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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.

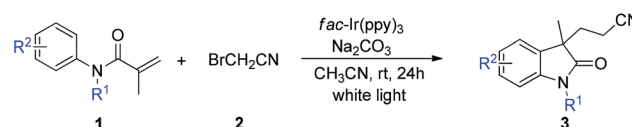
Oxindoles are an ubiquitous heterocycles motif in many natural products, pharmaceuticals and agrochemicals.¹ Moreover, oxindoles have significant biological activities and wide-ranging applications in organic synthesis.² Therefore, the search for sustainable and more efficient methods for the preparation 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 aryl-nitration,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 Pd-catalyzed oxidative method to afford nitrile-bearing indolinones, which involves α -C–H activation of both aniline and acetonitrile by the aid of stoichiometric $\text{PhI}(\text{OCO}^t\text{Bu})_2$ and AgF .^{12a} Subsequently, You and Zhu demonstrated Cu and Fe-catalysed 1,2-cyanoalkylarylation of *N*-aryl acrylamides for the construction of cyanomethylation of oxindoles using acetonitrile as cyanomethyl source, respectively.^{12b,12c} Sheng also

developed cyanomethylation of activated alkenes through a radical pathway using AIBN as the radical initiator.^{12e} 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 cyanomethyl-containing 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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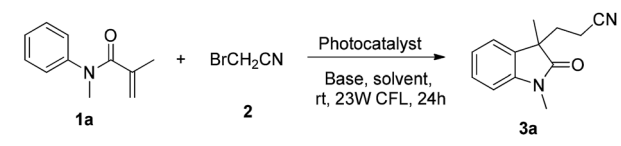
starting materials with K_2CO_3 as the base and *fac*-Ir(ppy)₃ (2 mol%) as the catalyst. To our delight, the transformation proceeded smoothly after 24 h of irradiation with a 23 W household fluorescent lamp (CFL) in CH_3CN at room temperature, affording the desired product **3a** in 76% yield (Table 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][PF₆], Ru(bpy)₃Cl₂·6H₂O, 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 CH_3CN . 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

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 ethyl-protected (**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, **3o–p**). *N*-Aryl acrylamides bearing a *meta*-substituent underwent cyanomethylation smoothly to give a mixture product of isomers in 95% yield with poor regioselectivity (**3q** : **3q'** = 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,

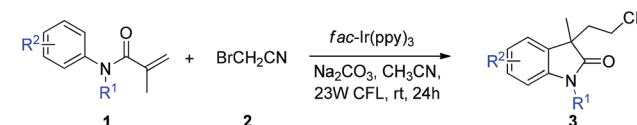
Table 1 Optimization of reaction conditions^a



Entry	Photocatalyst	Base	Solvent	Yield ^b (%)
1	<i>fac</i> -Ir(ppy) ₃	K ₂ CO ₃	CH ₃ CN	76
2	<i>fac</i> -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 ₂ CO ₃	CH ₃ CN	3
5	Eosin Y	K ₂ CO ₃	CH ₃ CN	5
6	<i>fac</i> -Ir(ppy) ₃	Li ₂ CO ₃	CH ₃ CN	79
7	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	CH ₃ CN	93
8	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	CH ₃ CN	82
9	<i>fac</i> -Ir(ppy) ₃	Na ₂ HPO ₄	CH ₃ CN	71
10	<i>fac</i> -Ir(ppy) ₃	K ₃ PO ₄	CH ₃ CN	41
11	<i>fac</i> -Ir(ppy) ₃	KOAc	CH ₃ CN	46
12	<i>fac</i> -Ir(ppy) ₃	NET ₃	CH ₃ CN	29
13	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	DMF	86
14	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	DMSO	69
15	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	CHCl ₃	87
16	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	MeOH	22
17	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	THF	85
18 ^d	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	CH ₃ CN	91
19 ^e	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	CH ₃ CN	95(93) ^c
20 ^f	<i>fac</i> -Ir(ppy) ₃	Na ₂ CO ₃	CH ₃ CN	71
21	None	Na ₂ CO ₃	CH ₃ CN	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.

Table 2 Scope of acrylamides^{a,b}



3a , 20%	3p , 30%	3q+3q' (1.6:1), 95%
3r , 95%	3s , 84%	3t , 84%

^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.

^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.



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