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Dual Visible-light Photoredox and Palladium(II) Catalysis for Dehydrogenative C2-Acylation of Indoles at Room Temperature

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Manash Kumar Manna,[ab] Gurupada Bairy[ab] and Ranjan Jana*[ab]

A highly regioselective direct C2-acylation of *N*-pyrimidine protected indole with aldehydes is reported at room temperature through the merger of visible light photoredox and palladium(II) catalysis. Late-stage acylation of tryptophan, selective mono-acylation of carbazole and the syntheses of tubulin inhibitors D-64131 and D-68144 are also demonstrated.

2-Acylindoles are ubiquitously found in numerous natural products and biologically active compounds.[1] Specifically, this medicinal scaffold is present in tubulin polymerization inhibitors,[2] histone deacetylase class inhibitors,[3] peroxisome proliferator-activated receptor (PPAR) agonists,[4] cyclooxygenase-2 (COX-2) inhibitors,[5] indoleamine 2,3-dioxygenase (IDO) inhibitors[6] and platelet derived growth factor (PDGF) receptor kinase inhibitors.[7] Inherently, Friedel-Crafts type acylation of indoles occurs at C3 position.[8] Whereas, 2-acylindoles are synthesized through nucleophilic addition of 2-lithioindole,[9] cross-coupling[10] and annulation.[11] However, these methods suffer from rigorous prefunctionalization steps, harsh reaction conditions etc. Thus, development of an expedient synthetic protocol for 2-aroylindoles under mild conditions is in high demand in drug discovery.

Recently, direct acylation of arenes through the cleavage of C-H bond represents a straightforward and promising strategy to access aromatic ketones.[12] In this vein, C2-acylation of indoles using glyoxalic acid or aldehydes as acylating agents has been reported.[13] However, all reported procedures for acylation occurs at high temperature. To circumvent, a dual catalytic approach merging transition-metal and photoredox catalysis is emerging which induces the desired redox processes in mild and selective manner.[14]

Here we report, an expedient synthesis of 2-acylindoles from readily available and inexpensive aldehydes through dehydrogenetive pathway at room temperature through the merger of visible light photoredox and palladium(II) catalysis.[15] We have also accomplished late-stage acylation of protected tryptophan and the synthesis of tubulin inhibitors D-64131 and D-68144 applying this protocol.

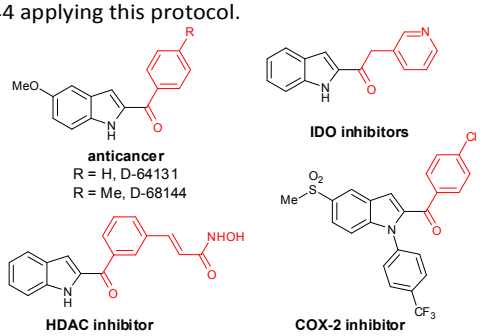

Figure 1. Representative Biologically Active 2-Aroylindoles

To develop this mild reaction condition for the C2-acylation of indole, we selected *N*-pyrimidine protected indole and *p*-tolualdehyde as acylating agent for the initial screening. We isolated the desired 2-acylindole (**2a**) in 52% yield in presence of $Pd(OAc)_2$ (10 mol %), $Ru(bpy)_3Cl_2$ (2.5 mol %) and aqueous solution of TBHP (3 equiv) in toluene under argon atmosphere at room temperature (entry 1, Table 1). Changing the solvent to MeCN the yield of the reaction was improved to 74% (entry 2, Table 1). Next we hypothesised that water may have some negative impact in the reaction. A decane solution of TBHP was used under the same condition and the desired product was obtained in 92% yield (entry 3, Table 1) which is our optimal condition for the acylation reaction. Decreasing the equivalent of TBHP the yield of the reaction is decreased. Other solvents like toluene, DCM, PhCN, THF produce the desired product in lower yield. Organic dyes like eosin Y, Rose bengal were screened as a photoredox catalyst and found less effective (entry 9, 10, Table 1). In absence of photoredox catalyst the desired product was obtained in15% yield (entry 11, Table 1). Increasing the reaction time to 48 h the yield of the reaction is slightly increased to 28% (entry 12, Table 1)

[a]*Organic and Medicinal Chemistry Division, CSIR-Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Jadavpur, Kolkata-700032, West Bengal, India*
[b]*Academy of Scientific and Innovative Research (AcSIR), Kolkata-700032, West Bengal, India*
E-mail: rjana@iicb.res.in
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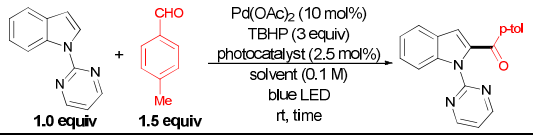
Table 1. Optimization of the Reaction Conditions[a]



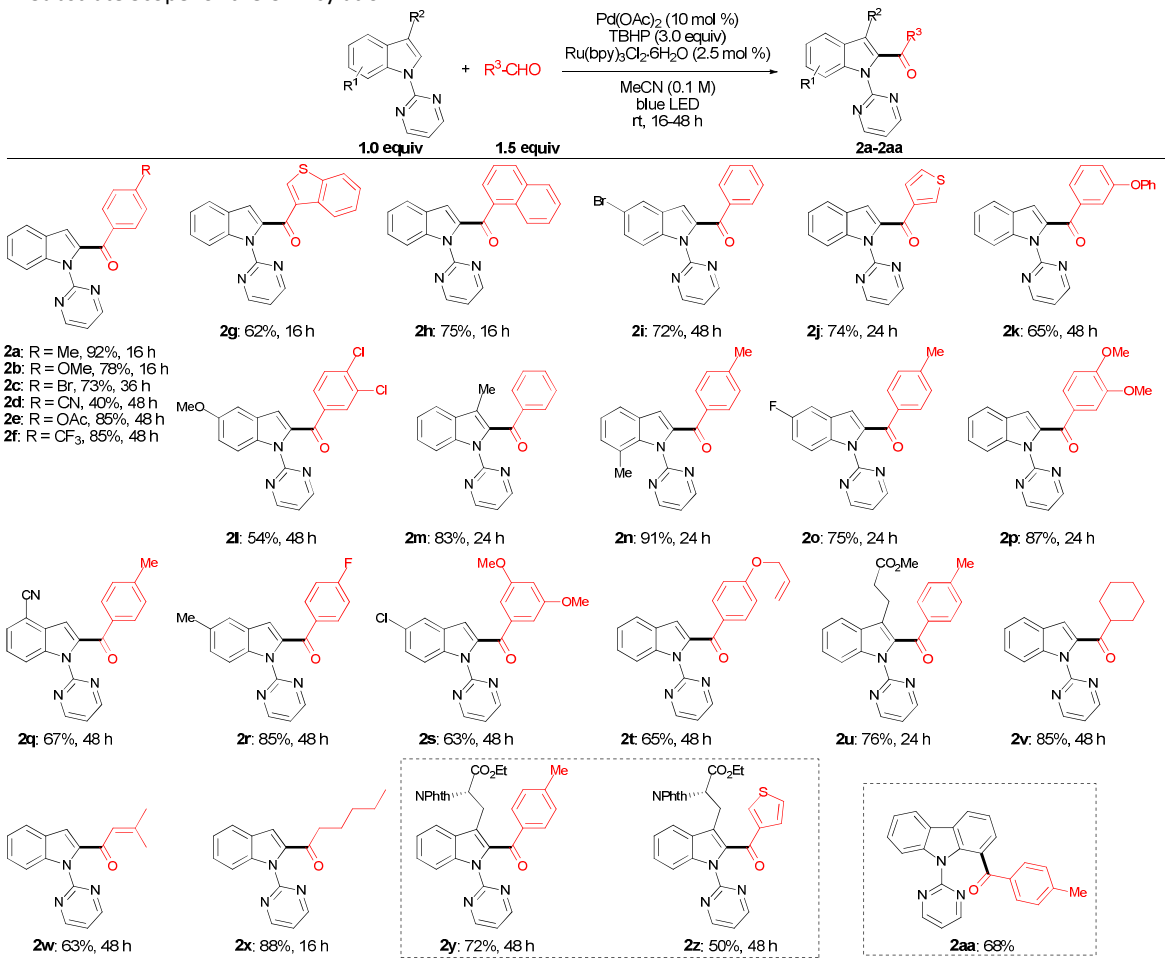
entry	photoredox catalyst (2.5 mol %)	solvent	reaction time	yield (%)[b]
1[c]	$Ru(bpy)_3Cl_2$	Toluene	16 h	52
2[c]	$Ru(bpy)_3Cl_2$	MeCN	16 h	74
3	**$Ru(bpy)_3Cl_2$**	**MeCN**	**16 h**	**92**
4	$Ru(bpy)_3Cl_2$	Toluene	16 h	60
5	$Ru(bpy)_3Cl_2$	PhCH	16 h	55
6	$Ru(bpy)_3Cl_2$	DCM	16 h	73
7	$Ru(bpy)_3Cl_2$	THF	16 h	37
8[d]	$Ru(bpy)_3Cl_2$	MeCN	16 h	0
9	Eosin Y	MeCN	16 h	19
10	Rose bengal	MeCN	16 h	38
11	-	MeCN	16 h	15
12	-	MeCN	48 h	28

[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to here are overall isolated yields. [c]aqueous solution of TBHP was used. [d]No $Pd(OAc)_2$ was used.

which exhibits that photoredox catalyst has a crucial role in this room temperature protocol.

With the optimised reaction condition in hand, we explored the substrate scope with a variety of substituted indole and aldehyde. Various functional groups on indole and aryl aldehyde such as alkyl, methoxy (**2b**, **2p**, **2s**), aryl ether (**2k**) ester (**2u**), acetate (**2e**), allyloxy (**2t**), cyano (**2d**, **2q**), trifluoromethyl (**2f**) are compatible under the reaction condition and produce the corresponding desired product in high to excellent yields. Halogen functional groups such as fluoro (**2o**, **2r**), chloro (**2l**, **2s**), bromo (**2c**, **2i**), remain intact and can be used for further synthetic manipulations. There is no prominent influence of electronic nature was observed since both electron withdrawing and donating functional group on indole as well as aldehydes furnished the desired products in high yields. However, *p*-cyanobenzaldehyde provided acylation product (**2d)** in moderate yield (40%) presumably due to the coordination with the catalyst. Heteroaromatic aldehyde such as thiophene-3-aldehyde, benzothiophene-3-aldehyde also afforded the desired product (**2g**, **2j**), in good yield. Besides aromatic aldehyde, aliphatic aldehydes such as n-hexyl (**2x**), cyclohexyl (**2v**), α, β unsaturated aldehyde, prenal (**2w**) also produce the desired product in good yield. Interestingly, C2-

Table 2. Substrate Scope for the C2-Acylation[a,b]



[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments.

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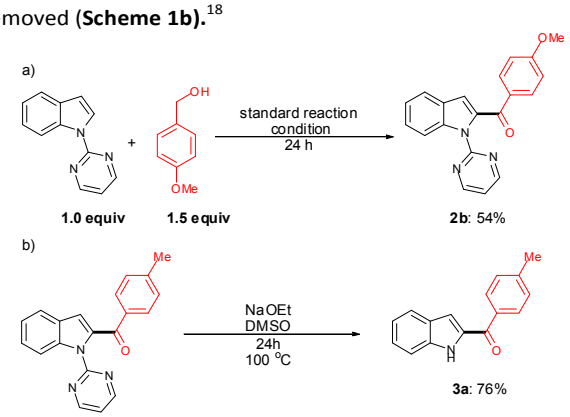
acylation product was formed exclusively under this mild conditions and no C7-acylation product was observed. While examining, we observed that 3-substituted indoles also provided the acylation product in high yield (**2m**, **2u**). Hence, we turned our attention to execute late-stage acylation of naturally abundant (L)-tryptophan.[16] Gratifyingly, protected tryptophan underwent acylation reaction smoothly providing the desired product in good to moderate yield (**2y**, **2z**). Since carbazole is known to generate a mixture of mono and di-acylation,[17] we were intended to examine this mild protocol in carbazole also. To our delight, exclusively mono acylation product was obtained in good yield (**2aa**).

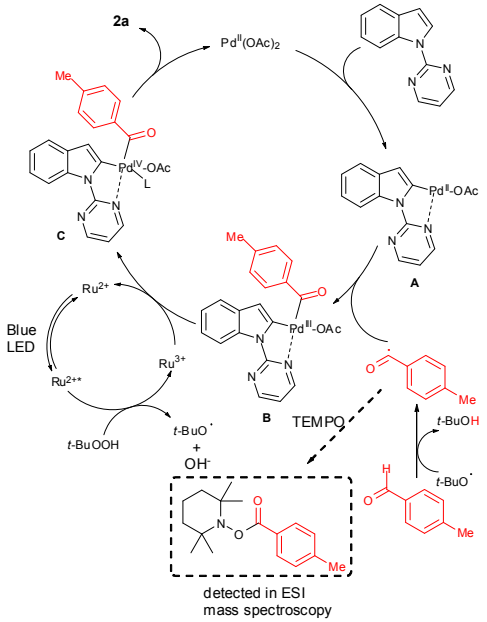
After successful utilization of aldehydes we were keen to examine benzyl amine, benzyl alcohol etc. as acylating agent which are oxidized to corresponding aldehydes *in situ* by Pd(II)/TBHP. A trace amount of desired product was obtained in case of benzyl amine whereas *p*-methoxybenzyl alcohol afforded the acylation product in 54% yield (**Scheme 1a**). Finally, heating the acylated product at 100 ^{o}C in presence of sodium ethoxide in DMSO the pyrimidine directing group was removed (**Scheme 1b).**[18]



Scheme 1. (a) Acylation with benzyl alcohol, **(b)** Removal of the directing group. [a,b]

[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments.

To understand the mechanism of the reaction a few control experiments were performed. To elucidate a SET type mechanism, the standard reaction was performed in presence of 1 equiv radical scavenger TEMPO. That reduced the yield of the reaction to 36%. But in presence of 2 equiv of TEMPO the reaction was completely shut down. No desired product was obtained under this condition. Also an adduct formation of TEMPO with the acyl radical was detected in ESI mass spectroscopy. Interestingly, in the absence of photoredox catalyst only 22% of the desired product was isolated even with 1 equiv of palladium(II)acetate. Thus typical Pd(II)/Pd(0) catalytic cycle may not be operational here rather hypervalent palladium species may be involved where photoredox catalyst oxidizes Pd(III) to Pd(IV). No reaction was observed in the absence of TBHP. From these control experiments and previous report a catalytic cycle was proposed for this transformation.[19] First in presence of light the Ru^{2+} is excited to Ru^{2+}* from its ground state. It transfer a single electron to *t*-BuOOH which cleaves the weak O-O bond to produce OH^- and *t*-$BuO^{\bullet}$ and itself oxidised to Ru^{3+}. The generated *t*-$BuO^{\bullet}$ abstract a hydrogen atom from aldehyde to form *t*-BuOH and acyl radical. On the other side *N*-pyrimidyl indole undergoes a directed palladation to the C2 position of indole and generates a five membered palladacycle cycle intermediate **A**. That undergoes oxidative addition with the generated acyl radical and furnish a cyclopalladated Pd(III) species **B** which may be oxidised to a Pd(IV) species **C** by a single electron transfer to Ru^{3+}. By single electron transfer Ru^{3+} reduced to Ru^{2+} and the catalytic cycle is completed for the photoredox catalyst. The Pd(IV) species **C** undergoes reductive elimination to produce the corresponding acylated product and Pd(II) species.



Scheme 2. Plausible Catalytic Cycle

To show the practical synthetic utility of the acylation strategy a gram-scale experiment was performed and the acylated product was obtained in 78% yield. Finally, we applied this methodology for the synthesis of two tubulin inhibitors D-64131 and D-68144 which exhibits antiproliferative activity at nanomolar concentration.[20] Direct acylation followed by

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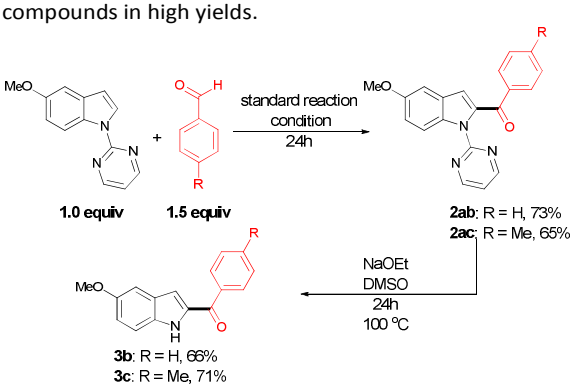
deprotection of the pyrimidine group lead to the desired compounds in high yields.



Scheme 3. Synthesis of Anticancer D-64131 and D-68144

Conclusions

In conclusion, we have developed a mild protocol for C2-acylation of *N*-pyrimidine-protected indoles merging visible light photoredox and palladium(II) catalysts. The reaction proceeds at room temperature via radical pathway providing acylation product in excellent yield and regioselectivity. The protocol has been applied for the late-stage functionalization of tryptophan and syntheses of tubulin inhibitors D-64131 and D-68144. Selective monoacylation of carbazole is also demonstrated.

Acknowledgements

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