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Direct C-3 arylation of *N*-acetylindoles with anisoles using phenyliodine bis(trifluoroacetate) (PIFA)

Yonghong Gu *, Dawei Wang

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

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ABSTRACT

The direct C-3 arylation of *N*-acetylindoles with anisoles was described in this Letter. In the presence of phenyliodine bis(trifluoroacetate) (PIFA) and $BF_3{\cdot}Et_2O$, the reaction of *N*-acetylindoles with anisoles provided C-3 arylindoles with high regioselectivity under mild conditions.

Indole derivatives are one of the most important structural motifs found in natural products and pharmaceuticals.[1] As an important class of indoles, arylindoles exhibit a wide range of biological activities, such as antibacterial, antifungal, antiprotozoal activities, gonadotropin-releasing hormone antagonists and h5-HT_{2A} receptor antagonists.[2] Therefore, the development of efficient methods for the syntheses of arylindoles has attracted great research interest in the last several decades.[3] Among them, transition metal-catalyzed direct arylation of indoles has been a major objective in the synthetic community.[4] This approach offers the possibility of direct C–H arylation of indoles with aryl halides, aryl boron compounds. Several highly selective Pd-catalyzed C-3 arylations of indoles have been developed by Sames's[5], Zhang and He's[6] Djakovitch's[7] Bellina and Rossi's[8] groups. In addition, Gaunt and co-workers reported a Cu(II)-catalyzed C-3 arylation of indoles with aryliodonium salts.[9] Remarkably, Fagnou and co-workers proposed a new strategy to synthesize arylindoles by the Pd-catalyzed direct coupling of *N*-acetylindoles with unfunctionalized arenes, both C-2 and C-3 arylindoles could be accessed by changing the Pd concentration and additives.[10] While these methods have proven to be the most powerful towards C-3 arylindoles, some of them suffered disadvantages from using excess transition metals, high temperatures and limitation of substrate scope. With an increasing emphasis on environmentally friendly synthesis, we are prompted to develop greener alternatives.

Recently, utilization of hypervalent iodine compounds as metal-free reagents in oxidative reactions received great attention for their low toxicity and mild reaction conditions.[11] Many new applications of hypervalent iodine compounds in C–C bond formation have been developed.[12] However, few examples of direct cross-coupling of two arenes with hypervalent iodine compounds were reported due to the difficulty to control homodimer formation and regioselectivity.[13] Kita and co-workers achieved a highly selective cross-coupling of thiophenes and pyrroles using PhI(OH)(OTs) as an oxidant.[13a] In addition, Canesi and co-workers reported a novel method for the cross-coupling of *N*-aryl methanesulfonamide and thiophenes using $PhI(OAc)_2$.[13c] To achieve the effective cross-coupling of two arenes, two aspects have to be considered: (1) selective activation of one of the aromatic compounds with hypervalent iodine reagents. (2) One arene must have a higher nucleophilicity than the specific aromatic compound being activated. Herein, we present a highly regioselective C-3 arylation of *N*-acetylindoles with anisoles using hypervalent iodine(III) reagents.

Initial attempts at C-3 arylation of free NH indole with anisole (**2a**) in the presence of phenyliodine(III) diacetate (PIDA) or phenyliodine(III) bis(trifluoroacetate) (PIFA) in various solvents (CH_2Cl_2, CF_3CH_2OH, CH_3CN and TFA) at room temperature failed to provide any desired products; only homodimer 4,4′-dimethoxybiphenyl was observed. Gladly, when *N*-acetylindole was subjected to the 1.5 equiv of PIFA and 1.0 equiv of **2a** in CH_2Cl_2 at room temperature for 24 h, the desired C-3 arylindole **3a** was obtained in 30% yield with 20% of homodimer 4,4′-dimethoxybiphenyl as a byproduct (Table 1, entry 1). When excess **2a** (2.0 equiv) was used, the product **3a** was obtained with a better yield (entry 2). Notably, activation of PIFA with Lewis acid $BF_3{\cdot}OEt_2$ improved the reaction dramatically (entry 3).[14] In contrast, PIDA was ineffective in this transformation (entry 4). After careful optimization of the reaction conditions (solvent and temperature), the best result was achieved when the reaction was carried out in the presence of 1.5 equiv of PIFA and 1.5 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 35 °C (entry 8).

With optimized conditions in hand, we started on an investigation of the reaction scope (Table 2). In the presence of 1.5 equiv of PIFA and 1.5 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2, the coupling reaction of *N*-acetylindoles **1** with anisoles **2** proceeded smoothly to give only C-3 arylated products **3**, no C-2 arylindoles were observed in this transformation. Notably, this coupling reaction occurred only at the *para*-position of anisole, no coupling product at the *ortho*-position of anisole was detected either. The reaction is compatible with both electron-withdrawing and electron-donating groups on the

* Corresponding author. Tel.: +86 551 3602470; fax: +86 551 3601592.
E-mail address: ygu01@ustc.edu.cn (Y. Gu).

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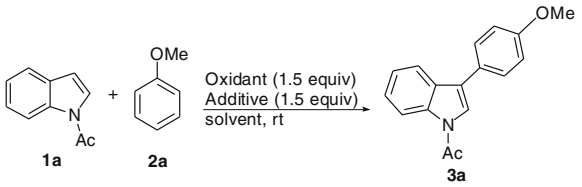
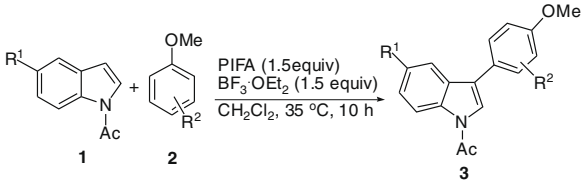
Table 1
Optimization of reaction conditions for the direct oxidative coupling of *N*-acetylindoles and anisoles[a]



Entry	Oxidant	Additive	Solvent	Yield[b] (%)
1	PIFA	None	CH_2Cl_2	30[c]
2	PIFA	None	CH_2Cl_2	41
3	PIFA	$BF_3{\cdot}OEt_2$	CH_2Cl_2	56
4	PIFA	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0
5	PIFA	$BF_3{\cdot}OEt_2$	CF_3CH_2OH	50
6	PIFA	$BF_3{\cdot}OEt_2$	TFA	0
7	PIFA	$BF_3{\cdot}OEt_2$	CH_3CN	0
8	PIFA	$BF_3{\cdot}OEt_2$	CH_2Cl_2	60[d]

[a] Unless otherwise specified, all the reactions were carried out using 0.2 mmol of **1a**, 0.4 mmol of **2a**, 0.3 mmol of oxidant and 0.3 mmol of additive in 1 mL solvent at room temperature for 24 h.
[b] Isolated yield after column chromatography.
[c] 0.2 mmol of **2a** was employed.
[d] The reaction was carried out at 35 °C for 10 h.

Table 2
Oxidative cross-coupling of *N*-acetylindoles with anisoles using PIFA[a]

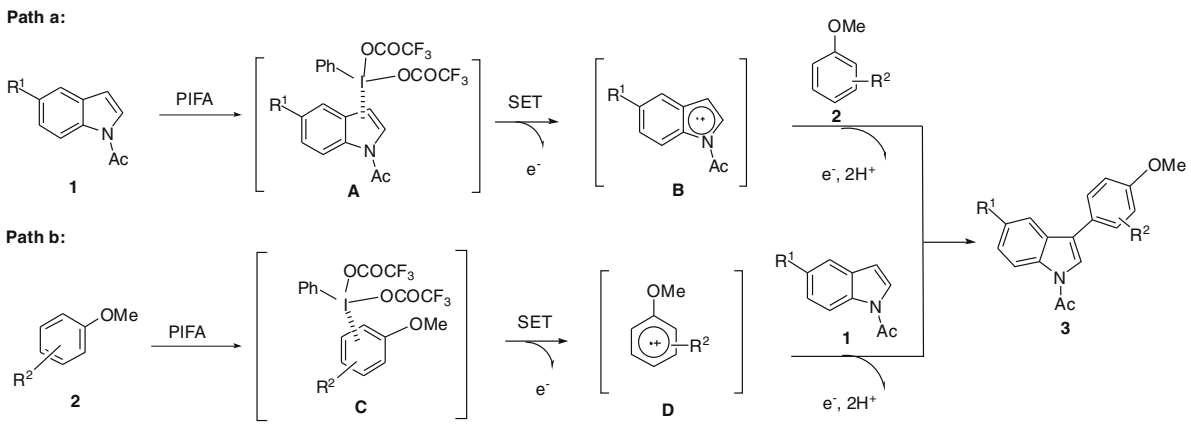


Entry	Indole		Anisole		Product	
	1	R^1	2	R^2	3	Yield[b] (%)
1	**1a**	H	**2a**	H	**3a**	60
2	**1b**	NO_2	**2a**	H	**3b**	85
3	**1c**	CO_2CH_3	**2a**	H	**3c**	75
4	**1d**	OCH_3	**2a**	H	**3d**	35
5	**1e**	Br	**2a**	H	**3e**	67
6	**1a**	H	**2b**	2-Me	**3f**	53
7	**1a**	H	**2c**	3-Me	**3g**	72
8	**1a**	H	**2d**	3-*t*-Bu	**3h**	61
9	**1a**	H	**2e**	2-OMe	**3i**	76
10	**1a**	H	**2f**	3-OMe	**3j**	80
11	**1a**	H	**2g**	2-CO_2Me		0
12	**1a**	H	**2h**	2-Br	**3k**	25
13	**1a**	H	**2i**	2-I	**3l**	23

[a] Reactions were carried out using 0.2 mmol of **1**, 0.4 mmol of **2**, 0.3 mmol of PIFA and 0.3 mmol of $BF_3{\cdot}OEt_2$ in 1 mL of CH_2Cl_2 at 35 °C for 10 h.
[b] Isolated yield after column chromatography.

indole substituents. The electron-withdrawing substituents on the indole facilitate the reaction. For example, when a strong electron-withdrawing group, such as nitro or ester, was introduced to 5-position of *N*-acetylindole, the reaction provided the corresponding products **3b** and **3c** in 85% and 75% yields, respectively (entries 2 and 3). However, when an electron-donating group, such as methoxy, was introduced to the 5-position of *N*-acetylindole, the reaction was much less efficient and the coupling product **3d** was obtained in a lower yield with some unidentified polar byproducts (entry 4). Importantly, this reaction tolerates halogen substituents which serve as valuable synthetic handles for further manipulation of the product. The coupling reaction of *N*-acetyl-5-bromoindole (**1e**) with **2a** proceeded well to give the product **3e** in 67% yield (entry 5). Next, we examined the substitution effect on the anisoles. The reaction of 2-methylanisole (**2b**) with *N*-acetylindole (**1a**) provided the product **3f** in 53% yield (entry 6). Comparably, when the methyl group was introduced to the *meta*-position of anisole, the reaction gave the product **3g** in 72% yield (entry 7). Furthermore, when the bulky *t*-butyl group was substituted at the *meta*-position of anisole, the reaction provided the corresponding product **3h** in a slight lower yield, probably due to steric hindrance (entry 8). On the contrary, electron-donating groups on the anisoles favored this transformation. The reactions of 2-methoxyanisole (**2e**) and 3-methoxyanisole (**2f**) with *N*-acetylindole (**1a**) afforded the products **3i** and **3j** in 76% and 80% yields, respectively (entries 9 and 10). However, when an electron-withdrawing group, such as ester, was introduced to the *ortho*-position of anisole, the reaction failed to occur at room temperature or elevated temperature (60–70 °C) (entry 11).[15] This could be attributed to the fact that the electron-withdrawing group significantly lowers the nucleophilicity of anisole. Finally, when bromine and iodine were substituted at the *ortho*-position of anisole, the reactions gave the coupling products **3k** and **3l** in moderate yields. Notably, these products are generally difficult to prepare with Pd-catalyzed cross-coupling reactions due to the incompatibility of C–Br and C–I bonds with the metal catalysts.

A possible mechanism of PIFA-induced C-3 arylation of *N*-acetylindoles is proposed in Scheme 1. The mechanism of this reaction proceeds through a radical cation intermediate generated by single electron transfer (SET) process, similar to that previously postulated



Scheme 1. Proposed mechanism for oxidative cross-coupling of *N*-acetylindoles with anisoles induced by PIFA.

for the oxidative cross-coupling of two arenes by PIFA.[13b] First, PIFA coordinates with *N*-acetylindoles to form complex A, followed by SET to generate radical cation intermediate B (Path a). Trapping the intermediate B by anisoles followed by one electron transfer and deprotonation leads to the coupling product **3**. Another possible way is that PIFA coordinates with anisole to form complex C firstly to generate radical cation intermediate D, which is attacked by *N*-acetylindoles to provide the coupling product **3** (Path b).

In conclusion, we have developed a novel method for the direct oxidative cross-coupling of *N*-acetylindoles with anisoles to provide C-3 arylindoles using PIFA as an oxidant. The attractive features of these reactions are a metal-free procedure, high regioselectivity and mild conditions. Further work on hypervalent iodine-mediated cross-coupling reactions of other heterocyclic compounds with arenes is underway in our laboratory.

Acknowledgements

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14. Lewis acid $BF_3{\cdot}OEt_2$ usually improved the PIFA-mediated oxidative coupling reaction. It is believed that trifluoroacetoxy ligand of PIFA might coordinate to $BF_3{\cdot}OEt_2$ and generate a reactive cationic iodine(III) intermediate. See Ref. 13b and references cited therein.
15. Most of starting 2-methoxycarbonylanisole (**2g**) was recovered and *N*-acetylindole (**1a**) was slowly decomposed during the extended reaction times or at the elevated temperatures.