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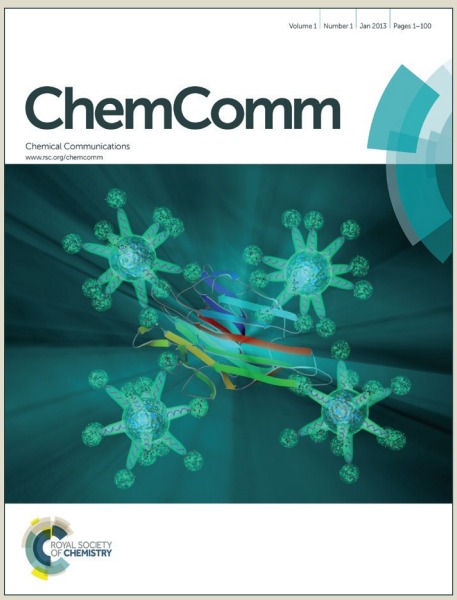

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ARTICLE TYPE

Visible light induced radical cyclization of *o*-iodophenylacrylamides: A concise synthesis of indolin-2-one

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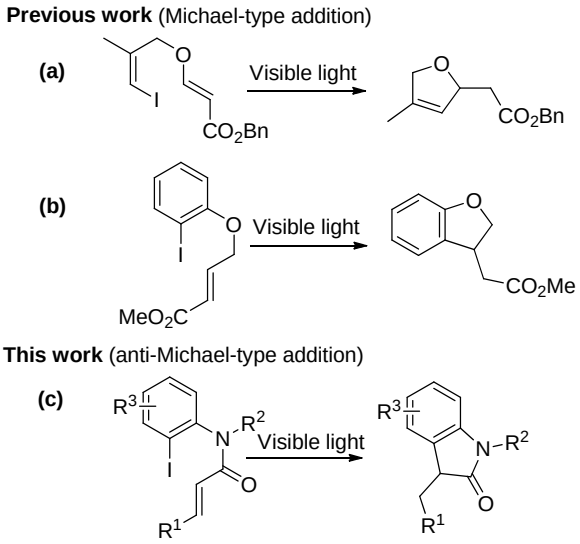
A [Ir(ppy)$_2$(dtb-bpy)]PF$_6$-catalyzed intramolecular radical cyclization of *o*-iodophenylacrylamides afforded indolin-2-ones in moderate to excellent yields via a 5-exo-trig radical cyclization under visible light is presented. This method provides a new access to the synthesis of indolin-2-ones under mild reaction conditions.

The indolin-2-one rings are a very important class of compounds due to their existence in numerous natural products, which display a wide range of physiological activities.[1] Substantial effort has been devoted to the development of methods for the preparation of indolin-2-one compounds. Classical synthetic methods for the synthesis of oxindole rings include the derivatization of other heterocycles (e.g. oxidation of indole,[2] Wolf-Kishner reduction of isatin[3]), the transition metal-catalyzed intramolecular amidation,[4] the Heck reaction[5] and the radical cyclization reactions, which were used to prepare oxindole derivatives under a radical initiator, such as SmI_2 or AIBN.[6] Despite these methods have provided some options for the synthetic community, the concise and efficient synthesis of indolin-2-ones from easily available substrates under mild conditions still remains a major challenge. As a result, a novel, mild and efficient method is still required for ready access to the various indolin-2-ones.

The visible–light induced chemical transformations serve as a new kind of photo radical reaction in radical-involving organic synthesis.[7] It has attracted much attention of many researchers ever since and the number of reports describing the photoredox catalysis under visible light has seen a recent surge.[8] However, most of the photoredox reaction to date has been limited only to the alkyl radicals,[9] the application to aryl radicals[10] has rarely been reported due to their instability. Lee[11] and Stephenson[12] have developed the intramolecular radical cyclization of alkenyl and aryl iodide via a radical addition onto the *β*-position (Michael-type addition) of *a*, *β*-unsaturated esters and amides affording a variety of cyclic compounds (**Scheme 1a**, **1b**).



Scheme 1. The intramolecular radical cyclization of alkenyl and aryl iodide

As part of our ongoing research in the development of new and efficient organic radical reactions,[13] we herein disclose a novel radical cyclization reaction for the preparation of indolin-2-ones under visible light (**Scheme 1c**). To the best of our knowledge, the radical cyclization reaction of *o*-iodophenylacrylamides moieties through an "anti-Michael" type addition of aryl radicals to give the corresponding indolin-2-ones under visible light has not been reported.

To begin with our study, we chose *N*-(2-iodophenyl)-*N*-methylbut-2-enamide (**1a)** (Table 1) as the model substrate to test the feasibility of visible-light photoredox catalysis. Treatment of **1a** (0.5 mmol) with Ru(bpy)$_3$Cl$_2$ (0.015 mmol) as a catalyst under the irradiation of a 12 W of white LED strip in the presence of Et_3N (5 mmol) at 35 °C for 24 h afforded the corresponding indolin-2-one **2a** in 16% yield (Table 1, entry 1). Considering that the catalysts usually play an important role in photoredox

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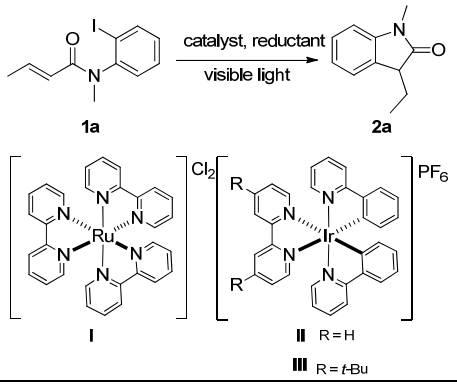
catalysis, other commonly used transitional metal photocatalysts, such as $[Ir(ppy)_2bpy]PF_6$, and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, were investigated to improve the reaction efficiency. To our delight, when $[Ir(ppy)_2bpy]PF_6$ was used as catalyst, the desired product can be obtained in 61% yield (entry 2). More importantly, the catalyst $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$, which has a higher redox potential (Ir^{III} / Ir^{II} vs Ru^{II} / Ru^{I})[14] could significantly increase the yield to 92% (Table 1, entry 3). Subsequently, we tested the solvents with $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ as the catalyst, and CH_3CN was found to be the solvent of choice (Table 1, entries 4-6). Screening of the amine reductants revealed that *i*-Pr_2NEt and *N, N*-dimethylaniline were less effective than Et_3N (Table 1, entries 9 and 10). Reducing the amount of reductant also lead to the decreased yield of **2a** (Table 1, entries 7 and 8). To our delight, lowering catalyst loading from 3 mol% to 1.0 mol% had no significant effect on the reaction efficiency (Table 1, entry 11). Finally, control experiments showed that both photocatalyst and visible light were necessary, no product was detected when the reaction was conducted either in the absence of photocatalyst or in the dark (Table 1, entries 12 and 13).

Table 1. Optimization of the reaction conditions.[a]

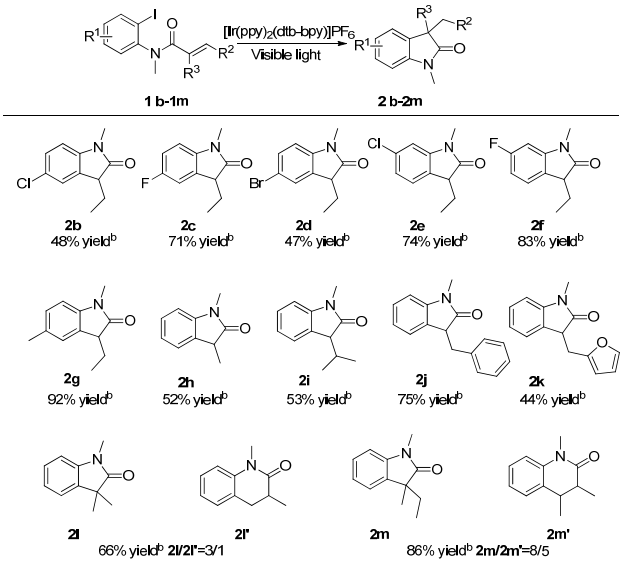


Entry	Catalyst	Solvent	Reductant (eq.)	Yield[b] (%)
1	**I**	CH_3CN	Et_3N (10)	16
2	**II**	CH_3CN	Et_3N (10)	61
3	**III**	CH_3CN	Et_3N (10)	99(92[c])
4	**III**	DCM	Et_3N (10)	75
5	**III**	MeOH	Et_3N (10)	59
6	**III**	DMF	Et_3N (10)	51
7	**III**	CH_3CN	Et_3N (5)	59
8	**III**	CH_3CN	Et_3N (2)	50
9	**III**	CH_3CN	*i*-Pr_2NEt (10)	55
10	**III**	CH_3CN	*N,N*-dimethylaniline(10)	6
11[d]	**III**	CH_3CN	Et_3N (10)	99
12[e]	**III**	CH_3CN	Et_3N (10)	0
13[f]		CH_3CN	Et_3N (10)	0

[a] Conditions: **1a** (0.5 mmol), catalyst (0.015 mmol), reductant (10 eq), solvent (5 mL), irradiation with 12 W white LED strip at 35 °C for 24 h. [b] GC yield based on diphenyl ether as an internal standard. [c] Isolated yield. [d] III(0.005 mmol). [e] Reaction was run in the dark. [f] Without catalyst.

With the reaction conditions established, we next investigated the scope of substrates for this protocol, and the results are listed in Table 2. Initially, both moderate electron-withdrawing groups and electron-donating groups at different positions of the aromatic ring did not compromise the reaction efficiency, affording the desired indolin-2-ones (**2b-g)** in moderate to good yields (Table 2, 47-92%). Interestingly, Substrates bearing other halogen atoms on the aromatic ring, such as **2b**, **2d**, and **2e** were well-tolerated under the reaction conditions; however, **2d** was obtained in a low yield because the dehalogenation of the product **2d** and the substrate **1d** was found during the reaction (see supporting information). Substrates bearing no substituent or more than one substituent

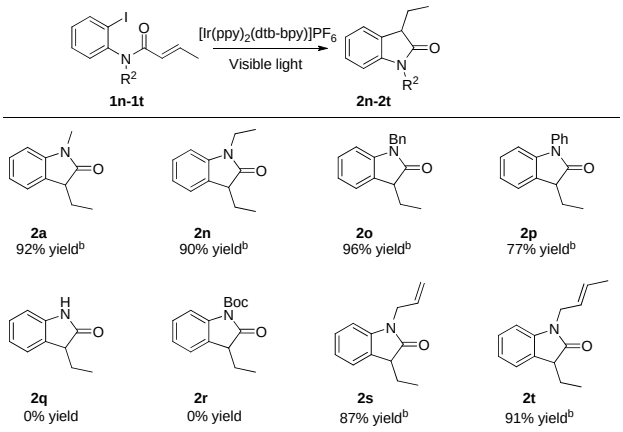
Table 2. Ir-catalyzed cyclization of *o*-iodophenylacrylamides [a]



[a] Conditions: **1b-1m** (0.5 mmol), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (0.005 mmol), Et_3N (5 mmol), CH_3CN (5 mL), irradiation with a 12 W of white LED at 35 °C for 24 h. [b] Isolated yield.

at *β*-position of *a*, *β*-unsaturated-amides resulted in relatively poor yields (**2h**, **2i**); *β*-Substituted aromatic and heteroaromatic substrates **1j** and **1k** could also participate in this transformation to give the desired product in 75% and 44% yield, respectively. Substrates bearing a substituent at *a*-position, **1l** and **lm,** afforded a mixture of **2l**+**2l′**(3:1) and **2m**+**2m′**(8:5) isomers in 66% and 86% yields, respectively, through a 5-exo-trig and a 6-endo-trig radical cyclization. [6c,e]

Table 3. Ir-catalyzed cyclization of various *N*-protected substrates [a]

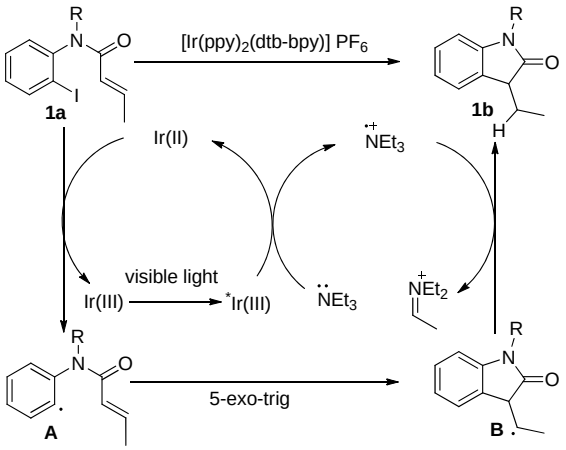


[a] Conditions: **1n-1t** (0.5 mmol), $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (0.005 mmol), Et_3N (5 mmol), CH_3CN (5 mL), irradiation with a 12 W of white LED at 35 °C for 24 h. [b] Isolated yield.

In addition, we have extended this radical cyclization reaction into various *N*-protected substrates as well (Table 3).

Different *N*-protected group showed that the electron-donating groups were appropriate for this reaction, affording the target products in excellent yields (Table 3, **2n-p**). However, no product was obtained when the substrate with an electron-withdrawing group or with a free *N*-H acryl amide was employed (Table 3, **2q** and **2r**). It should be noted that cyclization of crotonyl derivatives (Table 3, **2s-2t**) gave exclusively indolin-2-ones in good yields again with no trace of cyclization onto the allyl double, which is in consistent with the results reported by Jones et al.[15]

On the basis of the above experiments and related reports,[10] a plausible mechanism for the reaction was shown in Scheme **2**. Excitation of the metal catalyst under visible light afforded the excited Ir^{III}* species, which oxidizes Et_3N to give the reduced species Ir^{II}, along with the radical cation of the amine. The electron-rich metal complex Ir^{II} then reduces the aryl iodide **1a** to afford the key radical intermediate **A** and regenerates the photocatalyst Ir^{III}. The intramolecular radical addition of intermediate **A** to the *a*, *β*-unsaturated amide forms radical **B**, which can be rapidly reduced by a hydrogen-atom abstraction from the *a*-amino position of the iminium radical cation to give the indolin-2-one.[16]



Scheme 2. Proposed mechanism

In conclusion, we have developed an efficient visible light induced [Ir(ppy)(dtb-bpy)PF_6]-catalyzed reductive cyclization reaction of *o*-iodophenylacrylamides via a 5-exo-trig radical cyclization under mild reaction conditions, affording the biologically important indolin-2-ones in moderate to good yields. Further study towards expanding the application of photoredox catalysis in other reaction is currently underway in our laboratory.

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