Regioselective 1,6-Conjugate Addition of Boronic Acids and Grignard Reagents to Dienylpyridines

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Received 13 May 2011

Abstract: Functionalization of the lateral chain of dienylpyridines was achieved by the regioselective 1,6-addition of boronic acids catalyzed by rhodium(I) or Grignard reagents under iron(II) catalysis.

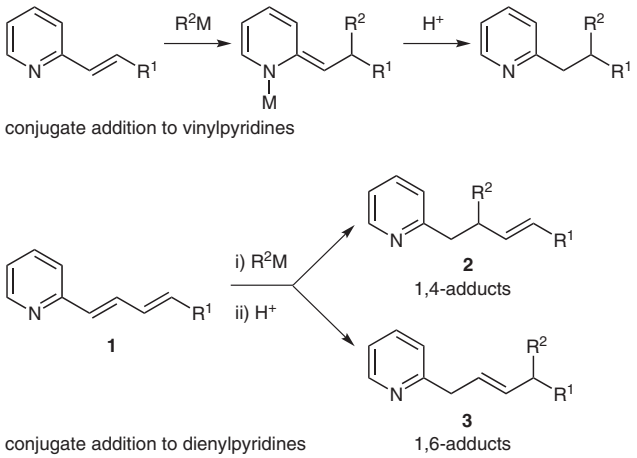
Key words: addition, catalysis, pyridines, rhodium, iron

The conjugate addition reaction of carbon nucleophiles to electron-deficient alkenes has become one of the most important C–C bond-forming reactions in organic synthesis. The most common functional groups used to activate alkenes toward conjugate addition include carbonyl groups, nitriles, sulfones, phosphonates, and nitro groups. However, other less common groups such as electron-deficient aromatic heterocycles have also been reported as activating groups for alkenes enabling the reaction with carbon nucleophiles.[1–3] Aromatic heterocyclic compounds are present in numerous biologically active natural products, agrochemicals, pharmaceuticals, and functional molecules. Therefore, new methods for the functionalization of this type of compounds are highly important.

In comparison with other heterocycles, pyridine rings have been reported as particularly challenging substrates for the activation of conjugate additions, as there is a considerable loss in aromaticity upon formation of the reaction intermediate. Also, this type of reaction has been found difficult in β-substituted compounds due to steric reasons.[3]

In comparison with alkenes, the addition to dienes has been much less considered in the literature[4] and constitutes a topic of current synthetic interest. These types of reactions are complicated by the multiple electrophilic sites of electron-deficient dienes, which may lead to 1,6- or 1,4-addition modes together with direct addition to the activating functional group.

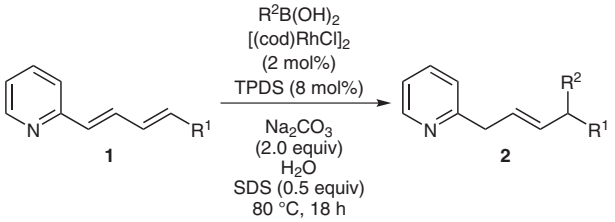
Despite success in the additions of carbon nucleophiles to alkenyl heterocycles, the possibility of functionalizing dienyl heterocycles by nucleophilic addition has received no attention. We report herein our findings in the regioselective additions of arylboronic acids and Grignard reagents to dienylpyridines[5] (Scheme 1).



Scheme 1

On the basis of previous reports on the addition of boronic acids to vinylpyridines and reactions of dienoic esters and ketones catalyzed by rhodium(I) in aqueous solvents,[2] at the onset of our study we considered the reaction of boronic acids with 2-(1,3-butadienyl)pyridine (**1a**). The results are gathered in Table 1. After testing several catalytic systems and reaction conditions,[6] we found that reaction was successful when using $[(cod)RhCl]_2$ (2 mol%) as catalyst in the presence of the water-soluble bis(*p*-sulfonatophenyl)phenylphosphine dihydrate dipotassium salt (TPDS, 8 mol%) and using Na_2CO_3 (2.0 equiv) as base in water together with sodium dodecylsulfate (SDS, 0.5 equiv) at 80 °C.

Table 1 Rhodium(I)-Catalyzed Additions of $R_2B(OH)_2$ to **1a**,**b**



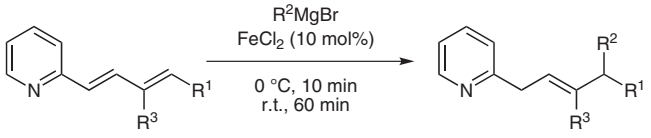
Entry	1	R^1	R^2	Yield of **2** (%, *E*/*Z* ratio)
1	**1a**	H	Ph	**2a** 75 (60:40)
2	**1a**	H	4-$MeOC_6H_4$	**2b** 70 (60:40)
3	**1a**	H	4-$F_3CC_6H_4$	**2c** 65 (60:40)
4	**1b**	Me	Ph	–

SYNLETT 2011, No. 15, pp 2234–2236
Advanced online publication: 12.08.2011
DOI: 10.1055/s-0030-1261183; Art ID: D14611ST

Under these reaction conditions the reaction of **1a** was achieved for phenylboronic acid (Table 1, entry 1) and either for boronic acids with electron-releasing (Table 1, entry 2) or electron-withdrawing substituents (Table 1, entry 3). The 1,6-conjugate addition product was obtained as the only adduct, with no traces of the 1,4-adduct. However, the reaction failed for δ-substituted systems as exemplified for **1b** (Table 1, entry 4).

In the search for a more reactive catalytic system, we found that these types of reactions could be carried out in a general fashion using Grignard reagents under iron(II) catalysis (Table 2).[7,8] Thus, electron-donating or electron-withdrawing groups were tolerated in the aryl moiety of the Grignard reagent, as well as steric hindrance in *ortho* position.[9]

Table 2 Iron(II)-Catalyzed Additions of R^2MgBr to **1**



Entry	1	R^1	R^2	R^3	Yield of **2** (%, *E*/*Z* ratio)
1	**1a**	H	Ph	H	**2a** 80 (60:40)
2	**1a**	H	4-$MeOC_6H_4$	H	**2b** 75 (65:35)
3	**1a**	H	4-FC_6H_4	H	**2c** 60 (50:50)
4	**1a**	H	2-$MeOC_6H_4$	H	**2d** 60 (60:40)
5	**1b**	Me	Ph	H	**2e** 80 (60:40)
6	**1b**	Me	4-$MeOC_6H_4$	H	**2f** 70 (75:35)
7	**1b**	Me	4-FC_6H_4	H	**2g** 70 (80:20)
8	**1b**	Me	2-$MeOC_6H_4$	H	**2h** 65 (60:40)
9	**1c**	Ph	4-$MeOC_6H_4$	H	**2i** 65 (50:50)
10	**1c**	Ph	4-FC_6H_4	H	**2j** 60 (50:50)
11	**1d**	*i*-Pr	4-$MeOC_6H_4$	H	**2k** 75 (60:40)
12	**1d**	*i*-Pr	4-FC_6H_4	H	**2l** 80 (50:50)
13	**1e**	Et	4-$MeOC_6H_4$	Me	**2m** 80 (0:100)
14	**1e**	Et	4-FC_6H_4	Me	**2n** 65 (0:100)

Substitution of the diene moiety at δ-position was possible (Table 2, entries 5–12), and even simultaneous substitution at δ- and γ-positions was tolerated (Table 2, entries 14 and 15). In all cases the 1,6-adducts were obtained exclusively even in the presence of bulky phenyl or isopropyl groups at δ-position. No conjugation of the newly generated C=C bond of the lateral chain with the pyridine ring was observed. With the exception of **2m**,**n**, which were obtained as a single *Z*-isomer,[10] the rest of compounds were obtained as mixtures of the corresponding *E*- and *Z*-isomers.

In conclusion, we have developed a new method which permits the functionalization of the lateral chain of dienylpyridines, which could be of use in the synthesis of new heterocycles.

Acknowledgment

Projects CTQ2010-16170 from the Spanish government and GR35/10-A from UCM are gratefully acknowledged for financial support.

References and Notes

(1) See, for example: (a) Hoffman, A.; Farlow, M. W.; Fuson, R. C. *J. Am. Chem. Soc.* **1933**, *55*, 2000. (b) Gilman, H.; Gainer, G. C. *J. Am. Chem. Soc.* **1949**, *71*, 2327. (c) Mathis, C.; Hogen-Esch, T. E. *J. Am. Chem. Soc.* **1982**, *104*, 634. (d) Dryanska, V.; Ivanov, C. *Synthesis* **1983**, 143. (e) Houpis, I. N.; Lee, J.; Dorziotis, I.; Molina, A.; Reamer, B.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1998**, *54*, 1185. (f) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021. (g) Clariana, J.; Gálvez, N.; Marchi, C.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999**, *55*, 7331. (h) Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9342. (i) Mineyama, K.; Maekawa, H.; Kohsaka, A.; Yamamoto, Y.; Nishiguchi, I. *Tetrahedron* **2009**, *65*, 7706. (j) Sun, H.-W.; Liao, Y.-H.; Wu, Z.-J.; Wang, H.-Y.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2011**, *67*, 3991.

(2) (a) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358. (b) Amengual, R.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905.

(3) (a) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373. (b) Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2010**, *6*, 669.

(4) Csákÿ, A. G.; de la Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080.

(5) For the synthesis of starting materials (**1**) from 2-methylpyridine, see: Braun, M.; Mroß, S.; Schwarz, I. *Synthesis* **1998**, 83.

(6) Recovery of starting material was observed when treating **1a** with $PhB(OH)_2$ using $[Rh(cod)]_2BF_4$ or $[Rh(cod)Cl]_2$ as catalysts (5 mol%) in the presence of $Ba(OH)_2$, K_3PO_4, or KOH (1.0 equiv) at 50 °C in dioxane–H_2O (4:1) for 18 h.

(7) (a) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603. (b) Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6860.

(8) Recovery of starting material was observed when treating **1a** with PhMgBr in THF in the presence of CuI (10 mol%) or in the absence of catalyst at r.t. for 18 h.

(9) **Typical Procedure for the Addition of Grignard Reagents to Dienylpyridines (1)**
Synthesis of (*Z*)-2-[4-(*p*-Methoxyphenyl)-3-methylhex-2-enyl]pyridine (2m)
To a stirred solution of **1e** (86.6 mg, 0.5 mmol) and $FeCl_2$ (6.4 mg, 0.05 mmol) in anhyd THF (3.5 mL) under Ar was added *p*-methoxyphenylmagnesium bromide (1.0 M in THF, 0.9 mmol, 0.9 mL) at 0 °C. The solution was stirred at 0 °C for 15 min and at r.t. for 1 h. The reaction was terminated by

the addition of a sat. NH_4Cl aq solution (5 mL). The organic products were extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed on silica gel (hexane–EtOAc = 8:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 4.7 Hz, 1 H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1 H), 7.07–7.22 (m, 4 H), 6.82 (dt, *J* = 8.7, 2.1 Hz, 2 H), 5.55 (t, *J* = 7.1 Hz, 1 H), 3.72–3.90 (m, 3 H), 3.78 (s, 3 H), 1.66–1.96 (m, 2 H), 1.54 (d, *J* = 1.0 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 18.9, 24.2, 36.9, 46.2, 55.3, 113.7 (2 C), 121.2, 122.7, 123.0, 128.7 (2 C), 135.8, 136.6, 139.7, 149.4, 157.9, 161.5.

(10) Determined by NOE measurement upon irradiation of the vinyl-H signal.