Palladium catalyzed cross-coupling reaction of 5-tributylstannyl-4-fluoropyrazole†

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Received (in Cambridge, UK) 4th January 2005, Accepted 15th February 2005
First published as an Advance Article on the web 1st March 2005
DOI: 10.1039/b419329f

The palladium catalyzed cross-coupling reactions of aryl iodides and 5-tributylstannyl-4-fluoropyrazole prepared from fluoro(tributylstannyl)acetylene proceeded smoothly giving the corresponding 5-aryl-4-fluoropyrazole in good yields.

Fluorinated heterocyclic compounds play an important role in various fields such as agrochemicals, pharmaceuticals, polymers and dyes.[1] For example celecoxib, as a famous anti-inflammatory agent containing both fluorine and a pyrazole ring, represents both above categories.[2] These circumstances suggest that it is still of importance to develop effective methods for the synthesis of fluorinated azaheterocyclic compounds. Among them, functionalized pyrazoles bearing fluorine(s) would be suitable candidates for the facile preparation of their derivatives. On the basis of this idea, we have recently reported the palladium catalyzed cross-coupling reactions of 5-tributylstannyl-4-trifluoromethylpyrazole.[3] Our attention was next paid to the synthesis of the corresponding ring-fluorinated pyrazoles due to the lack of efficient routes for the preparation of the 4-fluoropyrazole family.[4] We report herein the first preparation of 5-tributylstannyl-4-fluoropyrazole as a functionalized 4-fluoropyrazole and its cross-coupling reaction.

We planned the preparation of 5-tributylstannyl-4-fluoropyrazole using the 1,3-dipolar cycloaddition of diazomethane and fluoro(tributylstannyl)acetylene according to a slightly modified version of our procedure for that of 5-tributylstannyl-4-trifluoromethylpyrazole.[3] The requisite acetylene was prepared *in situ* from 1,1-difluoroethylene (**1**) and chlorotributylstannane (nBu$_3$SnCl) using 2 equivalents of *sec*-BuLi at a low temperature.[5] The GC-MS spectrometric analysis of the reaction mixture at −70 °C gave a single peak that corresponded to fluoro(tributylstannyl)acetylene (**2**). However, attempts to isolate **2** invariably resulted in its decomposition probably due to its thermal instability. Consequently, to the resulting solution containing **2** was successively added an excess of ethereal diazomethane solution at −30 °C to give the corresponding 5-tributylstannyl-4-fluoropyrazole (**3**) in 98% yield, exclusively (Scheme 1).‡

The regiochemistry of this pyrazole (**3**) was determined as follows. After this isomer was transformed to the corresponding non-stannylated pyrazole (Scheme 2), the structural assignment was performed on the basis of the comparison of the corresponding ^{19}F NMR chemical shift value in the literature.[6] The regiochemistry of the reaction can be explained in terms of HOMO–LUMO interactions as discussed in the literature.[7]

† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{19}F NMR data for **4**, **6b**–**6g** and **7**. See http://www.rsc.org/suppdata/cc/b4/b419329f/

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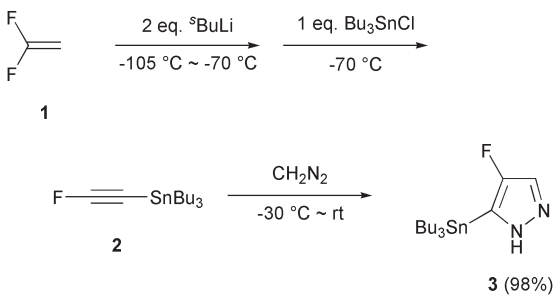
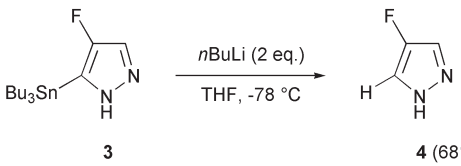
We next examined the palladium catalyzed cross-coupling reactions of **3** with 4-iodoacetophenone (**5**) as an aryl iodide under various conditions (Table 1). After several attempts, the optimal yield of the cross-coupling product was obtained (entry 9) when a mixture of **3**, **5** (1.1 equiv.) and [Pd(PPh$_3$)$_4$] (5 mol%) in DMSO was heated at 100 °C for 3 h.§ To our delight, the adduct (**6a**) gave single crystals suitable for X-ray crystallographic analysis.¶ A crystal packing drawing of **6a** is shown in Fig. 1. This X-ray analysis provided unambiguous proof of the regiochemistry of the fluorinated pyrazole. The features of the reaction are as follows: the use of DMSO was essential to the success of the reaction, to obtain the adduct in high yield.[8] Addition of CuTC and/or LiCl as additives to the reaction mixture remarkably improved the yield (entries 6 and 8), however, did not always do so for aryl iodides bearing an electron-donating group (*vide infra*). In the presence of these additives, the higher reaction temperature (100 °C) resulted in the decomposition of **3** to decrease the yield. From the viewpoint of the catalytic activity, PdCl$_2$(PPh$_3$)$_2$ was slightly inferior to Pd(PPh$_3$)$_4$.

Under the optimal conditions except for the reaction time, the cross-coupling reaction of **3** with a variety of aryl halides proceeded smoothly to give the corresponding pyrazoles in good to high yields (Table 2). Although slight scattering in yields was observed on varying the positions of the substituents on the aromatic rings, aryl iodides bearing not only an electron-withdrawing group but also an electron-donating group were suitable for the reaction. The corresponding aryl bromide was

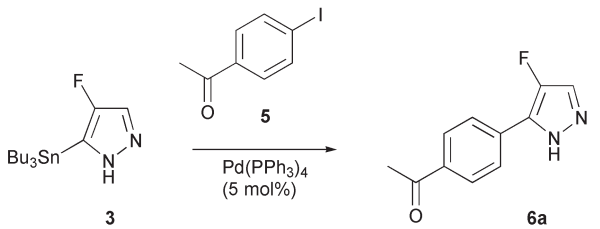


Scheme 1 One pot synthesis of 5-tributylstannyl-4-fluoropyrazole (**3**).



Scheme 2 Destannylation of **3**.

Table 1 Cross-coupling reaction of **3** with 4-iodoacetophenone (**5**) under various conditions[a]



Entry	CuTC[b] (mol%)	LiCl (mol%)	Time (h)	Solvent	Temperature (°C)	Yield[c] (%)
1	5	—	89	DMF	25	44
2	5	—	18	DMF	80	Trace
3	5	20	37	DMF	25	0
4	—	—	13	DMF	100	40
5	5	100	39	DMSO	25	28
6	5	20	17	DMSO	25	100
7	5	—	18	DMSO	25	45
8	—	20	2	DMSO	100	100
9	—	—	3	DMSO	100	100(91)[d]
10[e]	—	—	2	DMSO	100	84

[a] All reactions were conducted using **3** (1 equiv.) with 4-iodoacetophenone (**5**) (1.1 equiv.) in the presence of $Pd(PPh_3)_4$. [b] Cu(I) thiophene-2-carboxylate. [c] GC yield. [d] Isolated yield in parentheses. [e] $PdCl_2(PPh_3)_2$ was used instead of $Pd(PPh_3)_4$.

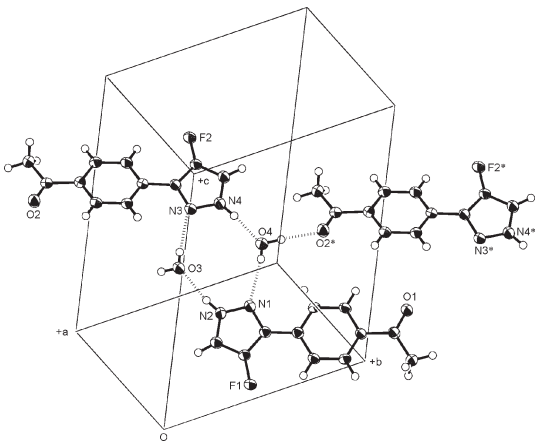
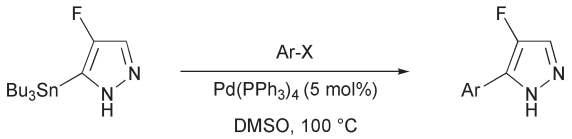


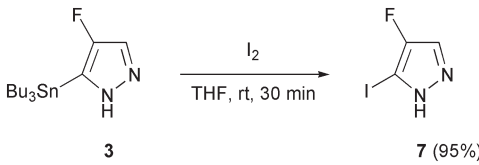
Fig. 1 Crystal packing of **6a**. Hydrogen bonds are shown by dotted lines.

Table 2 Cross-coupling reaction of **3** with various aryl halides[a]



Entry	Ar–X	Time (h)	Product	Yield[b] (%)
1	2,4-$Me_2C_6H_3I$	3	**6b**	94
2	2-ClC_6H_4I	16	**6c**	89
3	2-$(CO_2Me)C_6H_4I$	16	**6d**	83
4	3-$(MeO)C_6H_4I$	3	**6e**	74
5	4-$(MeO)C_6H_4I$	9	**6f**	59
6	4-$(NO_2)C_6H_4I$	5	**6g**	84
7	4-AcC_6H_4Br	2	**6a**	trace
8	2-Br-5-(NO_2)pyridine	2	—	35[c]
9	5-Br-pyrimidine	2	—	0

[a] All reactions were conducted using **3** (1 equiv.) with aryl halides (1.1 ~ 1.3 equiv.) in the presence of 5 mol% of $Pd(PPh_3)_4$ in DMSO at 100 °C. [b] Isolated yield. [c] GC yield. This product gradually decomposed during work-up.



Scheme 3 Iodination of **3**.

almost less effective (entry 7). Although one hetero-aromatic bromide afforded the corresponding adduct in a low yield, the adduct was unstable and its decomposition occurred during work-up (entry 8).

Finally, in addition to the cross-coupling reaction, introduction of iodine to **3** was also examined (Scheme 3). The reaction proceeded smoothly to give the corresponding 4-fluoro-5-iodopyrazole (**7**) in 95% yield.

In summary, we have demonstrated the facile synthesis of **3**, *via* the 1,3-dipolar cycloaddition reaction of **2** with diazomethane, in one step and its cross-coupling reaction for the construction of 4-fluorinated pyrazole derivatives. Further studies on their synthetic utility are progress in our laboratory.

We greatly thank F-Tech Co., Ltd for a gift of 1,1-difluoroethylene.

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Notes and references

‡ *Preparation* of **3**: a 100 mL two-neck flask equipped with a magnetic stir bar, a stopcock and a three-way stopcock, was charged with 18 mL of THF under argon. To the stirred mixture was added *sec*-BuLi (0.96 M in cyclohexane solution, 10.0 mL, 9.6 mmol) dropwise *via* syringe at −78 °C.

After this mixture had been stirred for an additional 10 min, the solution was cooled to −105 °C in a liquid N_2–ethanol bath. At this temperature, argon was replaced with 1,1-difluoroethylene (balloon). The mixture was gradually warmed to −70 °C. Chlorotributylstannane (Bu_3SnCl, 1.20 mL, 4.43 mmol) was added dropwise to the solution by syringe. After the addition had been completed, the reaction mixture was allowed to warm to −30 °C. To the resulting reaction mixture was added an excess of ethereal diazomethane solution and the mixture was gradually warmed to room temperature. After hexane (10 mL) and water (20 mL) were successively added to the solution, the organic layer was separated from the mixture. The resulting aqueous layer was extracted with hexane–ether (3:1) three times. After the combined organic layer was dried over sodium sulfate, and filtered through a short silica gel column (ether as an eluent), the eluate was concentrated *in vacuo*. The resulting oily residue was purified by silica gel chromatography (hexane–ethyl acetate, 3:1) to give the desired product (**3**) as a colorless oil (1.63 g, 98%): ν_{max} (neat)/cm^{-1} 3167; δ_H($CDCl_3$) 1.00 (9H, t, *J* 7.3 Hz), 1.04–1.24 (6H, m), 1.24–1.39 (6H, m), 1.44–1.68 (6H, m), 7.46 (1H, d, *J* 5.1 Hz), 9.97 (1H, s); δ_F($CDCl_3$) −176.25 (1F, s); GC-MS *m*/*z* 318 [86, M^+ − 57(Bu)], 317 (100); Anal. calcd for $C_{15}H_{29}FN_2Sn$: C, 48.03; H, 7.79; N, 7.47%. Found: C, 48.06; H, 7.68; N, 7.38%.

§ *Preparation* of **6a**: to a solution of **3** (117.1 mg, 0.312 mmol) and 4-iodoacetophenone (85.0 mg, 0.345 mmol) in DMSO (1 mL) was added $Pd(PPh_3)_4$ (18.1 mg, 5 mol%), and the mixture was heated to 100 °C. After being stirred for 3 h, the resulting mixture was quenched with ethyl acetate and water and extracted with ethyl acetate. After the usual work-up of an organostannane experiment,[9] the residue was purified by silica gel chromatography (hexane–ethyl acetate, 1:1) to give 57.7 mg of **6a** as a white solid in 91% yield: mp 159.2–160.8 °C; ν_{max} (neat)/cm^{-1} 3158, 1668; δ_H($CDCl_3$) 2.64 (3H, s), 7.55 (1H, d, *J* 4.2 Hz), 7.91 (2H, d, *J* 8.4 Hz), 8.02 (2H, d, *J* 8.4 Hz), 10.4 (1H, s); δ_F($CDCl_3$) −176.18 (1F, d, *J* 4.2 Hz); GC-MS *m*/*z* 204 (37, M^+), 189 (100); Anal. calcd for $C_{11}H_9FN_2O$: C, 64.70; H, 4.44; N, 13.72%. Found: C, 64.60; H, 4.56; N, 13.57%.

¶ Crystal data for **6a**: ($C_{11}H_9FN_2O{\cdot}H_2O$): M = 222.22, T = 93(2) K, triclinic, space group $P\bar{1}$, a = 8.329(15), b = 11.137(17), c = 11.87(3) Å, α = 76.62(7)°, β = 73.46(7)°, γ = 82.32(7)°, V = 1024(3) Å^3, Z = 4, Dx = 1.441 mg m^{-3}, μ = 0.113 mm^{-1}, λ = 0.71075 Å, θ_{max} = 27.48°, 11589 measured reflection, 4612 independent reflections, 308 refined parameters, GOF = 1.019, $R[F^2 > 2\sigma(F^2)]$ = 0.0778, $wR(F^2)$ = 0.2160. The intensity data were collected on a Rigaku RAXIS-RAPID diffractometer. The structure was solved by direct methods (SHELXS97[10]) and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares procedures on F^2 for all reductions (SHELXL97[11]). All hydrogen atoms were positioned geometrically and refined as riding. CCDC 258756. See http://www.rsc.org/suppdata/cc/b4/b419329f/ for crystallographic data in .cif or other electronic format.

1 T. Hiyama, in *Organofluorine Compounds*, ed. H. Yamamoto, Springer Verlag, New York, 2000; *Chemistry of Organic Fluorine Compounds II*, ed. M. Hudlicky and A. E. Pavlath, ACS Monograph 187, Washington, DC, 1995.

2 T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Doctor, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1347.

3 T. Hanamoto, Y. Hakoshima and M. Egashira, *Tetrahedron Lett.*, 2004, **45**, 7573.

4 For recent references, see: Q. Zhang and L. Lu, *Tetrahedron Lett.*, 2000, **41**, 8545; J. Ichikawa, M. Kobayashi, Y. Noda, N. Yokota, K. Amano and T. Minami, *J. Org. Chem.*, 1996, **61**, 2763; H. Yamanaka, T. Takekawa, K. Morita, T. Ishihara and J. T. Gupton, *Tetrahedron Lett.*, 1996, **37**, 1829; X. Shi, T. Ishihara, H. Yamanaka and J. T. Gupton, *Tetrahedron Lett.*, 1995, **36**, 1527; K. Funabiki, T. Ohtsuki, T. Ishihara and H. Yamanaka, *Chem. Lett.*, 1995, 239; H. Molines and C. Wakselman, *J. Org. Chem.*, 1989, **54**, 5618.

5 T. Hanamoto, Y. Koga, T. Kawanami, H. Furuno and J. Inanaga, *Angew. Chem. Int. Ed.*, 2004, **43**, 3582.

6 C. Reichardt and K. Halbritter, *Justus Liebigs Ann. Chem.*, 1975, 470.

7 Y. Kobayashi, T. Yamashita, K. Takahashi, H. Kuroda and I. Kumadaki, *Chem. Pharm. Bull.*, 1984, **32**, 4402; I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, Ltd., New York, 1976; K. N. Houk, J. Sims, C. R. Watts and L. J. Luskus, *J. Am. Chem. Soc.*, 1973, **95**, 7301.

8 X. Han, B. M. Stoltz and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 7600.

9 J. E. Leibner and J. Jacobus, *J. Org. Chem.*, 1979, **44**, 449.

10 G. M. Sheldrick, *SHELXS-97, Program for solution of crystal structures*, University of Göttingen, Germany, 1997.

11 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.