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Palladium-catalyzed oxidative C–H bond coupling of indoles and benzaldehydes: a new approach to the synthesis of 3-benzoylindoles

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ABSTRACT

A palladium-catalyzed dehydrogenative acylation of indoles using easily accessible aldehydes as the acyl source is described. This reaction provides a new approach for the synthesis of 3-acylindoles.

1. Introduction

Indole derivatives exhibit a broad range of useful pharmacological effects, including antibiotic, anti-inflammatory, antihypertensive, and antitumor activities.[1]

3-Acylindoles have been found to exhibit various pharmaceutical activities like anticancer and antidiabetic effects and inhibition of HIV-1 integrase and antinociceptive (Fig. 1). In 1991, it was reported that an indole derivative, **1**, unexpectedly inhibited contractions of the electrically stimulated mouse vas deferens.[2] Later work revealed that **1**, and a number of related compounds are antinociceptive and interact with the cannabinoid CB1 receptor and exhibit typical cannabinoid pharmacology in vivo.[3] Aminoalkylindole **2** is not only potent in vivo, but has high affinity for both the cannabinoid CB1 and CB2 receptors. Since then various indole derivatives with similar structural skeleton have been synthesized and their pharmacological activities have been investigated. For example compound **3** was identified as a potent inhibitor of tubulin polymerization and also as a cytotoxic agent against B16 melanoma cells.[4]

Due to the need for efficient ways to synthesize more elaborate structures possessing biological activity, the development of novel and convenient methods for the preparation of indole derivatives, among, which 3-acylindoles with valuable pharmaceutical activities, is of considerable importance in organic chemistry.

Numerous synthetic methodologies for the construction of 3-acylindoles have been developed in the past decades.[5] The Friedel–Crafts reaction is the classic method for the preparation of 3-acylindoles and most of the other reported methods are also based on the use of acid chlorides and modification of this process.[6] Therefore, development of new methods using alternant acylating agents is of considerable importance.

Classical methods have several drawbacks, notably Manich-type indole oligomerization in the presence of Lewis acids and generation of side products caused by addition of indole to 3-acylindole. Toxicity, commercial nonavailability and handling difficulty of the reagents are some of the other disadvantages.

Direct C–H functionalization has emerged over the past few years as an attractive strategy, from both scientific and environmental points of view to install many different types of bonds, including carbon–oxygen, carbon–halogen, carbon–nitrogen, carbon–sulfur and carbon–carbon linkages.[7]

In recent years, building a carbon–carbon linkage directly from two simple carbon–hydrogen (C–H) bonds has emerged as an

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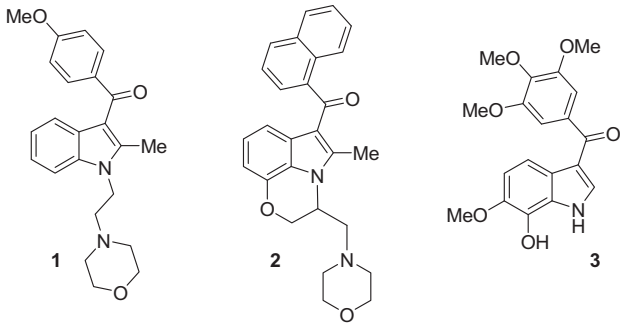


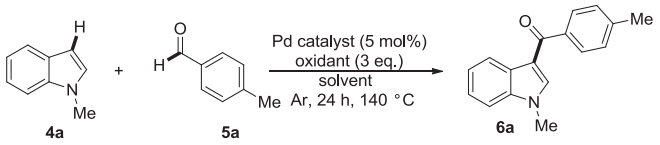
Fig. 1. Some bioactive compounds with a benzoylindole core structure.

attractive and challenging goal in catalysis.[8] This reaction is more atom economical and environmentally friendly than other cross-coupling reactions, and can be considered as a complementary strategy to the existing direct C–H bonds activations. Considerable advances in this field have recently been achieved.

2. Results and discussion

With an interest to develop catalytic C–H bond cross-coupling reactions, here we describe a versatile 3-acylindole synthesis by Pd catalyzed cross-coupling of indoles with aldehydes. *N*-methylindole (**4a**) and 4-methylbenzaldehyde (**5a**) were used as the substrates in the model reaction. In the initial trial, we were delighted that the desired product **6a** was obtained in 55% yield in the presence of oxidant TBHP (Table 1, entry 7).

Table 1
Optimization of the reaction conditions.[a]



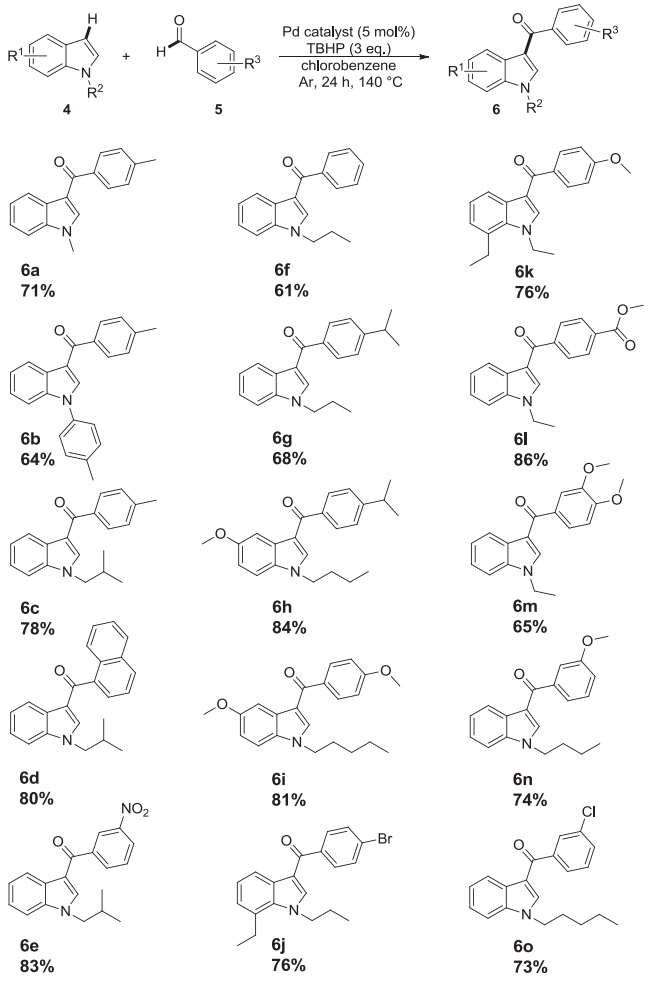
Entry	Pd catalyst	Oxidant	Solvent[a]	Yield (%)
1	$Pd(OAc)_2$	TBHP	NMP	0
2	$Pd(OAc)_2$	TBHP	CH_3CN	0
3	$Pd(OAc)_2$	TBHP	DMSO	0
4	$Pd(OAc)_2$	TBHP	DMF	0
5	$Pd(OAc)_2$	TBHP	DMAc	Trace
6	$Pd(OAc)_2$	TBHP	DCE	8
7	$Pd(OAc)_2$	TBHP	Toluene	55
8	$Pd(OAc)_2$	TBHP	DME	58
9	$Pd(OAc)_2$	TBHP	Diglyme	60
10	$Pd(OAc)_2$	TBHP	Neat	64
11	$Pd(OAc)_2$	TBHP	*tert*-Amyl alcohol	61
12	$Pd(OAc)_2$	TBHP	1,4-Dioxane	67
13	**$Pd(OAc)_2$**	**TBHP**	**PhCl**	**78**
14	$Pd(OAc)_2$	DTBP	PhCl	0
15	$Pd(OAc)_2$	$(PhCOO)_2$	PhCl	17
16	$Pd(OAc)_2$	$PhC(CH_3)_2OOH$	PhCl	34
17	$PdCl_2$	TBHP	PhCl	22
18	$Pd(COD)Cl_2$	TBHP	PhCl	31
19	$Pd(PPh_3)_2Cl_2$	TBHP	PhCl	36
20[b]	$Pd(OAc)_2$	TBHP	PhCl	0
21[c]	$Pd(OAc)_2$	TBHP	PhCl	59
22[d]	$Pd(OAc)_2$	TBHP	PhCl	38

[a] NMP: *N*-methyl-2-pyrrolidinone; DMSO: dimethylsulfoxide; DMF: *N*,*N*-dimethylformamide; DMAc: *N*,*N*-dimethylacetamide; DCE: 1,1-dichloroethane; DME: 1,2-dimethoxyethane; COD: cyclooctadiene.
[b] The reaction was performed at 25 °C.
[c] The reaction was performed at 120 °C.
[d] The reaction was performed under air.

Different organic solvents were screened. Chlorobenzene gave the best yield while solvents, such as 1,4-dioxane, *tert*-amyl alcohol, diglyme and DME afforded moderate yields of the product and DCE, DMAc, DMF, DMSO, NMP, and CH_3CN afforded poor results (Table 1, entries 1–13). The effectiveness of the oxidant was also examined. TBHP was the most suitable oxidant in this reaction. Other peroxides such as DTBP (di-*tert*-butylperoxide), $(PhCOO)_2$ and $PhC(CH_3)_2OOH$ were less effective (Table 1, entries 14–16), and no desired product was observed when oxygen was used as the sole oxidant. The optimal TBHP added to the reaction was 3 equiv. A screening of catalysts showed that $Pd(OAc)_2$ gave the best results while $PdCl_2$, $Pd(COD)Cl_2$ and $Pd(PPh_3)_2Cl_2$ were found to be inferior (Table 1, entries 17–19). The best activity was shown at 140 °C and the reaction provided a lower conversion at lower temperature (Table 1, entries 20 and 21).

With the optimized reaction conditions in hand, we next tested the scope of the reaction (Scheme 1). Aldehydes with electron withdrawing groups and 1-naphthylaldehyde gave good yields of the corresponding products. The presence of bromine on the benzene ring did not change the reaction pathway, and moderate yields of the product were obtained using this moderately electron poor aldehyde. Aldehydes with electron-donating groups gave a slightly lower yield of the product presumably due to the difficult C–H bond cleavage of aldehyde.

Although the reaction mechanism is not clear at this stage, but on the basis of the previous chemistry,[9] it is believed that this



Scheme 1. Scope of direct 3-acylation indoles with aldehydes. Indole derivatives (1 mmol), aldehyde derivatives (3 mmol), TBHP 70% aq (3 mmol), $Pd(OAc)_2$ (5 mol %) in chlorobenzene at 140 °C for 24 h.