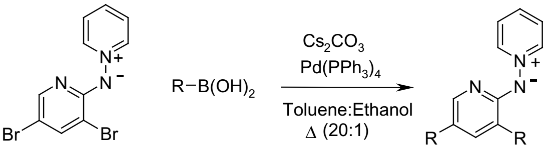
The same methodology used to prepare compounds **4** was adapted to the double coupling with **5**.[11] Using 3 equiv of boronic acid and 4 equiv of Cs_2CO_3, a series of diarylated aminides **6** (Table 2) was successfully obtained.

In conclusion, the Suzuki–Miyaura cross-coupling reaction between pyridinium *N*-haloheteroarylaminides and boronic acids works employing standard conditions and Cs_2CO_3 as base. The process results in a selective substitution of the negatively charged moiety in good yields, and provides a useful complementary strategy to the use of pyridinium *N*-azinylaminides as intermediates to prepare functionalized 2-aminoazines. These are important synthons in medicinal and heterocyclic chemistry. Efforts to widen the scope of the process on other *N*-aminides are in progress in our laboratory.

Table 1. Coupling of aminides **3a**,**b** and boronic acids[a]

Entry	R	Z	Reaction time (h)	Product	Yield (%)
1		CH	8	**4a**	90
2		CH	8	**4b**	88
3		CH	8	**4c**	70
4		CH	8	**4d**	91
5		CH	8	**4e**	75
6		CH	2	**4f**	95
7		CH	72	**4g**	64
8		CH	24	**4h**	85
9		N	15	**4i**	67
10		N	24	**4j**	45
11		N	2	**4k**	71

[a] Reaction conditions: aminide (1 equiv), boronic acid (1.5 equiv), $Pd(PPh_3)_4$ (5%) and Cs_2CO_3 (2 equiv) at reflux temperature of a mixture of toluene–ethanol (20:1, v/v).

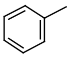
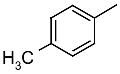
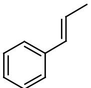
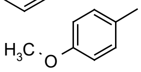


5

6a-d

Scheme 2.

Table 2. Double coupling of aminide **5** and boronic acids[a]

Entry	R	Reaction time (h)	Product	Yield (%)
1		8	**6a**	63
2		8	**6b**	56
3		3	**6c**	85
4		3	**6d**	90

[a] Reaction conditions: aminide (1 equiv), boronic acid (3 equiv), $Pd(PPh_3)_4$ (5%) and Cs_2CO_3 (4 equiv), reflux temperature of a mixture toluene–ethanol (20:1, v/v).

Acknowledgements

We wish to thank the Comisión Interministerial de Ciencia y Tecnología (CICYT-BQU2001-1508) for financial support, and the Ministerio de Educación y Cultura (MEC) for a studentship (M.J.R.).

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Álvarez-Builla, J.; Fajardo, M.; Gómez-Sal, P.; Gago, F. *Tetrahedron* **1994**, *50*, 4995–5012; (c) Burgos, C.; Delgado, F.; García-Navío, J. L.; Izquierdo, M. L.; Álvarez-Builla, J. *Tetrahedron* **1995**, *31*, 8649–8654; (d) García de Viedma, A.; Martinez-Barrasa, V.; Burgos, C.; Izquierdo, M. L.; Álvarez-Builla, J. *J. Org. Chem.* **1999**, *64*, 1007–1010; (e) De la Rosa, R.; Martinez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2000**, *41*, 5837–5840; (f) Martínez-Barrasa, V.; Delgado, F.; Burgos, C.; García-Navío, J. L.; Izquierdo, M. L.; Álvarez-Builla, J. *Tetrahedron* **2000**, *56*, 2481–2490; (g) Reyes, M. J.; Delgado, F.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2002**, *58*, 8573–8579; (h) Nuñez, A.; García de Viedma, A.; Martínez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002**, *7*, 1093–1096.

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10. *General procedure for cross-coupling*: Pd(PPh$_3$)$_4$ (57 mg, 5% mmol), the corresponding boronic acid (1.5 mmol), the corresponding aminide **3** (1 mmol) were dissolved in a toluene–ethanol mixture (20:1, 15 mL). Then, Cs$_2$CO$_3$ (2 mmol) was added, and the mixture was stirred under argon and refluxed for the reaction time indicated in Table 1. The course of the reaction was followed by TLC, HPLC and/or ^{1}H NMR. Once the starting material had been consumed, the catalyst was filtered off through Celite and washed with acetonitrile until no colour was observed in the filtrate. The filtrates were combined and evaporated to dryness. The crude product was purified by flash chromatography on a silica gel column with ethanol as the mobile phase, and recrystallized from a suitable solvent. Compound **4f** was isolated as a yellow oil, while compounds **4a** and **4h** were transformed into the corresponding hydrobromides before purification.

    N-(5′-Phenylpyridin-2′-yl)pyridinium aminide (**4a**): orange solid (299 mg, 90%), IR (KBr) $\nu_{\max}$ (cm^{-1}): 1594, 1466, 1378, 119, 768 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$OD): δ (ppm) 8.81 (2H, dd, $J = 7.0$ and 1.2 Hz); 8.05 (1H, tt, $J = 7.7$ and 1.2 Hz); 7.99 (1H, dd, $J = 2.6$ and 0.8 Hz); 7.84 (2H, dd, $J = 7.7$ and 7.0 Hz); 7.72 (1H, dd, $J = 8.9$ and 2.6 Hz); 7.52 (2H, dd, $J = 8.3$ and 1.3 Hz); 7.40 (2H, dd, $J = 8.3$ and 7.3 Hz); 7.26 (1H, tt, $J = 7.3$ and 1.3 Hz); 6.63 (1H, dd, $J = 8.9$ and 0.8 Hz); ^{13}C NMR (75 MHz CD$_3$OD): δ (ppm) 164.9, 144.9, 144.5, 140.0, 137.7, 137.0, 129.9, 128.5, 127.3, 126.4, 125.5, 112.3; MS (EI, *m/z*) 247 (44, M+1), 246 (100, M), 140 (48), 114 (25). *Hydrobromide*: Beige solid, mp 234–235 °C (EtOH–AcOEt). Anal. Calcd for $C_{16}H_{14}BrN_3\cdot 1/4H_2O$: C, 57.76; H, 4.39; N, 12.63. Found: C, 58.03; H, 4.37; N, 12.75.

11. *General procedure for double coupling*: the aminide **5** (1 mmol) and the corresponding boronic acid (3 mmol) were dissolved in a toluene–ethanol mixture (20:1, 15 mL). Then, Cs$_2$CO$_3$ (4 mmol) was added, followed by Pd(PPh$_3$)$_4$ (57 mg, 5% mmol). After the addition, the mixture was kept under argon with vigorous stirring for 5 min, and then refluxed until no starting material was detected. At the end, the mixture was filtered through Celite, and the residue washed with acetonitrile until no colour was observed in the filtrate. The filtrates were combined and evaporated to dryness, and the residue purified by flash chromatography through a silica gel column, using ethanol as the mobile phase. Compound **6b** was isolated as a yellow oil, compound **6d** was recrystallized from ethanol and compounds **6a** and **6c** were transformed into the corresponding hydrobromides, and then recrystallized from a suitable solvent.

    N-(3′,5′-Diphenylpyridin-2′-yl)pyridinium aminide (**6a**): yellow solid (204 mg, 63%), IR (KBr) $\nu_{\max}$ (cm^{-1}): 1592, 1420, 1385, 1311, 1144, 698 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$OD): δ (ppm) 8.63 (2H, dd, $J = 7.1$ and 1.3 Hz); 7.98 (1H, d, $J = 2.6$ Hz); 7.97 (1H, tt, $J = 7.7$ and 1.3 Hz); 7.72 (4H, m); 7.60 (1H, d, $J = 2.6$ Hz); 7.49 (2H, dd, $J = 7.4$ and 1.3 Hz); 7.42 (2H, ap. t, $J = 7.4$ Hz); 7.36 (2H, ap. t, $J = 7.4$ Hz); 7.32 (1H, tt, $J = 7.4$ and 1.3 Hz); 7.23 (1H, tt, $J = 7.4$ and 1.3 Hz); ^{13}C NMR (75 MHz CD$_3$OD): δ (ppm) 161.6, 145.3, 144.2, 140.4, 139.6, 138.4, 137.6, 130.4, 130.0, 129.7, 128.3, 128.1, 127.4, 126.5, 126.4, 124.9; MS (CI, *m/z*) 324 (100, M+1), 323 (47), 247 (39), 245 (46), 80 (48). *Hydrobromide*: Beige solid, mp 155–156 °C (EtOH–Et$_2$O). Anal. Calcd for $C_{22}H_{17}N_3\cdot 2HBr\cdot 1H_2O$: C, 52.51; H, 4.21; N, 8.35. Found: C, 52.36; H, 4.17; N, 8.39.