Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1503–1506

TETRAHEDRON LETTERS

2-(Fluorophenyl)pyridines by the Suzuki–Miyaura method: Ag_2O accelerates coupling over undesired *ipso* substitution (S_NAr) of fluorine

Jing Chen and Arthur Cammers-Goodwin*

University of Kentucky, Department of Chemistry, Lexington, KY 40506-0055, USA

Received 4 November 2002; revised 9 December 2002; accepted 9 December 2002

Abstract—Problematic *ipso* substitution was observed in the Suzuki–Miyaura coupling of pentafluorophenylboronic acid to make 2-pentafluorophenylpyridine. Strong bases favored coupling, but under these conditions fluorine in the product tended to undergo nucleophilic substitution. Inclusion of Ag_2O accelerated coupling over *ipso* substitution. © 2003 Elsevier Science Ltd. All rights reserved.

Recently, we needed to access a variety of 2-arylpyridines. Two general structural families presented problematic Suzuki–Miyaura coupling reactions:[1] fluorinated aromatic rings (**1** and **2**) and a derivative capable of chelation **3** (Fig. 1). The versatility of Suzuki-type couplings was manifest in the optimization of the reaction conditions to access these desired pyridine derivatives. The synthesis of **4** succeeded under conditions in which the synthesis of **3** failed. However, inclusion of CuI in the recipe to chelate **3** and liberate the Pd catalyst brought the isolated yield of **3** up to that of **4**. The synthetic details of **3** and **4** have been reported elsewhere.[2] This letter focuses on the development of Suzuki–Miyaura coupling reactions for the construction of 2-(fluoroaryl)pyridine derivatives **1** and **2** and may have general significance for Pd-catalyzed aryl cross coupling in which the products are sensitive to Lewis basic conditions. The difficulties encountered when trying to couple pentafluorophenyl boronic acid **5** are exemplified by the failure of **5** to couple to **6** under conditions favorable for the cross coupling of a variety of arylboronic acids possessing electron-withdrawing or -donating groups.[3] Furthermore literature searches for the reactions of **5** and its 2,5,6-trifluoro analogue revealed no Suzuki-type couplings. The reactions reported herein are the first for these readily available boronic acid derivatives.

Fluorinated aryl groups at the 2-position on the pyridine ring should be susceptible to *ipso* substitution[4] under most conditions of Suzuki-type aryl coupling reactions because a nucleophile is usually necessary to induce transmetallation from boron to palladium[1a] via

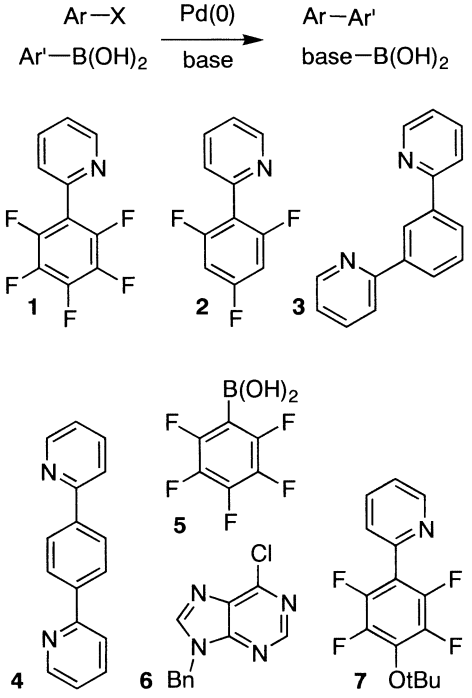


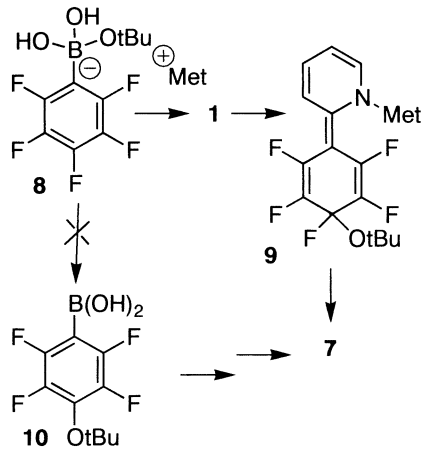
Figure 1. 2-Fluoroarylpyridine derivatives via Suzuki coupling.

Keywords: Suzuki coupling; aryl cross coupling; transmetallation; Pd catalyst.

* Corresponding author. E-mail: acgood1@uky.edu

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)02793-4

ate complex, **8**—a mechanistically related process to *ipso* substitution (S_NAr, **1** to **9** to **7**) (Scheme 1). Even the hindered *t*-butoxide anion added in this fashion resulting in the isolation of **7**. Nucleophilic aromatic substitution of F by O*t*Bu might have transformed **5** to **10** which could have gone on to produce **7**. However, the rate of coupling of compound **5** with 2-iodopyridine to produce **1** and subsequent *ipso* substitution of **1** to produce **7** must have been faster than the hypothetical conversion of **5** to **10** because the concentration of **1** increased as the reaction ran and subsequently diminished with the appearance of **7**. In reality, dynamic exchange between multiple species related to **5** and **8** was certainly more complex than Scheme 1 indicates because arylboronic acids accompany arylboronic anhydrides and triarylboroxine under these conditions.



Scheme 1. Hypothetical intermediates in the coupling of **5** and 2-iodopyridine. Conceptually, **7** could have come from **8** via **9** or **10**. This work indicated that **9** was the intermediate that led to **7**.

Compounds **1** and **2** remained elusive until known Suzuki-type reaction conditions were surveyed. Studying the chemical literature on Suzuki coupling suggested two possible ways around the undesired *ipso* substitution: (1) use fluoride as the nucleophile to expand the valence of the boron atom or (2) optimize reagents and reaction conditions to increase the rate of coupling relative to the rate of *ipso* substitution. Fluoride-induced Suzuki coupling to yield biaryl products has been reported.[5,6] However, in our hands fluoride failed to induce Suzuki coupling in the attempted synthesis of **1** and **2**. Even though trifluoroborate salts have been used to perform Suzuki coupling reactions,[7] this avenue was not taken for two reasons. Among the many successful examples, heavily fluorinated aryl rings were not reported. Furthermore there is much evidence that the fluorine atoms of aryltrifluoroborate starting materials exchange with oxygen-atom nucleophiles before coupling occurs.[8] Recently silver oxide was reported to induce Suzuki–Miyaura cross coupling of *n*-alkylboronic acids presumably by accelerating the B-to-Pd alkyl transfer step of the catalytic cycle.[9] We reasoned that Ag_2O might also accelerate B-to-Pd aryl transfers crucial to the catalytic cycles that would produce **1** and **2**. In the current study, Ag_2O was the key ingredient that accelerated the overall rate of coupling over the rate of *ipso* substitution, allowing the isolation of compounds **1** (76%) and **2** (32%). The conditions attempted in the optimization of **1** are summarized in the next section.[10–13]

Experimental

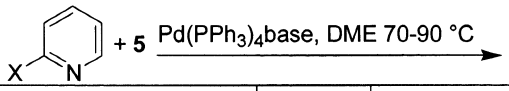
The ^1H and ^{13}C NMR spectra were referenced to residual $CHCl_3$ in the deuterated solvent (7.27 and 77.23 ppm, respectively). The ^{19}F NMR spectra were referenced to $CFCl_3$ (0 ppm). The procedures below used pentafluorophenylboronic acid (CAS 1582-24-7) and trifluorophenylboronic acid (CAS 182482-25-3) purchased from Aldrich Chem. Co. without further purification. All solvents used were dried and distilled.

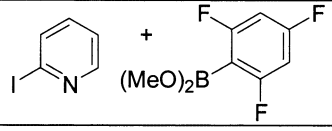
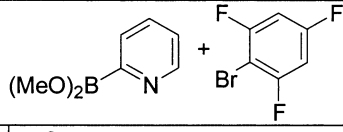
General procedure for coupling reactions

2-2,4,6-Trifluorophenylpyridine (2): The preparation of 2-2,4,6-trifluorophenylpyridine is representative. All operations were performed under a nitrogen atmosphere. An oven-dried, 50 mL flask, fitted with a condenser was charged with iodopyridine (0.73 g, 3.56 mmol), $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol), and 1,2-dimethoxyethane (DME, 20 mL). The bright yellow solution was stirred at room temperature for 20 min. Sequential addition of 1,3,5-trifluorophenyl boronic acid (0.72 g, 4.09 mmol), *t*-BuOK (0.80 g, 7.11 mmol), *t*-BuOH (3.6 mL) and Ag_2O (1.64 g, 7.08 mmol) resulted in a dark solution and the formation of a dark precipitate. The mixture refluxed under nitrogen at 85°C for 17 h. The mixture was cooled, concentrated in vacuum, and partitioned between EtOAc:H_2O (1:1, 120 mL). The layers were separated and the aqueous layer was washed with two additional 60 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuum. Silica gel column chromatography (hexane/EtOAc = 90:10) gave 2,4,6-trifluorophenylpyridine as a light yellow solid that crystallized from hexanes (32%); mp 54–56°C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.81 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.47 (dtdd, J = 7.7, ~1.2, ~1.2, ~1.2 Hz, 1H), 7.31 (ddd, J = 7.7, 4.9, 1.2 Hz, 1H), 6.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8 (dt, J = 251, 15.2 Hz), 160.9 (ddd, J = 252, 15.2, 9.8 Hz), 150.0, 148.9, 136.7, 126.1, 123.3, 114.8 (m), 100.89 (m); ^{19}F NMR (377 MHz, $CDCl_3$): δ 158.3 (m, 1F), 154.0 (t, J = 7.7 Hz, 2F); MS (IE) m/z 209 [M], 190 [M−F]. X-Ray diffraction confirmed connectivity, see supplemental section for structural details.

2-Pentafluorophenylpyridine (1): Using **5** in analogous conditions to those above, **1** is the major product after 30 min. Products **1** and **7** had similar retention times on SiO_2 under a variety of elution conditions; however, **1** was efficiently separated from **7** by crystallization from hexanes (76%), mp 63–65°C; ^1H NMR (400 MHz,

Table 1.



Entry	Base	time/ h.	Catalyst	Yield	Ref.
1	$2M_{(aq)}$ Na_2CO_3, X=Br	24	$Pd(PPh_3)_4$	0	10
2	$2M_{(aq)}$ KOH, X=Br	120	$Pd(PPh_3)_4$	0	10
3	KOH, X=Br	48	$Pd(PPh_3)_4$	0	11
4	2M *t*-BuOK in *t*-BuOH, X=Br	20-60	$Pd(PPh_3)_4$	0	11
5	KF, X=Br	20	Pd (black)	0	12
6	KF, X=I	21.5	$Pd(PPh_3)_4$	0	
7	KF + Ag_2O, X=I	21.5	$Pd(PPh_3)_4$	0	
8	TBAF, X=I	19	$Pd(PPh_3)_4$	0	
9	TBAF + Ag_2O, X=I	19	$Pd(PPh_3)_4$	3	
10	2M NaOH, X=I	17.5	$Pd(PPh_3)_4$	0	
11	2M NaOH + Ag_2O X=I	17.5	$Pd(PPh_3)_4$	40	
12	Ag_2O, 2M *t*-BuOK/ *t*-BuOH, X=I	17	$Pd(PPh_3)_4$	76	
					
13	Ag_2O, 1M Na_2CO_3	138	$Pd(PPh_3)_4$	1.5	13
14	Ag_2O, 1M KOH	96	$Pd(PPh_3)_4$	2.5	
15	Ag_2O, 2M *t*-BuOK/ *t*-BuOH	17	$Pd(PPh_3)_4$	32	
					
16	KOH	11	$Pd(PPh_3)_4$, NEt_4Br	2	13

$CDCl_3$): δ 8.78 (ddd, J=4.9, 1.8, 1.1 Hz, 1H), 7.85 (ddd, J=7.8, 7.8, 1.8 Hz, 1H), 7.49 (dm, J=7.8 Hz, 1H), 7.40 (ddd, J=7.8, 4.9, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 147.1, 144.8 (dm, J=250 Hz), 141.4 (dm, J=255 Hz), 138.0 (dm, J=252 Hz), 136.9, 126.1, 124.0, 115.6 (m); ^{19}F NMR (377 MHz, $CDCl_3$): δ 122.2 (m, 2F), 111.6 (t, J=21.4 Hz, 1F), 103.6 (m, 2F); MS (IE) m/z 245 [M], 226 [M–F]. X-Ray diffraction confirmed connectivity, see supplemental section for structural details.

2-2,3,5,6-Tetrafluoro-4-*t*-Butoxylphenylpyridine (7): Running the reaction above for 24 h. gave **7** as the major product that crystallized from hexanes (60%), mp 58–60°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (ddd, J=5.0, 1.8, 1.0 Hz, 1H), 7.83 (ddd, J=7.8, 7.8, 1.8 Hz, 1H), 7.51 (dm, J=7.8 Hz, 1H), 7.37 (ddd, J=7.8, 5.0, 1.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 148.1, 144.8 (dm, J=249 Hz), 143.9 (dm, J=245 Hz), 136.8, 134.7 (m), 126.2, 123.7, 115.3 (m), 85.6, 28.6; ^{19}F NMR (377 MHz, $CDCl_3$): δ 119.7

(m, 2F), 113.9 (m, 2F); MS (IE) m/z 299 [M], 284 [M–CH_3], 242 [M–C_4H_9], 223 [M–C_4H_9–F]. X-Ray diffraction confirmed connectivity, see supplemental section for structural details.

Experimentation to converge on viable syntheses of 1 and 2

The procedures attempted in the synthesis of **1** and **2** are summarized in Table 1. Inclusion of Ag_2O and strong oxygen-atom nucleophiles made notable improvements in the procedures (entries 12 and 15).

In all entries the mole ratio of base or Ag_2O to 2-halopyridine was 2:1, and the mole ratio of arylboronic acid to 2-halopyridine was 1.2:1. Reactions in the table above were typically run with 300 mg 2-halopyridine and the yields reported are isolated yields. In some entries reporting zero yields, the TLC chromatograms indicated no product so isolation was not attempted.

Supporting information available: Crystallographic information files (CIF) for compounds **1**, **2** and **7**, under the deposition numbers CCDC-196727, -196726 and -199362, are available gratis at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The authors thank the NSF (0111578) for financial support.

References

1. This reaction has been extensively reviewed. See: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470.
2. Sindkhedkar, M. D.; Mulla, H. R.; Wurth, M. A.; Cammers-Goodwin, A. *Tetrahedron* **2001**, *57*, 2991–2996.
3. (a) Havelková, M.; Dvořak, D.; Hocek, M. *Synthesis* **2001**, 1704–1710; (b) Lohse, O.; Thevenin, P.; Waldvogel, E. *Synlett* **1999**, 45–48.
4. For an example of nucleophilic aromatic substitution by amide bases on a 2-(4-fluorophenyl)pyridine derivative, see: (a) Strekowski, L.; Janda, L.; Patterson, S. E.; Nguyen, J. *Tetrahedron* **1996**, *52*, 3273–3282; Fluorinated pyridines undergo S_NAr with nucleophiles as mild as oximates and 4-nitrophenoxide. See: (b) Banks, R. E.; Jondi, W.; Tipping, A. E. *Chem. Commun.* **1989**, 1268–1269; (c) Aksenov, V. V.; Vlasov, V. M.; Yakobson, G. G. *J. Fluorine Chem.* **1982**, *20*, 439–458.
5. Wright, S. W.; Hageman, D. L.; Mcclure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097.
6. Benbow, J. W.; Martinez, B. L. *Tetrahedron Lett.* **1996**, *49*, 8829–8832.
7. (a) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103; (b) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107–109.
8. Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870.
9. Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213–7215.
10. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.
11. Zhang, H.; Shing, C. K. *Tetrahedron Lett.* **1996**, *37*, 1043–1044.
12. Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun.* **2001**, 775–775.
13. Fernando, S. R. L.; Maharoof, U. S. M.; Deshayes, K. D.; Kinstle, T. H.; Ogawa, M. Y. *J. Am. Chem. Soc.* **1996**, *118*, 5783–5790.