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# Synthesis of Isoquinolones by Visible-Light-Induced Deaminative [4+2] Annulation Reactions

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Herein a metal-free approach for the synthesis of isoquinolone derivatives by means of photoinitiated deaminative [4+2] annulation of alkyne and N-amidepyridinium salt is described. This protocol exhibits broad scope and good functional group tolerance and regioselectivity under benign reaction conditions. Preliminary studies suggest the critical amide radical derives from photocatalytic cleavage of N-N bond of N-amidepyridinium salt, which adds to the triple bonds of alkyne and undergo the annulation process to afford the desired isoquinolones.

Isoquinolones have attracted the attention of many chemists by virtue of their potential biological and pharmacological activities such as antifertility, antihistaminic, antitumor activity.<sup>1</sup> Besides, isoquinolones play an important role in organic synthesis, organic light-emitting diode and organocatalysts.<sup>2</sup> Up to date, great efforts have been devoted to the the synthesis of isoquinolone derivatives.<sup>3</sup> Being common and important chemical structures, amides have been widely used as building blocks in organic synthesis, e.g., inter-/intramolecular annulation between amide and alkynes resorting to metal catalyst, such as Co<sup>4</sup>, Rh<sup>5</sup>, Ru<sup>6</sup>, Ni<sup>7</sup>, Pd<sup>8</sup> and other metal<sup>9</sup>, has demonstrated to be powerful strategies for building isoquinolone skeletons (scheme 1a). Among them, versatile substituents (such as 8-aminoquinoline, N,O-bidentate, amideoxazoline and N-methoxy etc.) on N-atom of amide are often required to serve as the directing group and usually retain in the isoquinolone products<sup>10</sup>. With the resurgence of electrosynthesis, the combination of metal catalyst with electrocatalysis offers novel and elegant avenue to the construction of isoquinolones. For example, Ackermann and co-worker reported sustainable cobalt electrocatalysis manifolds to prepare isoquinolines from amides and terminal/internal alkynes.<sup>11</sup> Meanwhile, Lei discovered a similar cobalt-catalyzed electrooxidative [4+2] annulation of amide with ethyne.<sup>12</sup> Recently, Tang developed an electrosynthesis of polycyclic isoquinolone from amide and alkyne in the presence of Ru-

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catalyst.<sup>13</sup> In addition, dual catalytic approach to the formation of isoquinolones has also been achieved by merging metal catalyst with photoredox catalyst. In 2018, Sundararaju and co-workers reported photoinduced synthesis of isoquinolones from 8-quinolinyl-protected amides and alkynes by combining cobalt-mediated catalysis with photocatalysis.<sup>14</sup> Despite of indisputable advances, these metal-assisted annulation remain limitations such as the requirement of directing group, metal catalysis, and external sacrificial oxidants.

### Scheme 1. Synthesis of Isoquinolone Derivatives



N-substituted pyridinium salts have been considered as valuable radical sources for the generation of alkyl radical, N-radical, Oradical and other radicals in C-C and C-X bond-forming reactions.<sup>15</sup> Given the importance of N-centered radicals in the construction of N-containing structures, continuous efforts have been dedicated to the development of pyridinium salts as precursors for producing Nradicals under photoredox catalysis. In 2015, Studer developed a direct C-H amidation of (hetero)arenes by using N-aminopyridinium salts as the N-radical precursors.<sup>16</sup> The group of Akita applied N-Tsprotected 1-aminopyridinium salts to difunctionalization reactions of olefins.<sup>17</sup> On the other hand, Xu and co-workers also utilized Nprotected aminopyridinium to obtain N-radicals in respective difunctionalization of olefins,<sup>18</sup> aza-pinacol of reaction rearrangement of alkylidenecyclopropanes<sup>19</sup> and [3+2] annulation of styrenes.<sup>20</sup> Encouraged by these advances, we envisioned the

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amide radical is accessible by modulating the substituent of Nprotected pyridinium salt, in which the resulted amide radical could be trapped by alkynes to furnish isoquinolone derivations via [4+2] annulation, that would avoid the demand of directing groups under metal-free conditions. Herein, we report a photocatalytic approach for the synthesis of isoquinolones through deaminative [4+2] annulation between alkynes and N-amidepyridinium salts.

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Entry <sup>a</sup>	Photocatalyst	Solvent	Additive	Yield (%) <sup>b</sup>
1	Ru(bpy)₃PF <sub>6</sub>	DMSO		43
2	<pre>[Ir(dFCF<sub>3</sub>ppy)<sub>2</sub>(dtbbpy)]<sup>+</sup></pre>	DMSO		56
3	EosinY	DMSO		56
4	Na <sub>2</sub> [EosinY]	DMSO		68
5	Na <sub>2</sub> [EosinY]	DCM		32
6	Na <sub>2</sub> [EosinY]	MeOH		trace
7	Na <sub>2</sub> [EosinY]	MeCN		24
8 <sup>c</sup>	Na <sub>2</sub> [EosinY]	DMSO		46
9 <sup><i>d</i></sup>	Na <sub>2</sub> [EosinY]	DMSO	NaBF <sub>4</sub>	36
10	Na <sub>2</sub> [EosinY]	DMSO	Et₃N	0
11	Na <sub>2</sub> [EosinY]	DMSO	DBU	53
12	Na <sub>2</sub> [EosinY]	DMSO	K <sub>2</sub> HCO <sub>3</sub>	51
13	Na <sub>2</sub> [EosinY]	DMSO	NaBF <sub>4</sub>	72
14		DMSO	NaBF <sub>4</sub>	0
15 <sup>e</sup>	Na <sub>2</sub> [EosinY]	DMSO	NaBF <sub>4</sub>	0
16 <sup><i>f</i></sup>	Na <sub>2</sub> [EosinY]	DMSO	NaBF <sub>4</sub>	trace



light source and inert atmosphere were necessaryArtfororthis

deaminative annulation reaction (entries 14 16).10.1039/D0CC01333A

Scheme 2. Scope of alkynes in the deaminative [4+2] annulation<sup>a</sup>

<sup>*a*</sup> Unless otherwise noted, reactions were conducted with 0.1 mmol **1a**, 0.4 mmol **2a**, 0.15 mmol additive, 5.0 mol % photocatalyst in 1.0 mL solvent, under the irradiation of a 15 W blue LED bulb and N<sub>2</sub> atmosphere. <sup>*b*</sup> Isolated yields. <sup>*c*</sup> A 15 W white LED bulb. <sup>*d*</sup> Reactions were conducted with 0.1 mmol **1a**, 0.2 mmol **2a**. <sup>*e*</sup> Reaction performed in the dark. <sup>*f*</sup> Reaction conducted without degassing.

Initial attempt was began with the annulation between pyridinium salts 1a and alkyne 1-ethynyl-4-methoxybenzene 2a in the presence of Ru(bpy)<sub>3</sub>PF<sub>6</sub> (5.0 mol%) in DMSO under the irradiation of a 15 W blue LED bulb (Table 1). To our delight, the desired product 3aa was isolated in 43% yield (entry 1). Then several photocatalyst candidates were surveyed, among which Na<sub>2</sub>[Eosin Y] (5.0 mol%) showed the best result (entries 2-4). Further screening on solvents such as DCM, MeOH and acetonitrile indicated that DMSO provided the optimal reaction medium, affording 3aa in 68% yield (entries 4-7). The influence of light source was also examined by using a 15 W white LED bulb instead, which diminished the yield of 3aa to 46% (entry 8). In addition, reducing the equivalent of 2a afforded 3aa in lower 36% yield (entry 9). Moreover, comparison of different additives such as triethylamine, DBU, K2CO3 and NaBF4 exhibited that NaBF4 was superior additive to others to facilitate the [4+2] annulation (entries 10-13). Control experiments indicated that photocatalyst, visible-

Reaction conditions: 0.1 mmol  $1a,\ 0.4$  mmol  $2,\ 0.15$  mmol NaBF4, 5.0 mol % photocatalyst in 1.0 mL DMSO under a 15 W blue LED bulb in N2.

With the optimized conditions in hand, we then explored the scope and limitation of the reaction with diverse alkynes. As shown in Scheme 2, a variety of ethynylbenzene derivatives 2 with different pendants were subjected to the standard reaction conditions, which afforded the corresponding isoquinolone products in moderate to good yields. Electron-donating groups such as methoxyl, ethoxyl, methyl, propyl and tert-butyl on terminal alkynes enabled the [4+2] annulation to proceed in good efficiency (3aa-3af, 3ai). Various electron-withdrawing substituents such as fluoro, -chloro, -cyano and -nitro were also compatible with this annulation method (3aj-3al, 3an-3ao). Furthermore, undecorated ethynylbenzene, 2-ethynylnaphthalene and the heterocyclic 2ethynylthiophene were found to function as effective annulation partners to form related isoquinolone products (3ag-3ah, 3am). Notably, the successful reaction between prop-1-yn-1-ylbenzene with 1a further demonstrated the applicability of internal alkyne in this annulation protocol (3ap).

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Thereafter, further examination on the scope of various pyridinium salts **1** in the deaminative [4+2] annulation was carried out (Scheme 3). Substrates bearing electron-rich (such as -MeO and -Me) and electron deficient groups (such as -F, -CN and -CF<sub>3</sub>) at the para position were well suitable for this transformation (**3ba**, **3da**, **3ga-3ia**). Moreover, pyridinium salt with two substituents presented similar reactivity to deliver anticipated product (**3ea**). It is worthy of noting that the unprotected -OH group was well tolerated in the reaction conditions to afford the target product (**3ca**), which may provide potential applications in organic synthesis by further functionalization on -OH group. Besides, pyridinium salt with fused rings was competent substrate as well, affording the desired product **3fa** in 69% yield.

**Scheme 3.** Scope of N-amidepyridinium salts in the deaminative [4+2] annulation<sup>*a*</sup>



 $^{\it a}$  Reaction conditions: 0.1 mmol 1, 0.4 mmol 2a, 0.15 mmol NaBF4, 5.0 mol % photocatalyst in 1.0 mL DMSO under a 15 W blue LED bulb in N2.

Having established the scope of the photoinitiated [4+2] annulation, control experiments were subsequently carried out to gain insights into the reaction mechanism. First, the addition of a radical scavenger TEMPO into the standard reaction conditions yielded no desired isoquinolone product 3aa, which indicated the involvement of radical intermediates during the transformation (Scheme 4a). Then the Hantzsch ester, a common hydrogen radical donor, was used in the template reaction in which the benzamide was isolated in 71% yield after full consumption of starting materials (Scheme 4b). We hereby speculated the generation of an amidyl radical from pyridinium salt which led to the production of benzamide by coupling with hydrogen radical stemmed from the Hantzsch ester. To further add credence to the existence of amidyl radical intermediate, styrene 4a was used instead of 1-ethynyl-4methoxybenzene 2a. However, the anticipated ring-closing product 5aa failed to be detected by GC-MS (Scheme 4c). Subsequently, luminescence quenching experiments were conducted to determine the initial SET (single-electron-transfer) step of the photoredox process. As presented in Figure 1, the excited state of photocatalyst Na<sub>2</sub>[EosinY] was preferentially quenched by piridinium salt 1a over alkyne 2a, which indicated that the first SET step might occur between the excited Na<sub>2</sub>[EosinY] and piridinium salt **1a** through an oxidative quenching processi: 10.1039/DOCC01333A



Scheme 4. Control experiments



Figure 1. Luminescence quenching of photoexcited Na<sub>2</sub>[EosinY] at 575 nm by piridinium salt 1a and alkyne 2a in DMSO



Scheme 5. Proposed reaction mechanism

Based upon the above presented experimental results, a plausible reaction mechanism is described as depicted in Scheme 5. Under the irradiation with visible light, the PC (photoredox catalyst, Na<sub>2</sub>[EosinY]) reaches to its excited state , which is then oxidatively quenched by pyridinium salt **1a** to release the neutral amidyl radical **A** by cleavage of the N-N bond of **1a**. Subsequent regioselctive addition of the resulted N-radical **A** to the C=C bond of alkyne **2a** furnishes more stable intermediate **C**, which then convert into intermediate **D** by the intramolecular annulation. Finally, a SET

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process undergoes between intermediate  ${\bf D}$  and oxidative PC+ to afford the final product  ${\bf 3aa}$  after deprotonation.

# Conclusions

In summary, a deaminative [4+2] annulation method has been developed using photoredox catalysis under mild reaction conditions, in which a broad range of isoquinolone derivatives have been prepared without using directing groups in moderate to good yields in the absence of metal catalyst. This manifold well accepts various functional groups and shows good efficacy. In addition both terminal and internal alkynes are viable substrates in this protocol. We envision that this strategy will inspire further applications in the synthesis of natural products. However, this method suffers from atomeconomy limitation by losing triphenylpyridine from starting material when compared with the metal-catalyzed strategy. Therefore further investigations towards atom-economy annulation and novel application of radical annulation reaction in complicated molecules are ongoing in our laboratory.

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## **Conflicts of interest**

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There are no conflicts to declare.

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