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Visible-light induced tandem radical cyanomethylation and cyclization of *N*-aryl acrylamides: access to cyanomethylated oxindoles[†]

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A visible-light induced cyanomethylation of *N*-aryl acrylamides with bromoacetonitrile followed by intramolecular cyclization has been explored. This transformation exhibits a wide substrate scope and significant functional group tolerance, providing a facile synthetic approach and highly efficient access to cyanomethylated oxindoles.

Oxindoles are an ubiquitous heterocycles motif in many natural products, pharmaceuticals and agrochemicals.1 Moreover, oxindoles have significant biological activities and wide-ranging applications in organic synthesis.2 Therefore, the search for sustainable and more efficient methods for the preparation of oxindoles is of constant interest. Recently, catalytic difunctionalization of alkenes emerged as an attractive strategy for accessing structurally diverse heterocyclic compounds,³ for example, a tandem radical addition/cyclization of N-aryl acrylamides that provides an elegant method for the construction of the 3,3-disubstituted oxindole skeleton has been reported;4 and the radical process involving alkylarylation,⁵ diarylation,⁶ arylnitration,7 arylphosphorylation,8 aryltrifluoromethylation,9 and azidoarylation¹⁰ of N-aryl acrylamides have since been disclosed by several groups, allowing the effective formation of the oxindole framework.

Cyanomethylation oxindoles are of significant interest because cyanomethylation reaction is considered to be a privileged reaction which resulted products can be utilized as key intermediates in drug synthesis.¹¹ Some successful examples synthesizing cyanomethylated oxindoles have been reported in recent years.¹² For example, in 2011, Liu discovered a novel Pdcatalyzed oxidative method to afford nitrile-bearing indolinones, which involves α -C-H activation of both aniline and acetonitrile by the aid of stoichiometric PhI(OCO^tBu)₂ and AgF.^{12a} Subsequently, You and Zhu demonstrated Cu and Fecatalysed 1,2-cyanoalkylarylation of *N*-aryl acrylamides for the construction of cyanomethylation of oxindoles using acetonitrile as cyanomethyl source, respectively.^{12b,12e} Sheng also

School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China. E-mail: zhaoguo@sjtu.edu.cn developed cyanomethylation of activated alkenes through a radical pathway using AIBN as the radical initiator.^{12g} Nevertheless, stoichiometric amount of transition metals or promoter mediates are required in aforementioned examples. A milder and more efficient method for the synthesis of functionalized oxindoles is still highly desirable.

Nowadays, the visible-light photoredox catalysis strategy has been identified as a uniquely powerful and straightforward tool for synthetic transformations in organic chemistry, owing to its high efficiency and environmentally friendly mild reaction conditions.13 Several groups have been synthesized the oxindole derivatives by the means of UV light or visible-light photoredox catalysis.14 However, the visible-light photoredox catalysis approaches for their preparation of cyanomethylated oxindoles are extremely limited. As far as we know, only one example involving a visible-light catalyzed cyanomethylated of oxindoles has been reported by the Li group,^{12c} in which moderate yields and equivalent of 4-MeOC₆H₄N₂BF₄ reagent was used as promoter. As part of our ongoing interest in visible light photoredox catalytic reactions,15 we present a novel visible-light induced radical addition/cyclization cascade cyanomethylation of N-aryl acrylamides for the synthesis of valuable cyanomethylcontaining oxindoles using bromoacetonitrile as cyanomethyl radical source (Scheme 1).

Initially, we investigated this reaction using N-methyl-N-phenylmethacrylamide (1a) and bromoacetonitrile (2) as the



Scheme 1 Visible-light induced tandem cyanomethylation and cyclization of *N*-aryl acrylamides.

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starting materials with K₂CO₃ as the base and fac-Ir(ppy)₃ (2 mol%) as the catalyst. To our delight, the transformation proceeded smoothly after 24 h of irradiation with a 23 W household fluorescent lamp (CFL) in CH₃CN at room temperature, affording the desired product 3a in 76% yield (Table 1, entry 1). When this reaction was performed in the absence of base, only 15% yield of 3a was obtained, and most of the N-methyl-N-phenylmethacrylamide 1a was recovered (Table 1, entry 2). Encouraged by this result, the reaction conditions of this cascade were further optimized. Firstly, we screened the catalysts and found that other photoredox catalysts, such as $[Ir(dtbbpy)(ppy)_2][PF_6]$, $Ru(bpy)_3Cl_2 \cdot 6H_2O$, and Eosin Y, resulted in low reaction efficiency (Table 1, entries 3-5). Then we screened different bases (Table 1, entries 6-12). It turned out that Na₂CO₃ was the best base among the inorganic and organic bases tested, giving the product with 93% yield. A survey of commonly used solvents, such as DMF, DMSO, CHCl₃, MeOH, and THF, were tested (Table 1, entries 13-17). However, reaction in none of the above solvents afforded higher yield than that in CH₃CN. The highest yield was achieved when 2 equiv. of bromoacetonitrile was used (Table 1, entry 19). Increased to 4 equiv. or reduced to 1.5 equiv. of bromoacetonitrile led to



Entry	Photocatalyst	Base	Solvent	Yield ^{b} (%)
1	fac-Ir(ppy) ₃	K ₂ CO ₃	CH ₃ CN	76
2	fac-Ir(ppy) ₃	None	CH ₃ CN	15
3	[Ir(dtbbpy)(ppy) ₂][PF ₆]	K ₂ CO ₃	CH ₃ CN	12
4	Ru(bpy) ₃ Cl ₂ ·6H ₂ O	K_2CO_3	CH ₃ CN	3
5	Eosin Y	K ₂ CO ₃	CH ₃ CN	5
6	fac-Ir(ppy) ₃	Li_2CO_3	CH ₃ CN	79
7	fac-Ir(ppy) ₃	Na_2CO_3	CH ₃ CN	93
8	fac-Ir(ppy) ₃	NaHCO ₃	CH ₃ CN	82
9	fac-Ir(ppy) ₃	Na_2HPO_4	CH ₃ CN	71
10	fac-Ir(ppy) ₃	K_3PO_4	CH ₃ CN	41
11	fac-Ir(ppy) ₃	KOAc	CH ₃ CN	46
12	fac-Ir(ppy) ₃	NEt ₃	CH ₃ CN	29
13	fac-Ir(ppy) ₃	Na_2CO_3	DMF	86
14	fac-Ir(ppy) ₃	Na_2CO_3	DMSO	69
15	fac-Ir(ppy) ₃	Na_2CO_3	$CHCl_3$	87
16	fac-Ir(ppy) ₃	Na_2CO_3	MeOH	22
17	fac-Ir(ppy) ₃	Na_2CO_3	THF	85
18^d	fac-Ir(ppy) ₃	Na_2CO_3	CH ₃ CN	91
19^e	fac-Ir(ppy) ₃	Na_2CO_3	CH ₃ CN	$95(93)^{c}$
20^{f}	fac-Ir(ppy) ₃	Na_2CO_3	CH ₃ CN	71
21	None	Na_2CO_3	CH_3CN	0
22^g	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	CH ₃ CN	0

^{*a*} Reaction conditions: **1a** (88 mg, 0.5 mmol), **2** (180 mg, 1.5 mmol, 3 eq.), catalyst (2 mol%), base (1 mmol, 2 eq.), solvent (5 mL), rt, 24 h, under N₂ atmosphere. ^{*b*} Determined by ¹H NMR analysis with benzyl ether as an internal standard. ^{*c*} The value in parentheses was isolated yield. ^{*d*} 4 equiv. of **2** was used. ^{*e*} 2 equiv. of **2** was used. ^{*f*} 1.5 equiv. of **2** was used. ^{*g*} In the dark.

a lower yield of 91% and 71%, respectively (Table 1, entries 18 and 20). Control experiments suggested that photocatalyst and irradiation are indispensable to this transformation (Table 1, entries 21 and 22).

With the optimized reaction conditions in hand, we evaluated the scope of acrylamides with 2 (Table 2). Initially, the examination of different N-protecting groups revealed that methyl-protected (1a) was still the best choice, similar ethylprotected (1b) and benzyl-protected (1c) substrate gave slightly reduced yields, whereas the reactions of N-H derivatives failed (1d). Gratifyingly, various functional groups were well tolerated, and both electron-donating group (e.g., Me, OMe, ^tBu) and electron-withdrawing group (e.g., CN, COOMe, COMe) substituents at the para position of the aniline moiety proceeded efficiently to afford the cyclized products 3e-n in moderate to good yields. Notably, halogen functional groups such as F, Cl, and Br were well-tolerated leading to the corresponding halogen-substituted cyanomethylation of oxindoles in good yields (76-90%, 3i-k, Table 2), which offered the potential for further synthetic elaboration. For the N-aryl acrylamides containing ortho-position substituent groups exhibited a particularly distinct steric hindrance effect, and lower yields were observed as a result (Table 2, 30-p). N-Aryl acrylamides bearing a meta-substituent underwent cyanomethylation smoothly to give a mixture product of isomers in 95% yield with poor regioselectivity $(3\mathbf{q}: 3\mathbf{q}' = 1.6: 1)$. Moreover, 3,5-dimethyl N-aryl amides 3r also underwent the tandem reaction smoothly. In addition, naphthalene and tetrahydroquinoline derivative were also viable substrates to provide the corresponding oxindoles 3s and 3t with the same yield of 84% (Table 2, 3s-3t).

To gain additional mechanistic insights, 3 equiv. of TEMPO relative to **1a** was added to the reaction system, no desired product **3a** was observed and starting material was recovered,



^{*a*} Reaction conditions: **1** (0.5 mmol), BrCH₂CN (120 mg, 2 equiv.), base (2 equiv.), catalyst (2 mol%), CH₃CN (5 mL), irradiation with a 23 W household light bulb, rt, 24 h. ^{*b*} Yields of isolated products.



indicating that a radical process is probably involved in this reaction. On the basis of above results and previous literature reports,¹¹ a plausible mechanism was proposed (Scheme 2).

Initially, iridium catalyst was excited to generate the excited species fac-[Ir(ppy)₃]* under visible light irradiation, which then undergoes single electron transfer (SET) process with bromoacetonitrile **2** to generate cyanomethyl radical **A** and Ir^{IV} metal complex. Subsequently, the addition of cyanomethyl radical **A** to activated alkene **1a** afforded alkyl radical **B**, followed by intramolecular cyclization with aryl ring lead to intermediate **C**, which was further oxidized through SET process to give key carbocation **D** and regenerated the photocatalyst. Finally, deprotonation of **D** in the presence of a base gave the desired product **3a**.

Conclusions

In summary, we have disclosed an operationally convenient visible-light photocatalytic tandem cyanomethylation of *N*-aryl acrylamides using available bromoacetonitrile as starting material. The protocol presents a mild and efficient to furnish a variety of functionalized oxindoles. Both electron donating and electron withdrawing groups on the *N*-aryl acrylamides are tolerated in the reaction, and the corresponding products were obtained in moderate to good yields.

Conflicts of interest

There are no conflicts to declare.

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