A Novel Method for the Synthesis of 2-Trifluoromethylindoles from *N*-(*o*-Haloaryl)alkynylimines

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Received 3 March 2010

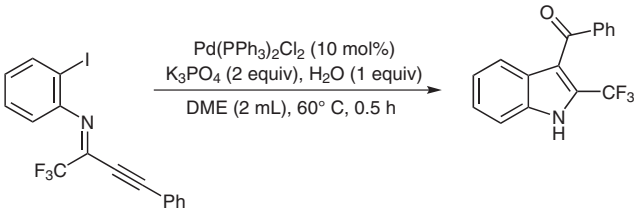
Abstract: Treatment of various types of *N*-(*o*-haloaryl)-alkynylimines in the presence of $Pd(PPh_3)_2Cl_2$ gave 2-trifluoromethylindoles in high yields. This approach provides a novel and facile access to the biologically important fluorine-containing indole derivatives.

Key words: indoles, trifluoromethyl, palladium, alkynylimine, heterocycles

The indole scaffold is a prominent and privileged structural motif found in numerous natural products and various synthetic compounds.[1] It is well known that the properties of a bioactive molecule can often be modulated by adding fluorine atoms since this leads to changes in solubility, lipophilicity, metabolic stability, conformation, hydrogen-bonding ability, or chemical reactivity.[2] Biologically active 2-trifluoromethylindole compounds have previously been reported. For example, 2-trifluoromethylated indoles are of significant pharmacological interest for their use as potent chemokine receptor 5 (CCR5) antagonists,[3] general anesthesia inducers,[4] tyrosine kinase inhibitors,[5] and antitumor compounds.[6]

In view of the importance of fluorine-containing indole compounds, considerable effort has been placed in developing an efficient method for the synthesis of trifluoromethylated indole derivatives. Classical methods include direct fluoroalkylation of indoles with perfluoroalkanoyl peroxides or perfluoroalkyl halides,[7] titanium-catalyzed carbonyl coupling of 2-acyltrifluoroacetanilides,[8] photochemical intramolecular cyclizations of trifluoroacetimidoyl iodide or trifluoroacetimidoyl telluride,[9] thermolysis of 2-(*N*-trifluoroacetylamino)benzylphosphonium salts, and intramolecular cyclization of *N*-trifluoroacetyl-*p*-benzoquinone.[10,11] Recently, Pd-catalyzed annulation of fluorine-comprising internal alkynes with 2-iodoanilines,[12] Grignard cyclization reaction of fluorinated *N*-arylimidoyl chlorides, and Cu-catalyzed coupling of 2-halotrifluoroacetanilides with β-keto esters were also reported.[13,14] However, most of them suffered from either poor yields or the limitation of starting materials. New methods for synthesizing fluorine-containing indole derivatives are still in need. Herein, we wish to describe a novel and facile synthesis of 2-trifluoromethylindole derivatives by palladium-catalyzed cyclization reaction of *N*-(*o*-haloaryl)alkynylimines.

Table 1 Optimization of Reaction Conditions[a]



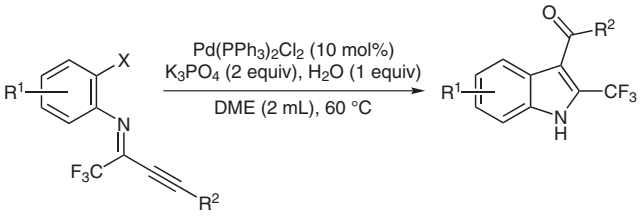
Entry	Catalyst	Base	Solvent	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2/Ph_3P$	K_3PO_4	DME	0.5	87
2	$PdCl_2/Ph_3P$	K_3PO_4	DME	15	25
3	$Pd_2(dba)_3{\cdot}CHCl_3/Ph_3P$	K_3PO_4	DME	0.5	94
4	$Pd(PPh_3)_2Cl_2/Ph_3P$	K_3PO_4	DME	0.5	96 (80)
5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	DME	0.5	95
6	$Pd(PPh_3)_2Cl_2$	K_2CO_3	DME	1	85
7	$Pd(PPh_3)_2Cl_2$	KOAc	DME	1	19
8	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	DME	1	15
9	$Pd(PPh_3)_2Cl_2$	K_3PO_4	DMSO	1	68
10	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MeCN	1	72
11	$Pd(PPh_3)_2Cl_2$	K_3PO_4	dioxane	1	21
12	$Pd(PPh_3)_2Cl_2$	K_3PO_4	H_2O	4	68
13	$Pd(PPh_3)_2Cl_2$	K_3PO_4	DME	2	47[c]
14	$Pd(PPh_3)_2Cl_2$	K_3PO_4	DME	1	66[d]

[a] Reactions were carried out on a 0.2 mmol scale in DME (2 mL) under nitrogen with H_2O (1.0 equiv), catalyst (10 mol%), and base (2 equiv) unless otherwise stated.
[b] Reported yields were based on **1a** determined by ^{19}F NMR. Values in parentheses are of isolated yield.
[c] $Pd(PPh_3)_2Cl_2$ (5 mol%) was used.
[d] K_3PO_4 (1 equiv) was used.

SYNLETT 2010, No. 9, pp 1418–1420
Advanced online publication: 20.04.2010
DOI: 10.1055/s-0029-1219904; Art ID: W03410ST

2-Iodo-*N*-(1,1,1-trifluoro-4-phenylbut-3-yn-2-ylidene)-aniline (**1a**) was chosen as a model substrate to screen the optimal reaction conditions (Table 1). Initial experiments were performed using H_2O (1 equiv), K_3PO_4 (2 equiv), in the presence of 10 mol% of $Pd(OAc)_2$ and 20 mol% of Ph_3P as the catalyst system in DME (dimethoxyethane) at 60 °C under nitrogen atmosphere. This reaction was completed after 0.5 hours, and the indole product was formed in 87% yield (Table 1, entry 1). Next, different palladium sources were screened, and preliminary results showed that the use of $Pd(PPh_3)_2Cl_2$ gave excellent yield of the product even without an additional ligand (Table 1, entries 2–5). Among the bases studied, K_3PO_4 provided the best result (Table 1, entries 6–8). We then probed the solvent effect and found that DME was considerably superior to DMSO, MeCN, dioxane, and H_2O (Table 1, entries 9–12). The attempt to reduce loading of the catalyst and base led to longer reaction times and lower yields (Table 1, entries 13 and 14).

Table 2 Synthesis of 2-Trifluoromethylindole Derivatives **2** from *N*-(*o*-haloaryl)alkynylimines[a]



Entry	X	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	Br	H	Ph	0.5	**2a**	80
2	Cl	H	Ph	5	**2a**	13
3	I	4-Me	Ph	0.5	**2b**	82.5
4	I	5-MeO	Ph	0.5	**2c**	78.4
5	I	4-F	Ph	1	**2d**	75.7
6	I	4-F_3C	Ph	3	**2e**	52.5
7	I	H	4-MeC_6H_4	0.5	**2f**	82.5
8	I	H	4-$MeOC_6H_4$	0.5	**2g**	85.4
9	I	H	3-$MeOC_6H_4$	0.5	**2h**	80.7
10	I	H	4-ClC_6H_4	0.5	**2i**	70.3
11	I	H	4-FC_6H_4	1	**2j**	59.4
12	I	H	2-ClC_6H_4	1	**2k**	70.3
13	I	H	2-naphthyl	1	**2l**	73.8
14	I	H	2-thienyl	0.5	**2m**	84.7
15	I	H	*t*-Bu	0.5	**2n**	85.7

[a] Reactions were carried out on a 0.3 mmol scale in DME (2 mL) under nitrogen with H_2O (1.0 equiv), catalyst (10 mol%), and base (2 equiv) unless otherwise stated.
[b] Isolated yield.

After optimization, the best reaction conditions were ascertained as 10 mol% $Pd(PPh_3)_2Cl_2$, 1 equiv of H_2O, and 2 equiv of K_3PO_4 in DME at 60 °C under nitrogen atmosphere (Table 1, entry 5).

Next, the scope and limitations of this annulation reaction were examined. Table 2 summarizes the results of the reactions of a variety of *N*-(*o*-haloaryl)alkynylimines under optimized reaction conditions. *N*-(*o*-Bromoaryl)alkynylimine could also give a good yield at 60 °C without loss of reactivity compared with chlorides (Table 2, entries 1 and 2). Then, the substituent effects were investigated. When R^1 was an electron-donating group, the product was isolated in good yield (Table 2, entries 3 and 4). Electron-withdrawing group such as F and CF_3 gave the products in lower yields with longer times (Table 2, entries 5 and 6). Further modifying the alkyne moiety revealed that when R^2 was an aromatic ring with an electron-donating group such as Me and MeO or a *tert*-butyl group, the reaction was completed within 30 minutes in good yield (Table 2, entries 7–9, 15), while electron-deficient aryl group needed prolonged reaction time to give products in lower yield (Table 2, entries 10–12).

A possible mechanism of this transformation is proposed. The first step is oxidative addition of Pd(0) with aryl halide, then carbo-palladation followed by reductive elimination of Pd(0) leading to 3-(1-iodo-1-phenyl)-methyleneindole as an intermediate,[9b] which is hydrolyzed under the reaction conditions to provide the final acylindole.

In conclusion, we have developed a novel and facile method for the synthesis of biologically important 2-trifluoromethyl-substituted indole derivatives from the easily prepared *N*-(*o*-haloaryl)alkynylimines. Using this protocol, a wide variety of functionalized 2-trifluoromethylindoles can be synthesized in good yields under mild conditions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the National Science Foundation of China (Nos. 20772145).

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