RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2017, **7**, 32559

Direct C-2 acylation of indoles with toluene derivatives *via* Pd(II)-catalyzed C–H activation†

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Received 29th May 2017
Accepted 16th June 2017

DOI: 10.1039/c7ra06004a

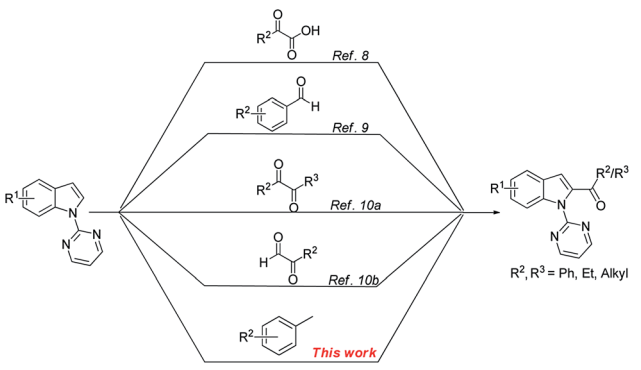
rsc.li/rsc-advances

A simple and efficient Pd-catalyzed method for the C2-acylation of indoles is described. Less toxic, stable, and commercially available toluene derivatives were used as acyl sources, with *tert*-butylhydroperoxide (TBHP) as oxidant and pivalic acid as additive, providing moderate to good yields.

Introduction

Acylated indoles are important structural motifs present in a number of biologically active natural products and serve as valuable intermediates in the synthesis of various dyes and pharmaceuticals.[1] Thus, the efficient construction of functionalized acyl indole analogues has been the focus of intense research efforts of synthetic chemists. With the advent of transition metal-catalyzed C–H bond functionalization,[2] this methodology has become the most straightforward one leading to functionalized indoles.[3] However, the regioselective C-2 functionalization of the indole nucleus in the presence of the electron rich C-3 position, still remains a challenging proposition for organic chemists.[4] To override this inherent selectivity, the introduction of a suitable *N*-protecting group would change the regioselectivity from C-3 to the more electrophilic C-2 position of the indole nucleus.[5] Towards this end, considerable progress has been achieved in recent years *via* metal-catalyzed oxidative cross-couplings (Scheme 1). These processes allow the use of less functionalized starting materials in a minimum number of operational steps.[6] In 2012, Li and co-workers developed a Rh-catalyzed oxidative direct C2-acylation of indoles with alkyl and aryl aldehydes through Csp^2–H activation.[7] Following this work, the group of Zhu disclosed a palladium-catalyzed decarboxylative C2-acylation of indoles with α-oxocarboxylic acids.[8] Subsequently, Liang and co-workers described a palladium-catalyzed C2-acylation of indoles with aryl and alkyl aldehydes *via* C–H functionalization.[9] Very recently, a palladium-catalyzed C2-acylation of *N*-pyrimidyl indoles with α-diketones[10a] and ethyl glyoxylate[10b] was reported. Despite the significant progress made in the area of C2-acylation of indoles, there are no reports on the formation of a C–C bond directly from the more challenging and inert Csp^3–H bond.[11,12] In continuation of our efforts to develop facile methods for the C–H functionalization *via* radical addition,[13] we were interested to use substrates without prefunctionalization for the creation of a new Csp^2–Csp^3 bond between the indole ring and an unactivated methyl substituent. Considering that readily available toluene derivatives are easy to handle, inexpensive, quite stable, with low toxicity,[11] and could be used as ideal *in situ* generated acylating reagents, we sought to develop a complementary method for the preparation of 2-acylindoles (Scheme 1).

We began to investigate the feasibility for oxidative cross-coupling between *N*-pyrimidyl indole and toluene by the identification of suitable reaction conditions. To this end, the model reaction between 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) with toluene (**2a**) was systematically examined (Table 1). As the use of a transition-metal catalyst is generally needed both for activating the alkyl C–H bond and for the subsequent coupling to form the C–C bond, we screened various Pd-catalysts with *tert*-butyl hydroperoxide (TBHP) as oxidant in toluene (entries 1–4).



Scheme 1 Previous reports towards C-2 acylation of *N*-pyrimidyl indoles.

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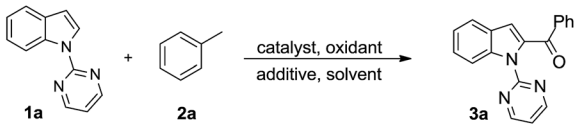
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra06004a

Table 1 Optimization of reaction conditions[a]



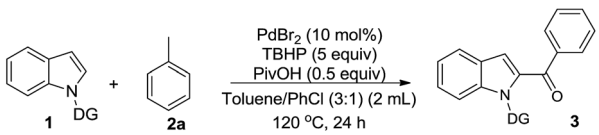
Entry	Catalyst	Oxidant	Solvent	Additive	Yield[b] (%)
1	$Pd(OAc)_2$	TBHP	Toluene	—	7
2	$PdCl_2$	TBHP	Toluene	—	33
3	$PdCl_2(PPh_3)_2$	TBHP	Toluene	—	33
4	$PdBr_2$	TBHP	Toluene	—	45
5	$PdBr_2$	DCP	Toluene	—	27
6	$PdBr_2$	DTBP	Toluene	—	39
7	$PdBr_2$	TBPB	Toluene	—	Trace
8	$PdBr_2$	TBHP	Toluene/EtOAc (1 : 1)	—	32
9	$PdBr_2$	TBHP	Toluene/DCE (1 : 1)	—	17
10	$PdBr_2$	TBHP	Toluene/PhCl (1 : 1)	—	47
11	$PdBr_2$	TBHP	Toluene/PhCl (2 : 1)	—	46
12	$PdBr_2$	TBHP	Toluene/PhCl (3 : 1)	—	50
13[c]	$PdBr_2$	TBHP	Toluene/PhCl (3 : 1)	—	57 (50)
14[d]	$PdBr_2$	TBHP	Toluene/PhCl (3 : 1)	—	51
15[c,e]	**$PdBr_2$**	**TBHP**	**Toluene/PhCl (3 : 1)**	**PivOH**	— (73)
16[c,e]	$PdBr_2$	TBHP	Toluene/PhCl (3 : 1)	CF_3COOH	nd
17[c,f]	$PdBr_2$	TBHP	Toluene/PhCl (3 : 1)	PivOH	70 (63)

[a] Reaction conditions: **1a** (0.1 mmol), oxidant (3 equiv., 0.3 mmol), catalyst (10 mol%), solvent (1 mL), sealed tube, 120 °C, 24 h. [b] NMR yields (isolated yields in parentheses). [c] TBHP 5 equiv. [d] TBHP 10 equiv. [e] Additive 0.5 equiv. [f] Additive 1 equiv. TBHP = *tert*-butyl hydroperoxide, DCP = dicumyl peroxide, DTBP = di-*tert*-butyl peroxide, TBPB = *tert*-butyl peroxybenzoate, PivOH = pivalic acid. nd = not detected.

The results revealed the superior catalytic activity of Pd catalysts having halide ions with $PdBr_2$ providing a better yield (entry 4). Subsequently, we investigated the effect of various oxidants on this transformation and found that TBHP was the most suitable oxidant (45% yield), with other oxidants affording poorer reactivities (entries 5–7 *vs.* 4, also see ESI Table S1†). The above-obtained positive results encouraged us to explore co-solvents with toluene for achieving satisfying yields (entries 8–12). Using chlorobenzene as a co-solvent with toluene in a 3 : 1 ratio (v/v) led to a slightly higher yield (entry 12). Increasing the stoichiometry of TBHP to 5 equiv. resulted in higher yield (57%) of the desired product (entry 13). However a further increase led to a decrease in yield (entry 14). A significant influence of the additive on reaction was observed as the use of 0.5 equiv. of PivOH resulted in a relatively high yield of 73% (entry 15). However, either increasing the amount of PivOH or adding another acid additive (CF_3COOH) was relatively ineffective (entries 16 and 17).

A survey of other directing groups (Table 2) established that besides the *N*-2-pyrimidyl group (**1a**, entry 1) only the *N*-2-pyridyl group (**1b**, entry 2) is effective, albeit to a lower extent. The other reported directing groups for C-2 functionalization of indoles failed to yield any product under the optimized conditions (entries 3–6). Under the optimized reaction conditions (Table 1, entry 15), the substrate scope of this synthetic methodology was examined. As summarized in Table 3, a number of toluene derivatives were employed as acylation reagents to react with *N*-pyrimidyl indole (**1a**) to generate the desired acylation products (**3a–o**).

Table 2 Optimization of directing group



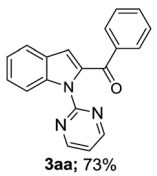
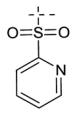
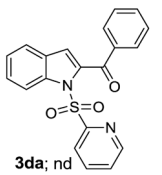
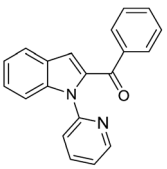
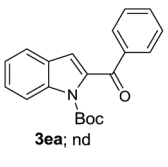
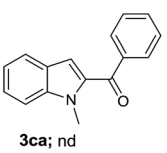
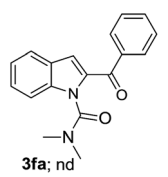
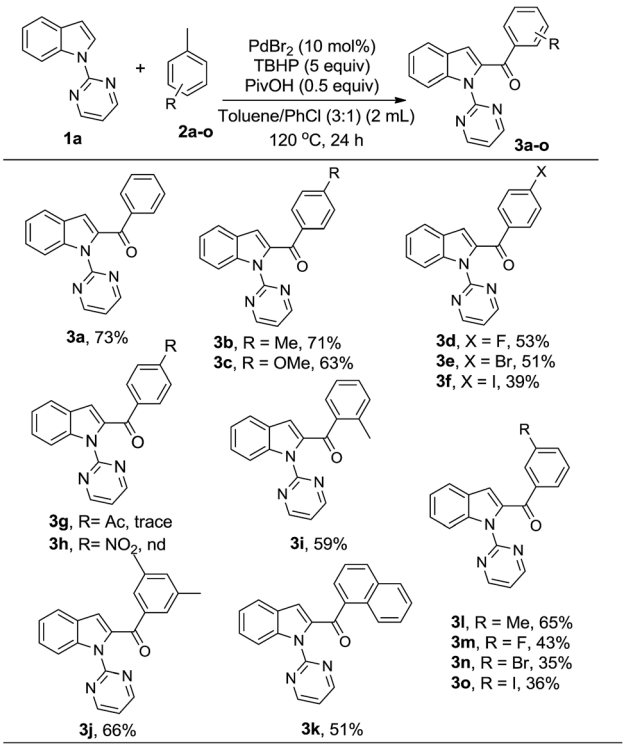
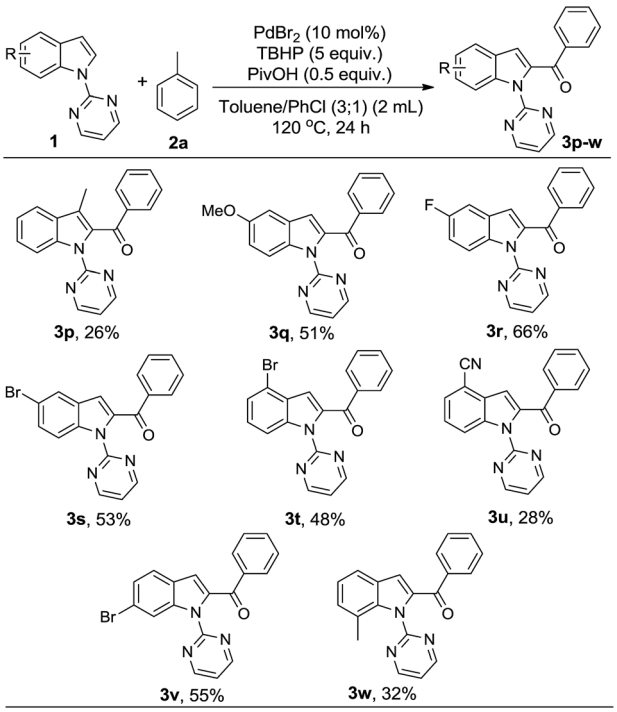
Entry	DG	Product	Entry	DG	Product
1		 **3aa**; 73%	4		 **3da**; nd
2		 **3ba**; 66%	5		 **3ea**; nd
3		 **3ca**; nd	6		 **3fa**; nd

Table 3 Scope of toluene derivatives[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), toluene derivatives (1.5 mL), TBHP (5 equiv.), $PdBr_2$ (10 mol%), PhCl (0.5 mL), PivOH (0.5 equiv.), sealed tube, 120 °C, 24 h. [b] Isolated yield. nd = not detected.

Table 4 Scope of indoles[a,b]



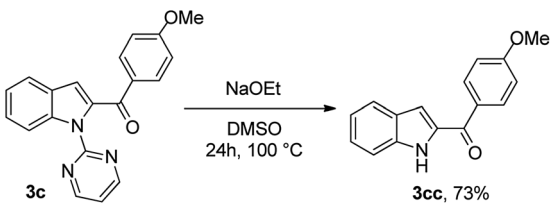
[a] Reaction conditions: **1** (0.2 mmol), toluene (1.5 mL), TBHP (5 equiv.), $PdBr_2$ (10 mol%), PhCl (0.5 mL), PivOH (0.5 equiv.), sealed tube, 120 °C, 24 h. [b] Isolated yield.

In general, reaction of **1a** with toluene derivatives bearing electron-donating groups (such as CH_3, OCH_3) or weakly electron-withdrawing groups (such as Cl, Br, I) in *para*-position gave moderate to good yields (**3b–f**). However, the reaction was completely hampered in the presence of strongly electron-withdrawing groups such as acetyl (**3g**) and nitro (**3h**). In case of *o*-xylene (**3i**) and mesitylene (**3j**), the reaction took place on only one methyl group while the others remained untouched. This could be due to the fact that after oxidation of one of the methyl groups to the carbonyl group, its electron-withdrawing property renders the subsequent oxidations unfavorable.[12a] 1-Methylnaphthalene was also found to be a suitable coupling partner for the reaction (**3k**). Furthermore, the presence of a methyl group or a halo group in the *meta*-position of the aromatic ring was well tolerated (**3l–3o**).

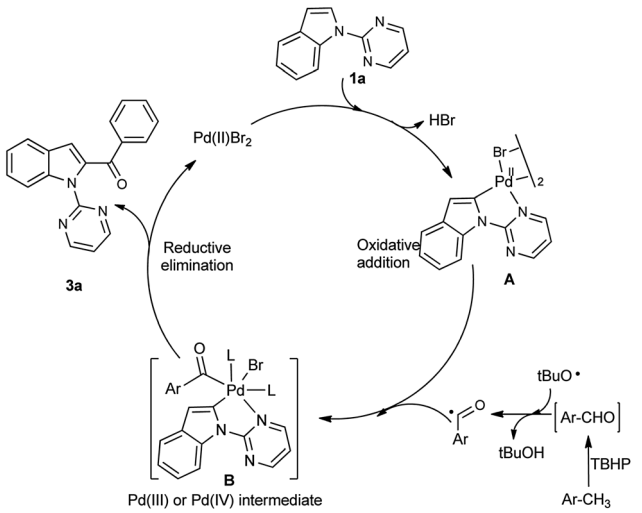
Next, the substituent effect on the indole ring was investigated using toluene as coupling partner (Table 4). The reaction worked well with a variety of functional groups at the 3-, 4-, 5-, 6- and 7-position of the indole, such as F, Br, CH_3, and CH_3O (**3p–3w**) with moderate yields. Interestingly, it was observed that indoles bearing a substitution at the 5- or 6-position provide the corresponding products with slightly higher yields (**3q–s**, **3v**) while moderate yields were observed for 4- or 7-substituted indoles (**3t**, **3w**). However, a sterically hindering 3-substitution (**3p**) or the presence of a strongly electron-withdrawing group such as cyano on the indole ring (**3u**) gave an inferior yield. No reaction was observed with benzimidazole derivatives even after prolonged reaction time.

To enhance the synthetic utility of this process, facile removal of the *N*-pyrimidyl group, was carried out in a traceless fashion using sodium ethoxide in DMSO for 24 h at 100 °C, with an overall yield of 73% **3cc** (Scheme 2).

Based on the previous research about C2-acylation of indoles with toluene as acylation reagent,[11,12] we proposed a plausible reaction mechanism as shown in Scheme 3. First, Pd(II)Br_2 reacted with the C2 position of the indole (**1a**) directed by the pyrimidin-2-yl to generate the five-membered cyclopalladated intermediate **A**. Subsequently, intermediate **A** would react with the benzoyl radical (formed *in situ* from the oxidation of toluene by TBHP), to produce the reactive Pd(IV)[14] or dimeric Pd(III)[15] species **B**. Finally, the cyclopalladated intermediate **B** underwent reductive elimination to give the desired product **3a**. Meanwhile, the Pd(II) species was regenerated for the next catalytic cycle.



Scheme 2 Traceless removal of the directing group.



Scheme 3 Plausible reaction mechanism.

Conclusions

We have developed an operationally simple and efficient Pd-catalyzed method for the synthesis of C2-acylated indoles. Low toxic, stable, and commercially available toluene derivatives were used as acyl source, with TBHP as oxidant and PivOH as additive. The reaction exhibited a satisfying functional group tolerance. The generality and operational simplicity of this method make it attractive for the alternative construction of 2-acylindoles.

Acknowledgements

YZ is grateful to the China Scholarship Council (CSC) for providing a visiting doctoral fellowship. UKS and NS are thankful to University of Leuven (KU Leuven) for a postdoctoral fellowship. FS is grateful to Flanders Innovation & Entrepreneurship (VLAIO) for providing a PhD scholarship. We acknowledge the support by COST (European Cooperation in Science and Technology) Action (CA15106) CH-Activation in Organic Synthesis. The research was financially support by The Ministry of Education and Science of the Russian Federation (the Agreement number 02.a03.0008).

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