

A Facile Synthesis of Various Fluorine-Containing Indole Derivatives via Palladium-Catalyzed Annulation of Internal Alkynes

Jungha Chae, Tsutomu Konno,* Takashi Ishihara, and Hiroki Yamanaka

Department of Chemistry and Materials Technology, Kyoto Institute of Technology,
Matsugasaki, Sakyo-ku, Kyoto 606-8585

(Received December 15, 2003; CL-031234)

The palladium-catalyzed annulation reaction of a variety of fluorine-containing internal alkynes with 2-iodoaniline derivatives took place smoothly to give the corresponding 2,3-disubstituted indole derivatives in good to excellent yields.

Indole derivatives, widely distributed in nature as the amino acid tryptophan, its metabolites, and indole alkaloids, are very useful as lead compounds for the discovery or development of novel biologically active compounds, as they are known to have various significant biological activities.¹ Consequently, much effort has been done for developing a new methodology for the construction of such molecules.² In the field of medicinal chemistry, on the other hand, introduction of a fluoroalkyl group into lead molecules has been employed as one of the most efficient methods for modification of the lead compounds in view of the biological activity.³ It is not surprising, therefore, that fluoroalkylated indole derivatives have attracted much attention of many synthetic chemists thus far. There have been several synthetic methods for the fluoroalkylated indole derivatives. For example, fluoroalkylated indoles are prepared by direct fluoroalkylation of indoles with perfluoroalkanoyl peroxides⁴ or perfluoroalkyl halides.⁵ However, the direct fluoroalkylation very often suffers from poor yields of the desired fluoroalkylindoles. Although, the thermolysis of 2-(N-trifluoroacetylaminobenzylphosphonium salts⁶ or the intramolecular cyclization of *N*-trifluoroacetyl-*p*-benzoquinone imine⁷ gives the desired indoles in good yields, multi-step preparations are required for the starting substrates. Such drawbacks actually make these methods less attractive. Herein we wish to describe a practical and facile synthesis of fluoroalkylated indole derivatives by the palladium-catalyzed annulation of internal alkynes possessing a fluoroalkyl group.⁸

The palladium-catalyzed reaction of trifluoromethylated acetylene **1a**⁹ ($R = p\text{-ClC}_6\text{H}_4$) and 2-iodoaniline was chosen for our initial investigation of the annulation process. Thus, to a solution of 10 mol % of $\text{Pd}(\text{PPh}_3)_4$ and 1.0 equiv. of Et_3N in DMF (4 mL) was added 1.0 equiv. each of **1a** and 2-iodoaniline, and the mixture was heated at 80 °C for 4 h. As a result, the regioisomers **2a** and **3a** were obtained in 39% yield in a ratio of 69:31,¹⁰ the starting material being recovered in 52% yield (Table 1, Entry 1). The addition of 2.0 equiv. of aniline resulted in the formation of **2a** and **3a** in a higher regioselective manner in 51% yield. Additionally, increasing the amount of palladium catalyst brought about higher yield (75%), though 11% of **1a** still remained unreacted. Eventually, the starting material was completely consumed when the reaction was performed for 8 h, the mixture of **2a** and **3a** being afforded in 85% yield in a ratio of 78:22. We next examined the effect of ligand on palladium as

Table 1. Investigation of the reaction conditions

$\text{F}_3\text{C}\equiv\text{R}$		1a		$\text{Pd}(\text{PPh}_3)_4$ Et ₃ N (1.0 equiv.) DMF, 80 °C, Time	2a	3a
$R = p\text{-ClC}_6\text{H}_4$						
Entry	Aniline /equiv.	$\text{Pd}(\text{PPh}_3)_4$ /mol %	Time/h	Yield ^a /% of 2a + 3a	Ratio ^b (2a : 3a)	Recovery ^a /% of 1a
1	1	10	4	39	69:31	52
2	2	10	4	51	78:22	37
3	2	20	4	75	77:23	11
4	2	20	8	85 (79)	78:22	0

^aDetermined by ¹⁹F NMR. Value in parentheses is of isolated yield.

^bDetermined by ¹⁹F NMR.

shown in Table 2.

The use of tri(2-furyl)phosphine as a ligand led to a significant decrease of the efficiency of the reaction, **2a** and **3a** being formed in only 20% yield, together with a large amount of unreacted **1a** (Entry 2). In sharp contrast to the result in Entry 1, the palladium catalyst prepared from $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and PPh_3 gave a low yield of the desired products, strongly suggesting that dba ligand may decrease the efficiency of the reaction (Entry 3). In the case of tri(*tert*-butyl)phosphine and tri(*o*-tolyl)phosphine, the annulation took place smoothly to give the corresponding indole derivatives in excellent yield, but, the regioselectivity decreased significantly. In particular, **3a** was produced preferentially (**2a**:**3a** = 34:66) when tri(*o*-tolyl)phosphine was employed as a ligand (Entry 5).

Table 2. Screening of ligand

Entry	Catalyst/20 mol%	Yield ^a /% of 2a + 3a	Ratio ^b (2a : 3a)	Recovery ^a /% of 1a
1	$\text{Pd}(\text{PPh}_3)_4$	85 (79)	78:22	0
2	$1/2[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3] + 4\text{P}(2\text{-furyl})_3$	20	90:10	79
3	$1/2[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3] + 4\text{PPh}_3$	33	88:12	55
4	$1/2[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3] + 4\text{P}(t\text{-Bu})_3$	94	53:47	0
5	$1/2[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3] + 4\text{P}(o\text{-Tol})_3$	90	34:66	0

^aDetermined by ¹⁹F NMR. Value in parentheses is of isolated yield.

^bDetermined by ¹⁹F NMR.

Next, the scope and limitations of this annulation reaction were examined by allowing a wide variety of internal alkynes to react with various 2-iodoanilines under optimized reaction conditions (Table 2, Entry 1). The results are summarized in Table 3. As can be seen in Entries 1–9, various fluorine-containing internal alkynes could participate nicely in the annulation reaction. Thus, the alkynes bearing an electron-donating group (Me, MeO) as R gave the corresponding indoles in good yields

Table 3. The scope and limitations of palladium-catalyzed annulation of fluorine-containing internal alkynes

Entry	Rf	R	R ¹	R ²	Yield ^a /% of 2 + 3	Ratio ^b (2 : 3)
1	CF ₃	<i>p</i> -ClC ₆ H ₄	H	H	85 (79)	78:22
2 ^c	CF ₃	<i>p</i> -MeC ₆ H ₄	H	H	84 (81)	88:12
3 ^c	CF ₃	<i>p</i> -MeOC ₆ H ₄	H	H	79 (73)	91:9
4	CF ₃	<i>p</i> -EtO ₂ CC ₆ H ₄	H	H	98 (92)	68:32
5	CF ₃	<i>p</i> -O ₂ NC ₆ H ₄	H	H	70 (65)	53:47
6 ^c	CF ₃	<i>o</i> -ClC ₆ H ₄	H	H	64 (59)	76:24
7	CF ₃	<i>m</i> -ClC ₆ H ₄	H	H	86 (80)	72:28
8	CF ₃	Ph(CH ₂) ₃	H	H	53 (47)	81:19
9	CHF ₂	<i>p</i> -ClC ₆ H ₄	H	H	84 (70)	100:0
10 ^c	CF ₃	<i>p</i> -ClC ₆ H ₄	Cl	H	90 (79)	84:16
11	CF ₃	<i>p</i> -ClC ₆ H ₄	CH ₃	H	85 (82)	81:19
12 ^c	CF ₃	<i>p</i> -ClC ₆ H ₄	NO ₂	H	61 (57)	84:16
13 ^c	CF ₃	<i>p</i> -ClC ₆ H ₄	H	OMe	68 (65)	88:12
14 ^d	CF ₃	<i>p</i> -ClC ₆ H ₄	Cl	Cl	87 (74)	84:16

^aDetermined by ¹⁹F NMR. Values in parentheses are of isolated yields. ^bDetermined by ¹⁹F NMR. ^cStirred for 24 h. ^dStirred for 48 h.

with good regioselectivity.

Introduction of an electron-withdrawing group (CO₂Et, NO₂) into benzene ring in **1** led to a decrease of the regioselectivity, though the reaction took place smoothly (Entries 4 and 5). It should be noted that the position of substituent on the benzene ring in **1** influenced slightly on the reaction. Thus, the alkyne having a chloro group at *ortho* position resulted in formation of the desired product in 64% yield, whereas the corresponding *meta*- or *para*-isomer afforded the satisfactory results (> 80% yield) (Entry 6 vs Entries 1 and 7). The alkyne bearing an aliphatic side chain as R could also be applied for the annulation reaction successfully (Entry 8). Additionally, changing a fluoroalkyl group from a CF₃ to a CHF₂ group caused the increase of the regioselectivity. We also examined the annulation of **1a** with various 2-iodoaniline derivatives as shown in Entries 10–14. It was found that no significant influence of the substituents R¹ and R² of aniline ring was observed for the yield and the regioselectivity, though prolonged reaction times were required.

In almost all cases (except for Entries 1, 6, and 7), **2a** or **3a** could easily be obtained in a pure form by simple silicagel column chromatography.

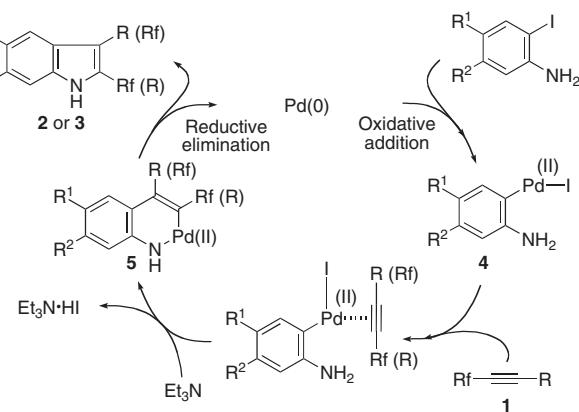
The reaction presumably proceeds via (1) oxidative addition of aryl iodide to Pd(0), (2) coordination of the alkyne **1** to the

metal center of the arylpalladium intermediate **4** and subsequent insertion into the Ar–Pd bond, (3) nitrogen displacement of the halide in the resulting vinylic palladium intermediate to form a six-membered heteroatom-containing palladacycle **5**, and (4) reductive elimination to form indoles **2** or **3** to regenerate Pd(0) (Scheme 1).

In conclusion, we have accomplished the convenient synthesis of fluoroalkylated indoles via palladium-catalyzed annulation reaction of fluorine-containing alkynes. This method is applicable for various types of fluorine-containing alkynes and 2-iodoaniline derivatives, leading to **2** and **3** as a separable mixture.

References and Notes

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- 10 The structures of **2** and **3** were determined on the basis of chemical shifts in ¹⁹F NMR compared with that described in the literature (Ref. 5c). Thus, the signals observed at the upper or lower fields are that of 2-fluoroalkyl- or 3-fluoroalkylindole derivatives, respectively.

**Scheme 1.** Mechanism.