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Synthesis of 3-Acylindoles by Visible-Light Induced Intramolecular Oxidative Cyclization of *o*-Alkynylated *N,N*-Dialkylamines

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Supporting Information

ABSTRACT: A visible-light photoredox synthesis of 3-acylindoles through intramolecular oxidative cyclization of *o*-alkynylated *N,N*-dialkylamines is developed. The reaction proceeds effectively under mild reaction conditions using air as the oxidant, and only water is generated as a side product. A plausible mechanism involving the addition of α-amino alkyl radicals to alkynes, followed by C—O bond formation, is proposed.

3-Acylindoles represent an important class of biologically active heterocyclic compounds which have been widely employed as core structures for developing pharmaceutically important molecules.[1] For example, pravadoline (Figure 1, **I**) is a marketed anti-inflammatory and analgesic drug.[2] Ramosetron (Figure 1, **II**) has been used as a serotonin 5-HT$_3$ receptor antagonist for the treatment of nausea and vomiting.[3] 3-Aroylindole compound **III** (BPR0L075, Figure 1) exhibits potent in vitro activity against a variety of human tumor cell lines.[4] As a consequence, the development of an efficient method for the synthesis of 3-acylindoles has become a subject of great interest.[5−12] The classical methods to synthesize 3-acylindoles are Friedel—Crafts reaction,[5] Vilsmeier—Haack reaction,[6] and indole Grignard reaction.[7] The other significant approaches include transition-metal-catalyzed C3—H activation of indoles by using α-oxocarboxylic acids,[8] anilines,[9] nitriles,[10] and electron-rich olefins[11] as the acyl sources. Although excellent preparative methods for the synthesis of 3-acylindoles using preformed indoles have been developed, the assembly of 3-acylindoles from readily available nonindole core starting materials using a simple and expedient procedure still remain scarce.[12,13] In this context, Liang and co-workers reported an elegant method for the synthesis of 3-acylindoles via palladium—copper-cocatalyzed intramolecular oxidative coupling of *o*-alkynylated *N,N*-dialkylamines.[13a] A similar protocol was also realized by Patel using a catalytic amount of CuI without the requirement of palladium as the cocatalyst.[13b] Both reactions were proposed to proceed via an iminium intermediate with excess amounts of TBHP as oxidants at high temperatures.

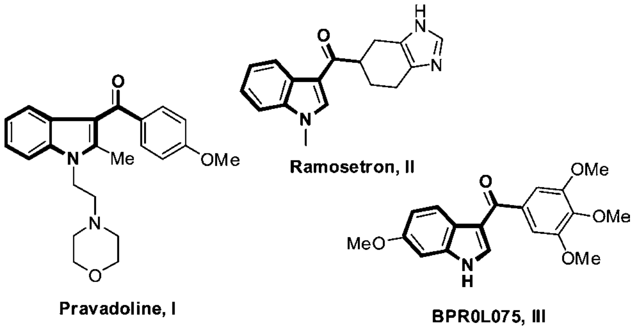

Figure 1. Examples of bioactive 3-acylindoles.

On the other hand, α-amino alkyl radicals have also been proven as reactive intermediates in various transformations.[14] The photoinduced one-electron oxidation of a tertiary amine followed by deprotonation under UV light irradiation is a well-established method for the generation of α-amino radicals.[15] Compared to high energy UV light, visible light is infinitely available, environmentally benign, and easy to handle. Its green chemistry features make visible-light promoted chemical reactions receive considerable attention in recent years.[16] With tris(bipyridine) ruthenium or iridium complexes as the photoredox catalysts, visible-light induced in suit generation of α-amino alkyl radicals and their addition to electron-deficient alkenes,[17] isocyanates,[18] and azodicarboxylate esters[19] have been described by several groups. In the presence of oxygen, Yu[20a] and Rueping[20b] demonstrated the radical addition/cyclization reactions between tertiary anilines with electron-deficient alkenes. Moreover, Rueping also reported the photoredox catalyzed synthesis of indole-3-carbaldehydes through a sequential C—C bond formation/aromatization/carbon—carbon bond cleavage process involving α-amino alkyl radicals (Scheme 1a).[20b] However, to our knowledge, visible-light promoted radical addition to alkynes followed by C—O bond formation was rarely reported to date.[16] We hypothesized that α-amino alkyl radicals **A** generated from tertiary amines **1** could undergo intramolecular radical addition to C—C triple bonds to produce vinyl radicals **B**. Subsequently, intermediate **B** could be captured by molecular oxygen or superoxide anion radical $O_2^{\bullet -}$ to provide vinyl peroxides **C**, whereby intramolecular abstraction of the hydrogen atom occurs to form 3-

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Scheme 1. Visible-Light Photoredox Synthesis of 3-Acylindoles

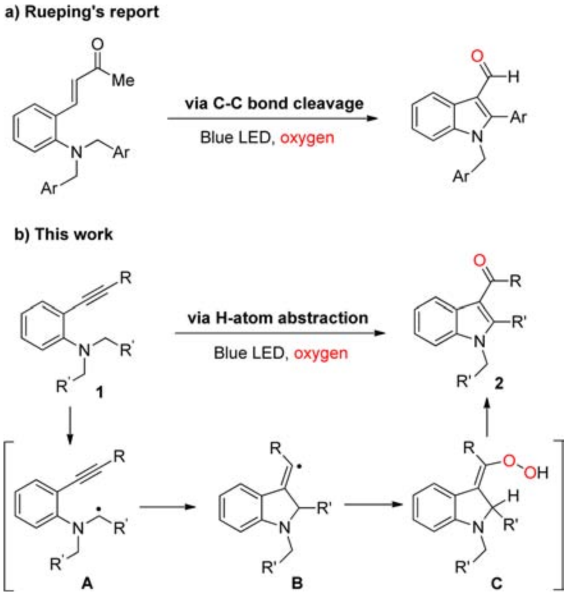
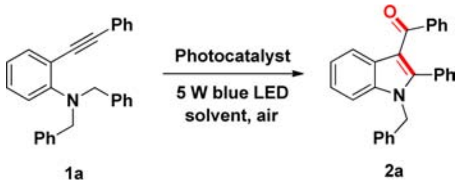


Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst (mol %)	base (equiv)	yield[b] (%)
1	$Ru(bpy)_2Cl_2·6H_2O$ (5)	none	40
2	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	none	60
3	$Ru(phen)_3Cl_2$ (5)	none	45
4	$Ru(bpz)_3Cl_2$ (5)	none	43
5	*fac*-$Ir(ppy)_3$ (5)	none	46
6	Eosin Y (10)	none	50
7	Rose Bengal (10)	none	28
8	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	K_2CO_3 (3)	75
9	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	KH_2PO_4 (3)	65
10	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	K_3PO_4 (3)	60
11	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	NaOAc (3)	65
12[c]	$Ir(ppy)_2(dtbbpy)PF_6$ (5)	K_2CO_3(3)	21
13[d]	$Ir(ppy)_2(dtbbpy)PF_6$ (1.5)	K_2CO_3 (3)	80

[a] A solution of **1a** (0.2 mmol) and photocatalyst in DMSO (4 mL) was irradiated by 5 W blue LED under air at rt for 36 h. [b] Yields were measured by ^1H NMR with mesitylene as the internal standard. [c] The reaction was carried out in 2 mL of MeCN. [d] A mixture of DMSO (2 mL) and MeCN (2 mL) was used as the solvent; reaction time 16 h.

acylindoles (Scheme 1b). As a continuation of our interest in visible-light photoredox radical chemistry,[21] we now report a visible-light induced intramolecular oxidative cyclization for the synthesis of 3-acylindoles, in which air was used as the oxidant with water as the only side product.

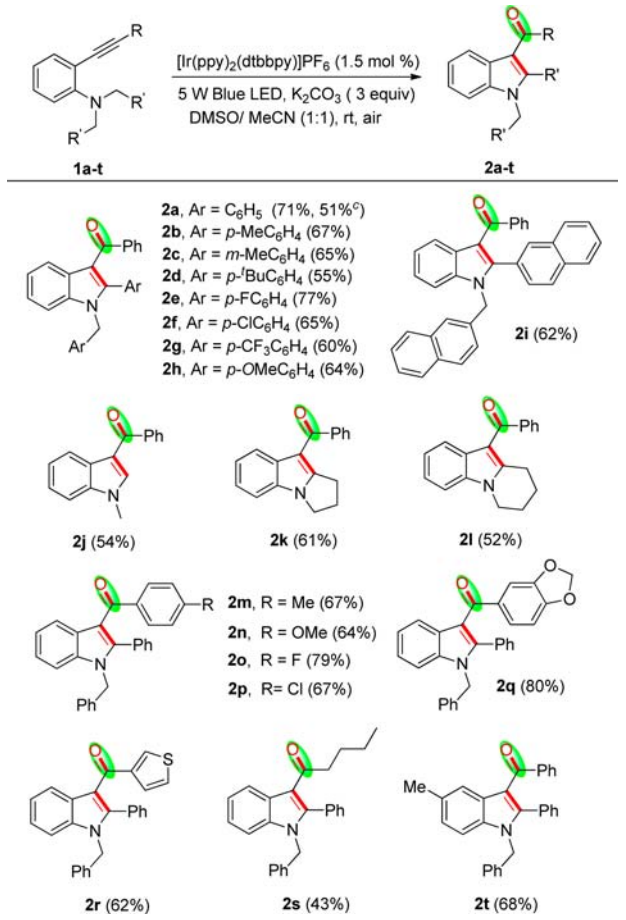
We initially prepared *N,N*-dibenzyl-2-(phenylethynyl) aniline **1a** through the Sonogashira coupling of phenylacetylene with 2-iodoaniline followed by benzylation of the resulted *o*-alkynylated amine under basic conditions. Irradiation substrate **1a** with 5 W blue LED in the presence of $Ru(bpy)_3Cl_2·6H_2O$ in DMSO for 36 h gave the desired 3-benzoylindole **2a** in 40% yield (Table 1, entry 1). The yield was significantly improved when 5 mol % of $Ir(ppy)_2(dtbbpy)PF_6$ was used as the photocatalyst (Table 1, entry 2). Other Ru or Ir complexes such as $Ru(phen)_3Cl_2$, $Ru(bpz)_3Cl_2$, *fac*-$Ir(ppy)_3$ were also examined, but they were not better than $Ir(ppy)_2(dtbbpy)PF_6$ (Table 1, entries 3−5). Notably, organic dyes eosin Y and Rose Bengal were also effective catalysts for the reaction, albeit affording the products with diminished yields (Table 1, entries 6 and 7). Further optimization on the reaction conditions revealed the addition of bases could effectively increase the yields of **2a**, and the use of K_2CO_3 gave the best results (Table 1, entries 8−11). A survey of solvents demonstrated that DMSO is the best choice (see Table S1 in Supporting Information (SI)). However, when MeCN was used as the solvent, *o*-alkynylated amine **1a** was completely consumed in 10 h, giving a mixture of **2a** and several unidentified byproducts (Table 1, entry 12). This observation promoted us to examine the use of the mixture of MeCN and DMSO as the solvents, in which the reaction might be accomplished in a shorter time. Finally, the reaction was found to give a neat conversion to **2a** in the 1:1 mixture of MeCN and DMSO in 16 h, and the catalyst loading could be further reduced to 1.5 mol % (Table 1, entry 13).

To demonstrate the generality of this new reaction, different dibenzyl substituted substrates **1b−i** were examined under the optimized reaction conditions. As shown in Scheme 2, the transformation proceeded quite smoothly and afforded the desired 3-aroylindoles **2b−i** in good yields. Both electron-donating groups such as *p*-Me, *m*-Me, *p*-^{t}Bu, *p*-OMe and electron-withdrawing groups such as *p*-F, *p*-Cl, *p*-CF_3 on the phenyl ring of the benzyl moiety could be well-tolerated. In another case, 2-(2-naphthyl)-3-acylindole **2i** was successfully assembled from **1i** in a yield of 62% under the irradiation of blue LED. One of the important attributes of this approach is its possibility to introduce various substituted aryl groups onto the 2-position of indoles under mild conditions. In addition, we were delighted to find that *o*-alkynylated *N,N*-dimethylamines **1j** was also suitable for the reaction. Notably, the substrates with a five-membered ring (**1k**) and a six-membered ring (**1l**) underwent intramolecular cyclization smoothly, affording the corresponding 3-aroylindoles **2k** and **2l** in yields of 61% and 52% respectively. Next, the present protocol was extended to the substrates with other triple-linked aromatics (**1m−q**) and a heteroaromatic ring (**1r**), and they all worked efficiently and gave good yields of the desired products. It is worth mentioning that *ortho*-alkylacetylenic substituted *N,N*-dibenzylamine **1s** also worked well to give the indole product **2s** in moderate yield. Finally, the reaction was found to be not significantly affected by the methyl group *para* to the nitrogen atom, in which the desired indole **2t** was isolated in 68% yield.

When *N*-benzyl-*N*-methyl-2-(phenylethynyl) aniline **1u** was employed as the substrate, the reaction gave a mixture of 3-benzoylindole **2u** and **2u′** in isolated yields of 40% and 22% respectively. This result indicates that the benzyl group more easily undergoes the single-electron oxidation than the methyl group under the present reaction conditions (Scheme 3).

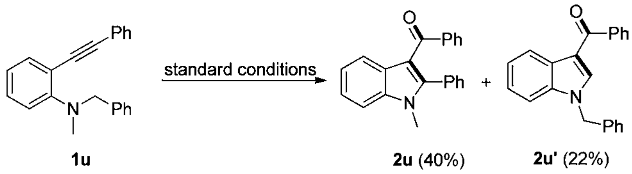
In principle, all the reactions were carried out under anhydrous conditions. In the presence of H_2O^{18} (5 equiv), the photoredox reaction of **1a** gave 3-acylindole **2a** with a diminished yield (52%) without any ^{18}O enriched at its carbonyl group. This result indicates that oxygen atom in the ketone did not originate from the water. Therefore, a tentative mechanism for this reaction is proposed in Scheme 4.[22]

Scheme 2. Synthesis of 3-Acylindoles 2 from Amines 1[a,b]



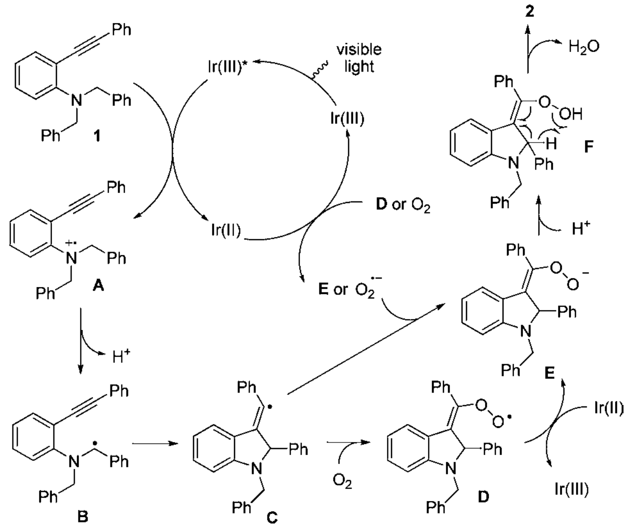
[a] Reaction conditions: amine **1** (0.2 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1.5 mol %), K_2CO_3 (0.6 mmol), DMSO/MeCN (1:1, 4 mL), 5 W blue LED, rt, air balloon, 16 h. [b] Isolated yield. [c] The reaction was carried out on 13.4 mmol scale.

Scheme 3. Reaction of *N*-Benzyl-*N*-methyl-2-(phenylethynyl) Aniline 1u



Initially, photoexcitation of Ir(III) by visible-light generates excited Ir(III)*. Single-electron transfer (SET) from substrate **1** to Ir(III)* generates Ir(II) and radical cation **A**, which undergoes facile deprotonation to give α-amino alkyl radical **B**.[20] Intramolecular radical addition to C−C triple bonds occurs to produce vinyl radicals **C**.[23] Intermediate **C** is captured by oxygen, leading to the formation of superoxide radical **D**.[24] Single-electron reduction of **D** by Ir(II) regenerates the Ir(III) catalyst with concomitant formation of intermediate **E**. Another possible route to get access to **E** is the regeneration of Ir(III) via aerobic oxidation, followed by addition of superoxide radical anion $O_2^{\bullet-}$ to vinyl radicals **C**. Finally, the protonation of **E** gives vinyl hydrogen peroxide **F**, whereby intramolecular abstraction of the hydrogen atom affords the 3-acylindoles **2**.[25]

Scheme 4. A Plausible Mechanism



In summary, we have developed a simple and efficient method for the synthesis of 3-acylindoles by means of visible-light irradiation of *o*-alkynylated *N*,*N*-dialkylamines. Various 2-aryl-3-acylindoles were assembled in good yields under mild conditions using air as the oxidant and carbonyl sources. This protocol allows the formation of C−C and C−O bonds simultaneously through an intramolecular oxidative path involving the α-amino alkyl radical.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data, NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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