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

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**S** Supporting Information

ABSTRACT: A visible-light photoredox synthesis of 3acylindoles through intramolecular oxidative cyclization of oalkynylated 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  $\alpha$ -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.<sup>1</sup> For example, pravadoline (Figure 1, I) is a



Figure 1. Examples of bioactive 3-acylindoles.

marketed anti-inflammatory and analgesic drug.<sup>2</sup> Ramosetron (Figure 1, II) has been used as a serotonin 5-HT<sub>3</sub> receptor antagonist for the treatment of nausea and vomiting.<sup>3</sup> 3-Aroylindole compound III (BPR0L075, Figure 1) exhibits potent in vitro activity against a variety of human tumor cell lines.<sup>4</sup> As a consequence, the development of an efficient method for the synthesis of 3-acylindoles has become a subject of great interest.<sup>5-12</sup> The classical methods to synthesize 3acylindoles are Friedel-Crafts reaction,<sup>5</sup> Vilsmeier-Haack reaction,<sup>6</sup> and indole Grignard reaction.<sup>7</sup> The other significant approaches include transition-metal-catalyzed C3-H activation of indoles by using  $\alpha$ -oxocarboxylic acids,<sup>8</sup> anilines,<sup>9</sup> nitriles,<sup>10</sup> and electron-rich olefins<sup>11</sup> 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.<sup>12,13</sup> 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.<sup>13a</sup> A similar protocol was also realized by Patel using a catalytic amount of CuI without the requirement of palladium as the cocatalyst.<sup>13b</sup> Both reactions were proposed to proceed via an iminium intermediate with excess amounts of TBHP as oxidants at high temperatures.

On the other hand,  $\alpha$ -amino alkyl radicals have also been proven as reactive intermediates in various transformations.<sup>14</sup> The photoinduced one-electron oxidation of a tertiary amine followed by deprotonation under UV light irradiation is a wellestablished method for the generation of  $\alpha$ -amino radicals.<sup>15</sup> 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.<sup>16</sup> With tris(bipyridine) ruthenium or iridium complexes as the photoredox catalysts, visible-light induced in suit generation of  $\alpha$ -amino alkyl radicals and their addition to electron-deficient alkenes,<sup>17</sup> isocyanates,<sup>18</sup> and azodicarboxylate esters<sup>19</sup> have been described by several groups. In the presence of oxygen, Yu<sup>20a</sup> and Rueping<sup>20b</sup> demonstrated the radical addition/ cyclization reactions between tertiary anilines with electrondeficient 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  $\alpha$ -amino alkyl radicals (Scheme 1a).<sup>20b</sup> However, to our knowledge, visiblelight promoted radical addition to alkynes followed by C-O bond formation was rarely reported to date.<sup>16</sup> We hypothesized that  $\alpha$ -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



acylindoles (Scheme 1b). As a continuation of our interest in visible-light photoredox radical chemistry,<sup>21</sup> 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 2iodoaniline followed by benzylation of the resulted oalkynylated amine under basic conditions. Irradiation substrate 1a with 5 W blue LED in the presence of  $Ru(bpy)_3Cl_2 \cdot 6H_2O$  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)<sub>3</sub>Cl<sub>2</sub>, Ru(bpz)<sub>3</sub>Cl<sub>2</sub>, fac-Ir(ppy)<sub>3</sub> 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-



|                 | Ph<br>Photocatalys<br>5 W blue LEE<br>solvent, air | t<br>Ph<br>Ph<br>2a | h<br>Ph                             |
|-----------------|--|---------------------|-------------------------------------|
| entry           | photocatalyst (mol %)                              | base (equiv)        | yield <sup><math>b</math></sup> (%) |
| 1               | $Ru(bpy)_2Cl_2 \cdot 6H_2O(5)$                     | none                | 40                                  |
| 2               | $Ir(ppy)_2(dtbbpy)PF_6$ (5)                        | none                | 60                                  |
| 3               | $Ru(phen)_{3}Cl_{2}(5)$                            | none                | 45                                  |
| 4               | $Ru(bpz)_3Cl_2$ (5)                                | none                | 43                                  |
| 5               | fac-Ir(ppy) <sub>3</sub> (5)                       | none                | 46                                  |
| 6               | Eosin Y (10)                                       | none                | 50                                  |
| 7               | Rose Bengal (10)                                   | none                | 28                                  |
| 8               | $Ir(ppy)_2(dtbbpy)PF_6(5)$                         | $K_2 CO_3 (3)$      | 75                                  |
| 9               | $Ir(ppy)_2(dtbbpy)PF_6(5)$                         | $KH_2PO_4$ (3)      | 65                                  |
| 10              | $Ir(ppy)_2(dtbbpy)PF_6(5)$                         | $K_{3}PO_{4}(3)$    | 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 <sup>d</sup> | $Ir(ppy)_2(dtbbpy)PF_6$ (1.5)                      | $K_{2}CO_{3}(3)$    | 80                                  |

<sup>*a*</sup>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. <sup>*b*</sup>Yields were measured by <sup>1</sup>H NMR with mesitylene as the internal standard. <sup>*c*</sup>The reaction was carried out in 2 mL of MeCN. <sup>*d*</sup>A mixture of DMSO (2 mL) and MeCN (2 mL) was used as the solvent; reaction time 16 h.

donating groups such as p-Me, m-Me, p-<sup>t</sup>Bu, p-OMe and electron-withdrawing groups such as p-F, p-Cl, p-CF<sub>3</sub> 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 3benzoylindole 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 <sup>18</sup>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.<sup>22</sup>





<sup>*a*</sup>Reaction conditions: amine 1 (0.2 mmol),  $Ir(ppy)_2(dtbby)PF_6$  (1.5 mol %),  $K_2CO_3$  (0.6 mmol), DMSO/MeCN (1:1, 4 mL), 5 W blue LED, rt, air balloon, 16 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> 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  $\alpha$ -amino alkyl radical **B**.<sup>20</sup> Intramolecular radical addition to C–C triple bonds occurs to produce vinyl radicals **C**.<sup>23</sup> Intermediate **C** is captured by oxygen, leading to the formation of superoxide radical **D**.<sup>24</sup> 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**.<sup>25</sup>

Scheme 4. A Plausible Mechanism



In summary, we have developed a simple and efficient method for the synthesis of 3-acylindoles by means of visiblelight irradiation of *o*-alkynylated *N*,*N*-dialkylamines. Various 2aryl-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  $\alpha$ -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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