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Synthesis of 3-Acylindoles by Palladium-Catalyzed Acylation of Free (N–H) Indoles with Nitriles

Tao-Shan Jiang and Guan-Wu Wang*

CAS Key Laboratory of Soft Matter Chemistry, Hefei National Laboratory for Physical Sciences at Microscale, and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China

gwang@ustc.edu.cn

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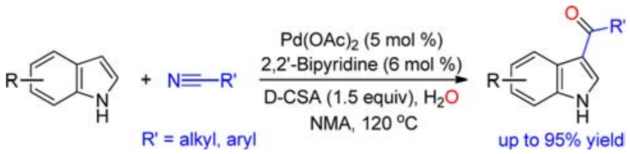
ABSTRACT



An efficient palladium-catalyzed synthesis of 3-acylindoles using free (N–H) indoles and nitriles has been developed. The acylation reaction proceeded well under the Pd(OAc)$_2$/2,2′-bipyridine system and with D-(+)-camphorsulfonic acid as the additive. A possible mechanism involving carbopalladation of nitriles and subsequent hydrolysis of ketimines is proposed.

Since indoles exist abundantly in many biologically active natural products and pharmaceutical compounds,[1] their synthesis and further functionalization are of considerable importance.[2,3] Among many efforts, 3-acylation of indoles attracts much interest due to their versatile synthetic values and core structures in many biologically active indole derivatives, such as alkaloids, inhibitors of HIV-1 integrase, and anticancer and antidiabetic compounds.[4] To date, the well-known synthetic procedures of 3-acylindoles mainly include Friedel–Crafts acylations (Scheme 1, **a**),[5] Vilsmeier–Haack type reactions,[6] and indole Grignard reactions.[7] Other methods involve nitrilium salts with dialkyl carbenium ions[8] and pyridinium salts.[9] As an indole is multiatom and highly nucleophilic in nature, the most frequently used Friedel–Crafts acylation requires troublesome *N*-protection, especially for indoles bearing an electron-donating group with a stoichiometric Lewis acid promoter and strict exclusion of moisture.[5] The existing methods often involve uncommonly used acylated reagents or unbenign reaction conditions.[6–9] Therefore, a novel and operationally simple acylation reaction of indoles is highly desired. Recently, Su and co-workers reported a convenient and general method for formylation and acylation of free (N–H) indoles via Ru- or Fe-catalyzed oxidative coupling using anilines as the carbonyl source (Scheme 1, **b**).[10]

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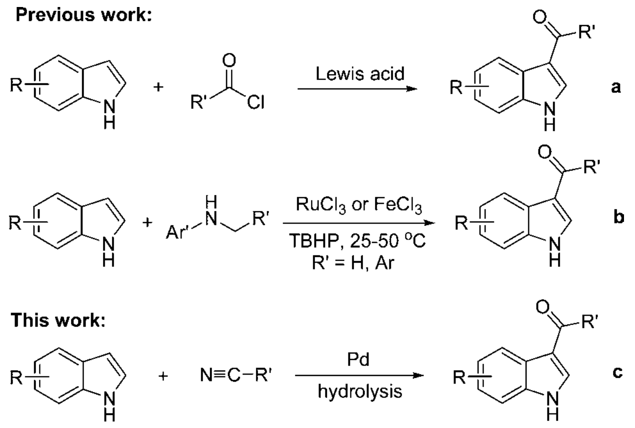
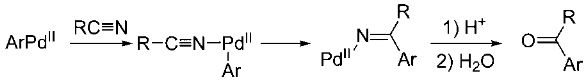
10.1021/ol303440y

Scheme 1. Synthesis of 3-Acylindoles



In the 1970s, transition-metal-catalyzed synthesis of aryl ketones through the carbopalladation of nitriles and subsequent hydrolysis of ketimine intermediates was first reported.[11] In recent years, this methodology has attracted much attention from the Larock group,[12] the Lu group,[13] and others.[14] In these reactions, the *in situ* formed transition metal complex reacts with a nitrile through carbometalation to give a nitrile addition product. Protonation of the addition product affords a ketimine, and subsequent hydrolysis under acidic conditions provides an aryl ketone (Scheme 2).

Scheme 2. General Process for the Reaction of Palladium Complex with Nitrile



ligand is omitted for clarity

Our group recently developed an efficient protocol for the Pd(II)-catalyzed desulfitative addition reaction of arylsulfinic acids with nitriles to afford a variety of aryl ketones.[15] The acylation of free (N−H) indoles is more challenging than that of *N*-substituted indoles. As a continuous work, we envisioned that the acylation of free (N−H) indoles with nitriles catalyzed by a Pd(II) species may lead to 3-acylindoles (Scheme 1, **c**).[16]

To prove our working hypothesis, we first performed the reaction of indole **1a** (23.4 mg, 0.2 mmol) with 4-methylbenzonitrile **2a** (2 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), 2,2′-bipyridine (12 mol %), and H_2O (2 equiv) in 1 mL of the chosen solvent. To our delight, when HOAc and DMA were used as the solvent, the desired product **3aa** was obtained in 20% and 23% yields, respectively (Table 1, entries 1 and 2). Although the reaction in entry 1 gave a poor yield, **2a** was completely consumed due to the hydrolysis of nitrile itself. In entry 2, large amounts of **1a** and **2a** remained. Then various acids were screened as the additive to examine their effect on the reaction. Gratifyingly, the yield was improved to 51% (Table 1, entry 3) when 2 equiv of $MeSO_3H$ was employed. Other acids including pivalic acid and TFA were not beneficial to the catalytic system (Table 1, entries 4 and 5). The yield was slightly increased to 56% when the volume of the solvent was decreased from 1.0 to 0.5 mL (Table 1, entry 6). Further optimizations (Table 1, entries 7−10) allowed the use of fewer amounts of **2a** and the acid (1.5 equiv of **2a**, 1.5 equiv of $MeSO_3H$) with comparable yields (Table 1, entry 7 vs 6). The influence of solvent on the reaction efficiency was also significant; when *N*-methylacetamide (NMA) was chosen as the solvent, the yield was enhanced to 68% (Table 1, entry 11). Furthermore, replacing the additive $MeSO_3H$ with D-(+)-camphorsulfonic acid (D-CSA) provided the desired product in 74% yield (Table 1, entry 12). Much to our pleasure, the reaction at a larger scale with less catalyst and additive loading by using 0.4 mmol of **1a**, 0.6 mmol of **2a**, 5 mol % of $Pd(OAc)_2$, 6 mol % of 2,2′-bipyridine, and 2 equiv of H_2O at 120 °C in 1.0 mL of solvent for 36 h furnished **3aa** in 75% yield, slightly higher than that at the 0.2 mmol scale (Table 1, entry 13 vs 12). The reaction did not occur in the absence of a palladium catalyst (Table 1, entry 14).

With the optimized reaction conditions in hand (Table 1, entry 13), the substrate scope and limitation for the Pd-catalyzed reaction of indoles with nitriles was explored and is summarized in Scheme 3. Both electron-withdrawing and -donating substitutents on the phenyl rings of nitriles and indoles were suitable for the reaction, giving 3-acylindoles in good to excellent yields. For aryl nitriles, the electron-withdrawing groups on the aromatic ring were generally preferable to the electron-donating groups (**3af−ai** vs **3aa−ae**). However, the *ortho* substituted nitrile did not give the desired product due to the steric hindrance effect (**3ac**). Notably, the C−Br bond remained intact during the reaction and product **3ag** was obtained in excellent yield (91%), providing an attractive and useful handle to introduce new groups for further modification of indole products. 4-Cyanopyridine was also tolerant and afforded product **3aj** in moderate yield (61%) under a higher catalyst loading and prolonged reaction time. We then selected various substituted indoles to react with

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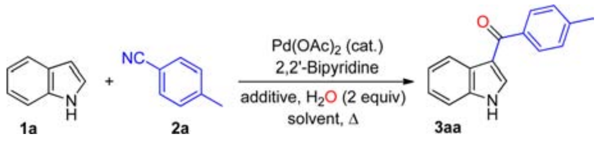
Table 1. Optimization of Reaction Conditions[a]



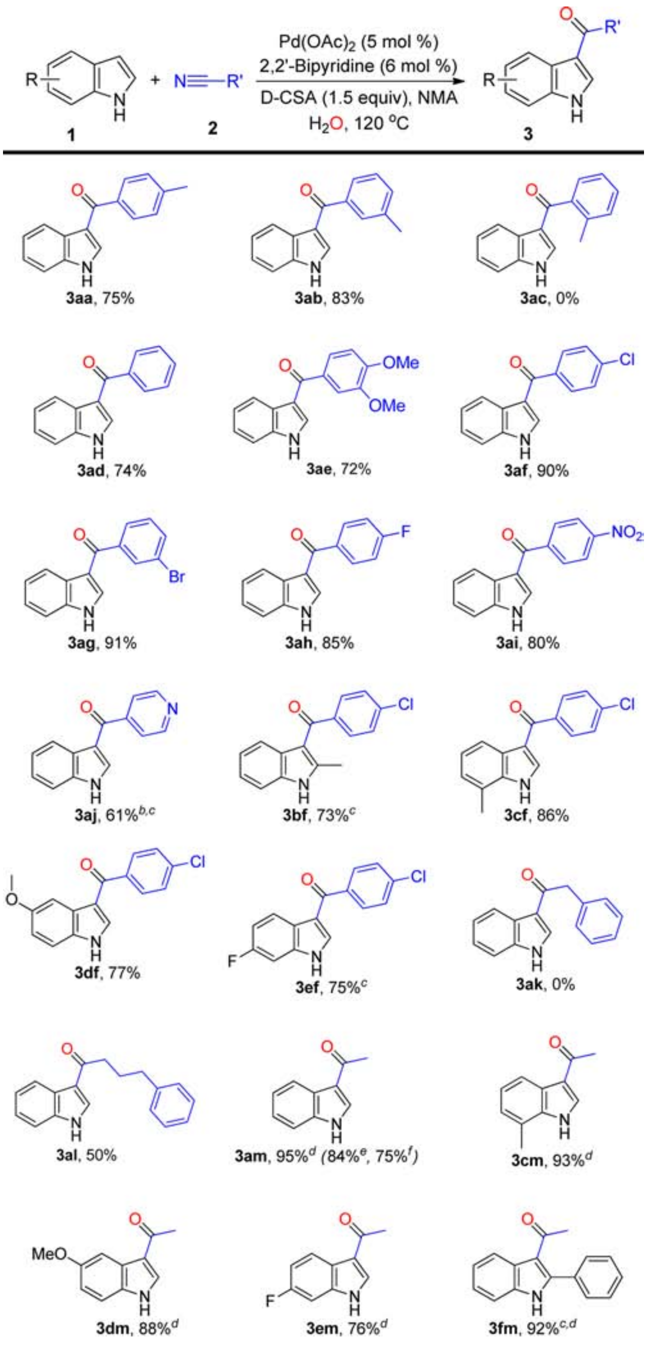
entry	2a (equiv)	additive (equiv)	solvent (mL)	temp (°C)	yield (%)
1	2	none	HOAc (1)	120	20
2	2	none	DMA (1)	120	23
3	2	MsOH (2)	DMA (1)	120	51
4	2	PivOH (2)	DMA (1)	120	27
5	2	TFA (2)	DMA (1)	120	trace
6	2	MsOH (2)	DMA (0.5)	120	56
7	1.5	MsOH (1.5)	DMA (0.5)	120	55
8	1.2	MsOH (1.5)	DMA (0.5)	120	50
9	1.5	MsOH (1.2)	DMA (0.5)	120	48
10	1.5	MsOH (1.5)	DMA (0.5)	100	33
11	1.5	MsOH (1.5)	NMA (0.5)	120	68
12	1.5	D-CSA (1.5)	NMA (0.5)	120	74
13[b]	1.5	D-CSA (1.5)	NMA (1.0)	120	75
14[c]	1.5	D-CSA (1.5)	NMA (0.5)	120	nr

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.2 mmol), Pd(OAc)$_2$ (10 mol %), 2,2′-bipyridine (12 mol %), and H$_2$O (0.4 mmol) for 24 h. [b] Reaction conditions: 0.4 mmol scale, 5 mol % of Pd(OAc)$_2$, 6 mol % of 2,2′-bipyridine, and 2 equiv of H$_2$O in 1.0 mL of solvent for 36 h. [c] The reaction was carried out without Pd(OAc)$_2$. D-CSA: D-(+)-camphorsulfonic acid. DMA: *N*,*N*-dimethylacetamide. NMA: *N*-methylacetamide.

4-chlorobenzonitrile; the corresponding products **3bf**–**ef** were obtained in 73–86% yields. For the reactions with 2-methylindole and 6-fluoroindole, a longer reaction time was required to give satisfactory yields of **3bf** and **3ef**. We finally examined the reaction of indoles with alkyl nitriles. Phenylacetonitrile is known to smoothly react with other types of substrates.[12,14a,14c,14e,14f,15] Nevertheless, no desired product (**3ak**) was detected in our catalytic system. Interestingly, when 4-phenylbutanenitrile was used, product **3al** could be generated in 50% yield. To our pleasure, replacing the nitriles with 1 mL of acetonitrile allowed the reaction to proceed very well and provided 3-acylindoles **3am**–**em** in 76–95% yields under our optimized conditions. The yields for indoles bearing electron-rich groups were higher than those with electron-deficient groups. Even the sterically hindered 2-phenyl-1*H*-indole could undergo acylation well, and **3fm** was obtained in 92% yield. When cyanoacetic acid or ethyl cyanoacetate was used, the same product **3am** was formed via a decarboxylative process.

Based on the previous literature[14c,f,g,15] and particularly the electrospray ionization mass spectrometry (ESI/MS) study[14c,f] on similar reactions, a plausible mechanism to rationalize the acylation reaction is shown in Scheme 4. In the presence of a strong Brønsted acid, the free (N–H) indoles can easily form the iminium salt by protonation of the carbon–carbon double bond.[17] Then the reaction pathway involves the following key steps: (1) palladation at C3 of an indole with [(bpy)Pd(OAc)$_2$] **A** gives an active

Scheme 3. Palladium-Catalyzed Acylation of Indoles with Nitriles[a]



[a] Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol) and Pd(OAc)$_2$ (5 mol %), 2,2′-bipyridine (6 mol %), D-CSA (0.6 mmol), H$_2$O (0.8 mmol) in NMA (1.0 mL) at 120 °C for 36 h. [b] Pd(OAc)$_2$ (10 mol %), 2,2′-bipyridine (12 mol %). [c] The reaction time was 48 h. [d] 1 mL of CH_3CN was used. [e] 5.0 equiv of 2-cyanoacetic acid was used. [f] 5.0 equiv of ethyl 2-cyanoacetate was used.

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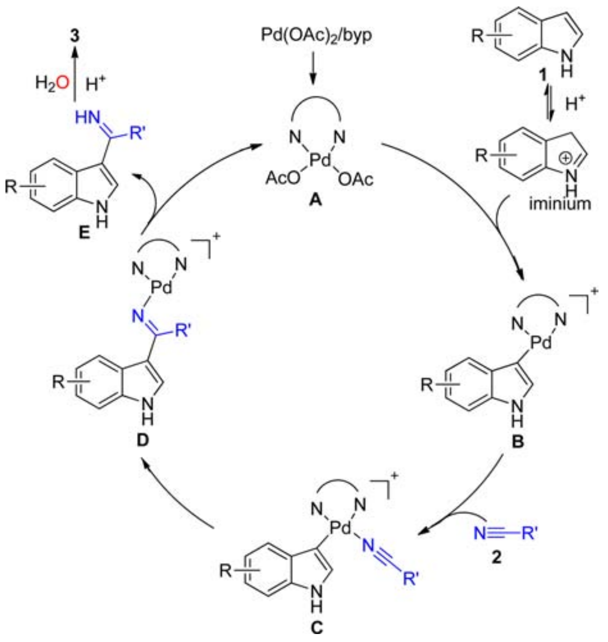
Scheme 4. Possible Reaction Mechanism for the Formation of 3-Acylindoles



cationic palladium complex **B**; (2) coordination of the nitrile generates intermediate **C**; (3) carbopalladation of the nitrile forms ketimine complex **D**; (4) protonation of the complex **D** to afford the free ketimine **E** and subsequent hydrolysis lead to 3-acylindole. In this catalytic system, the strong Brønsted acid D-CSA plays important roles: it may activate indole to form the iminium salt as well as promote the formation of cationic palladium complex **B** and the hydrolysis of ketimine **E**.

In conclusion, we have successfully developed an efficient strategy for the palladium(II)-catalyzed addition reaction of free (N–H) indoles with nitriles to afford a variety of 3-acylindoles in good to excellent yields. In the present protocol, the challenging acylation of free (N–H) indoles is accomplished in the presence of D-(+)-camphorsulfonic acid and 2,2′-bipyridine, broadening the scope of indole reactions.

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Supporting Information Available. Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.