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Regioselective One-Step Synthesis of 4-Fluoroalkylated Isoquinolines via Carbopalladation Reaction of Fluorine-Containing Alkynes

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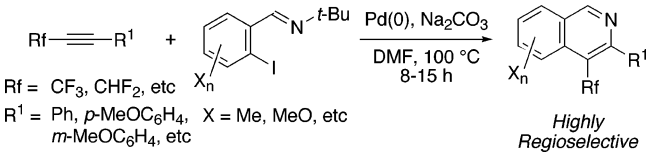
Received August 11, 2005

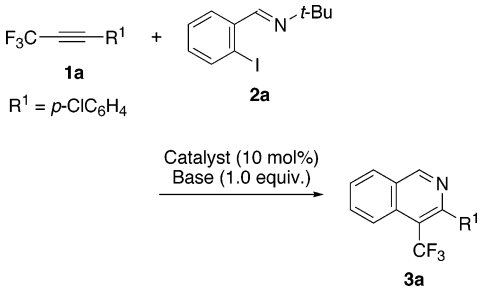


The palladium-catalyzed annulation reaction of fluoroalkylated alkynes with various 2-iodobenzylidenamines was investigated. In the presence of a catalytic amount of $Pd(PPh_3)_4$, the reaction took place smoothly to give the corresponding 4-fluoroalkylated isoquinoline in high yield as a single isomer. No other regioisomer was detected.

The isoquinoline backbone is very often found in numerous natural products as well as in drug candidates possessing interesting biological activities.[1] Accordingly, this has encouraged the development of a number of classical approaches for the synthesis of the isoquinoline ring system, including the Pictet−Spengler reactions,[2] Bischler−Napieralski reactions,[3] etc.[4]

In medicinal chemistry, on the other hand, the introduction of fluorine atom(s) into lead molecules has been quite often employed as one of the most efficient methods for modification of the lead molecules in view of the biological activities.[5] It is not surprising, therefore, that fluorine-containing isoquinoline derivatives have attracted much attention from many synthetic chemists. Despite such potential utility, there have been quite limited studies on the preparation of fluorine-containing isoquinoline derivatives thus far.[6] Herein we wish to describe an efficient approach to such molecules via an annulation reaction of fluoroalkylated alkynes with various 2-iodobenzylidenamine derivatives in detail.

TABLE 1. Investigation of the Reaction Conditions



entry	catalyst	base	yield[a] of **3a** (%)
1	$Pd(PPh_3)_4$	Na_2CO_3	87
2	$Pd(PPh_3)_4$	K_2CO_3	15
3	$Pd(PPh_3)_4$	NaOAc	47
4	$Pd(PPh_3)_4$	KOAc	36
5	$Pd(PPh_3)_4$	Et_3N	65
6	$^1/_2[Pd_2(dba)_3] + 4PPh_3$	Na_2CO_3	72
7	$^1/_2[Pd_2(dba)_3] + 4PCy_3$	Na_2CO_3	76
8	$^1/_2[Pd_2(dba)_3] + 4P(n\text{-}Bu)_3$	Na_2CO_3	55
9	$^1/_2[Pd_2(dba)_3] + 4P(o\text{-}Tol)_3$	Na_2CO_3	80
10	$^1/_2[Pd_2(dba)_3] + 4P(t\text{-}Bu)_3$	Na_2CO_3	81
11[b]	$Pd(PPh_3)_4$	Na_2CO_3	87
12[c]	$Pd(PPh_3)_4$	Na_2CO_3	7
13	$Ni(cod)_2$	Na_2CO_3	0
14	$Ni(cod)_2 + 4PPh_3$	Na_2CO_3	0
15	$RhCl(PPh_3)_3$	Na_2CO_3	0
16	$[Rh(cod)_2]BF_4$	Na_2CO_3	0

[a] Determined by ^{19}F NMR. [b] Five mole percent catalyst was used. [c] One mole percent catalyst was used.

Our initial studies were focused on the palladium-catalyzed annulation reaction of trifluoromethylated alkyne **1a**[7] with 2-iodobenzylidenamine **2a** (Table 1).[8] Thus, treatment of 1.0 equiv of **1a** with 1.5 equiv of **2a** in DMF at 100 °C for 8 h in the presence of 10 mol % $Pd(PPh_3)_4$ and 1.0 equiv of Na_2CO_3 gave the corresponding 4-(trifluoromethyl)isoquinoline **3a** in 87% yield (entry 1). In this case, no trace of the regioisomer **4a** was detected (Figure 1). As shown in entries 2−5, we found that bases such as K_2CO_3, NaOAc, KOAc, and Et_3N were not effective. We also investigated the ligand effect by using PCy_3, $P(n\text{-}Bu)_3$, $P(o\text{-}Tol)_3$, and $P(t\text{-}Bu)_3$, as described in entries 6−10. We found that bulky ligands, such as

(1) (a) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629. (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic Publishers: Amsterdam, 1998; Vol. 1.

(2) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 74−150.

(3) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 151−190.

(4) Gensler, W. J. In *Organic Reactions*; Adams, R., Ed.; Wiley: New York, 1951; Vol. 6, pp 191−206.

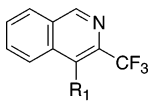
(5) (a) O'hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645−652. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123−3197. (c) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381−436.

(6) There have been several reports on the synthesis of fluoroalkylated isoquinoline derivatives so far. See: (a) Poszávácz, L.; Simig, G. *Tetrahedron* **2001**, *57*, 8573−8580. (b) Akiyama, T.; Kato, K.; Kajitani, M.; Sakaguchi, Y.; Nakamura, J. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3531−3537.

(7) As for the preparation of the fluorine-containing alkynes, see: (a) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2003**, *59*, 7571−7580. (b) Brisdon, A. K.; Crossley, I. R. *Chem. Commun.* **2002**, 2420−2421. (c) Yoneda, N.; Matsuoka, S.; Miyaura, N. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2124−2126. (d) Hiyama, T.; Sato, K.; Fujita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1352−1354. (e) Bunch, J. E.; Bumgardner, C. L. *J. Fluorine Chem.* **1987**, *36*, 313−317.

(8) As for the annulation reaction of nonfluorinated alkynes with *N*-benzaldehyde imine, see: (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437−3444. (b) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359−1362. (c) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557−3560. (d) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042−8051. (e) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035−4038. (f) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553−556.

10.1021/jo051700v CCC: $30.25
Published on Web 10/29/2005

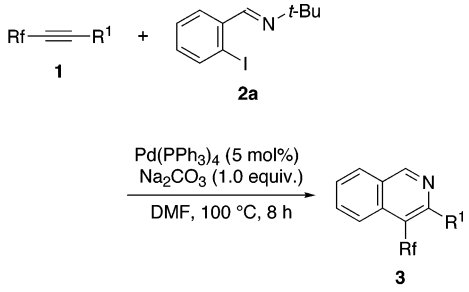


4a

R^1 = *p*-ClC_6H_4

FIGURE 1. Regioisomer.

TABLE 2. Annulation of Various Fluorine-Containing Alkynes with 2a



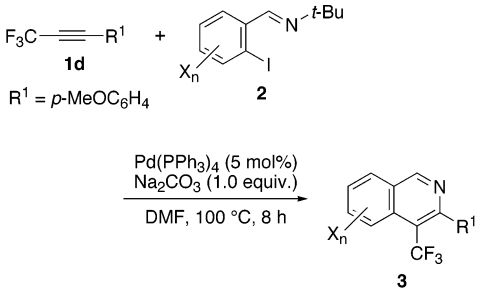
entry	Rf	R^1	substrate	yield[a] of **3** (%)
1	CF_3	Ph	**1b**	87 (**3b**)
2	CF_3	*p*-ClC_6H_4	**1a**	87 (**3a**)
3	CF_3	*p*-MeC_6H_4	**1c**	87 (83) (**3c**)
4	CF_3	*p*-$MeOC_6H_4$	**1d**	92 (92) (**3d**)
5	CF_3	*o*-$MeOC_6H_4$	**1e**	87 (79) (**3e**)
6	CF_3	*m*-$MeOC_6H_4$	**1f**	77 (70) (**3f**)
7	CF_3	*p*-$EtO_2CC_6H_4$	**1g**	65 (48) (**3g**)
8	CF_3	*p*-$O_2NC_6H_4$	**1h**	46 (40) (**3h**)
9	CF_3	$C_6H_5(CH_2)_3$	**1i**	15 (**3i**)
10	CF_3	$PhMe_2Si$	**1j**	0
11	CF_3	EtO_2C	**1k**	0
12	CF_3	HO, *n*-C_6H_{13}	**1l**	0
13	CHF_2	*p*-ClC_6H_4	**1m**	83 (**3j**)
14	$H(CF_2)_3$	*p*-ClC_6H_4	**1n**	54 (**3k**)

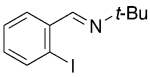
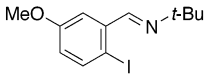
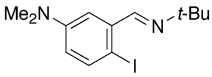
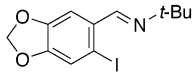
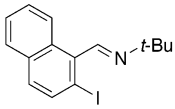
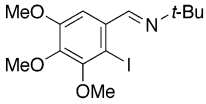
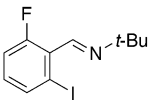
[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.

$P(o\text{-Tol})_3$ and $P(t\text{-Bu})_3$, were very effective. A decrease in the amount of the palladium catalyst from 10 to 5 mol % did not influence the chemical yield (entry 11); however, the use of 1 mol % catalyst caused a significant decrease in the yield (entry 12). It is noteworthy that other metal catalysts, such as $Ni(cod)_2$, $Ni(cod)_2$ + $4PPh_3$, $RhCl(PPh_3)_3$, and $[Rh(cod)_2]BF_4$, were completely ineffective as catalysts.

With the optimized reaction conditions (Table 1, entry 11), we next examined the annulation reaction of various fluoroalkylated alkynes **1** with **2a** as shown in Table 2. As described in entries 1−4, alkynes possessing various substituents, such as Cl, Me, or MeO, on the benzene ring could participate nicely in the annulation reaction to give the corresponding isoquinoline derivatives **3a**−**d** in high to excellent yields. Additionally, the position of the substituent on the benzene ring in the alkynes did not influence the reaction at all (entries 4−6). However, the yield was somewhat eroded when the alkynes bearing an electron-withdrawing group, such as an ethoxycarbonyl or a nitro group, on the benzene ring were employed (entries 7 and 8). The use of an aliphatic side chain as R^1 also led to a significant decrease in the yield[9] (entry 9). Furthermore, the alkynes having a silyl or an ethoxycarbonyl group and the γ-trifluoromethylated propargyl alcohol were found to be completely inactive

TABLE 3. Annulation of 1d with Various Imines



entry	imine		yield[a] of **3** (%)
1		(**2a**)	92 (92) (**3d**)
2		(**2b**)	86 (82) (**3l**)
3		(**2c**)	83 (**3m**)
4[b]		(**2d**)	85 (76) (**3n**)
5[b]		(**2e**)	93 (87) (**3o**)
6[c]		(**2f**)	Trace
7		(**2g**)	78 (**3p**)

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields. [b] Stirred for 15 h. [c] Stirred for 48 h.

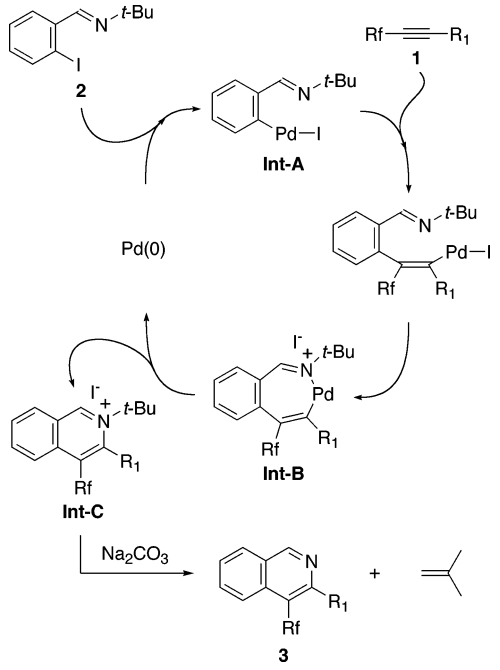
(entries 10−12). Difluoromethylated alkynes, on the other hand, could be successfully applied for the annulation reaction (entry 13), whereas a slight decrease in the yield was observed in the case of the alkyne having a hexafluoropropyl group as Rf (entry 14).

Next, our attention was directed toward the annulation reaction of **1d** with various imines. The results are summarized in Table 3.

As shown in entries 2 and 3, 5-substituted 2-iodobenzaldehyde imines could also participate nicely in the annulation reaction to afford the corresponding 4-(trifluoromethyl)isoquinolines **3l** and **3m** in high yields. Additionally, 4,5- or 5,6-disubstituted 2-iodobenzaldehyde imines could be applied successfully in the annulation reaction, though a longer reaction time of 15 h was necessary for completion of the reaction (entries 4 and 5). However, the substitution at the 3-position on the benzene ring retarded the reaction significantly (entry

(9) The same phenomenon was observed in the annulation reactions. See: (a) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *Tetrahedron* **2004**, *60*, 11695−11700. (b) Konno, T.; Chae, J.; Ishihara, T.; Yamanaka, H. *J. Org. Chem*. **2004**, *69*, 8258−8265. (c) Chae, J.; Konno, T.; Ishihara, T.; Yamanaka, H. *Chem. Lett*. **2004**, *33*, 314−315.

SCHEME 1. Plausible Mechanism



6). On the other hand, the introduction of the electron-withdrawing group into the benzene ring did not influence the reaction at all (entry 7).

The structural assignment of **3** was made as follows. The single-crystal X-ray analysis of **3d** could be carried out successfully, indicating that **3d** was not a 3-trifluoromethylated isoquinoline but a 4-trifluoromethylated one (see the Supporting Information). The structure of the other products was determined by the comparison of the chemical shifts in ^{19}F NMR.

These results may allow us to draw the reaction mechanism as described in Scheme 1.

Thus, the reaction presumably proceeds via (1) oxidative addition of 2-iodobenzaldehyde imine derivatives **2** to Pd(0), (2) coordination of the alkyne **1** to the metal center of the arylpalladium intermediate **Int-A** and subsequent insertion into the Ar−Pd bond, (3) nitrogen displacement of the halide in the resulting vinylic palladium intermediate to form a seven-membered heteroatom-containing palladacycle **Int-B**, (4) reductive elimination to form **Int-C** to regenerate Pd(0), and (5) the elimination of isobutene to form the isoquinoline **3**.[10]

In conclusion, we have accomplished the convenient and one-step synthesis of fluoroalkylated isoquinolines via a palladium-catalyzed annulation reaction of fluorine-containing alkynes, leading to the exclusive formation of 4-fluoroalkylated regioisomers in good yields.

Experimental Section

Typical Procedure for the Synthesis of Fluorine-Containing Isoquinoline. To a solution of $Pd(PPh_3)_4$ (0.026 g, 0.024 mmol), Na_2CO_3 (0.05 g, 0.488 mmol), and 2-iodobenzylidenamine (0.206 g, 0.72 mmol) in DMF (6 mL) was added 3,3,3-trifluoro-1-phenyl-1-propyne (83 mg, 0.488 mmol) at room temperature. After being heated for 8 h at 100 °C, the mixture was quenched with aq $NaHCO_3$, and extracted with Et_2O three times. The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/EtOAc (3:2) to afford 3-phenyl-4-trifluoromethylisoquinoline **(3b)** (116 mg, 0.42 mmol): yield 87%; ^{1}H NMR ($CDCl_3$) δ 7.46−7.57 (5H, m), 7.72 (1H, t, J = 7.46 Hz), 7.86 (1H, t, J = 7.41 Hz), 8.08 (1H, d, J = 8.05 Hz), 8.28 (1H, d, J = 7.65 Hz), 9.39 (1H, s); ^{13}C NMR ($CDCl_3$) δ 117.6 (q, J = 29.8 Hz), 124.3 (q, J = 3.9 Hz), 124.7 (q, J = 276.0 Hz), 127.3, 127.8, 127.9, 128.3, 128.4, 128.9 (d, J = 1.3 Hz), 132.0, 133.2, 140.9, 153.1, 154.9; ^{19}F NMR ($CDCl_3$) δ −51.63 (3F, s); IR (KBr) ν 3032, 1695, 1622, 1576 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{12}F_3N$ 274.0844, found (M + H) 274.0838.

Supporting Information Available: Characterization data, ^{1}H NMR spectra, and ^{13}C NMR spectra of **3a**−**h**, **3i**, and **3l**−**p**, and X-ray data of **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A similar reaction mechanism in the annulation of nonfluorinated internal alkynes has been reported. See ref 8d. An alternative mechanism has also been reported. See: (a) Girling, T. R.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1317−1323. (b) Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett*. **1982**, *41*, 4281−4284.