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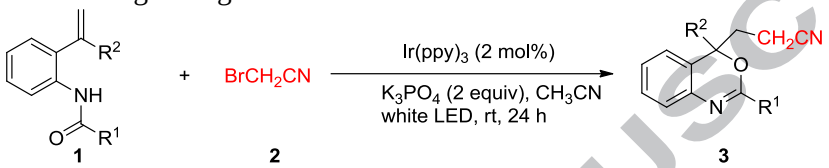

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Synthesis of 4-cyanoethylated benzoxazines by visible-light-promoted radical oxycyanomethylation of olefinic amides with bromoacetonitrile

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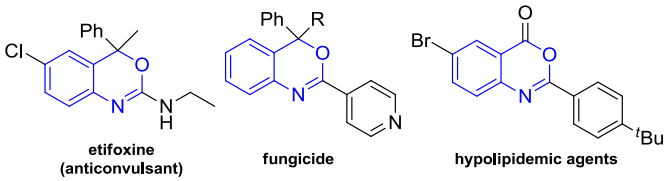
ABSTRACT

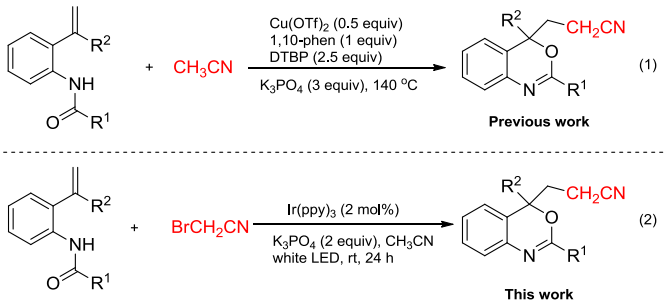
A facile and efficient protocol for the visible-light-promoted radical oxycyanomethylation of olefinic amides with bromoacetonitrile has been developed, affording a series of 4-cyanoethylated benzoxazine derivatives in moderate to excellent yields. The reaction featured with diverse functional group tolerance and mild reaction conditions.

Cyanoalkyl moieties are important structural motifs that widely exist in biologically active natural products and medicines.[1] Moreover, the cyano served as precursors of carboxylic acids, esters, amides, amines, aldehydes, and ketones.[2] Therefore, considerable efforts have been paid into the development of more efficient cyanoalkylation reactions in recent years.[3] Among the well-developed reactions, transition-metal catalyzed C(sp^3)–H bond oxidative functionalization of alkyl nitriles are of particular interest, as these strategies could introduce cyanoalkyl groups into the target frameworks in a step-economical fashion, however, excess of chemical oxidant and elevated reaction temperature are often required in these procedures.[4] Alternatively, visible-light-induced photocatalytic difunctionalization of alkenes with cyclobutanone oxime[5] or bromoacetonitrile[6] represents another useful cyanoalkylation reaction, which can avoid the use of stoichiometric redox reagents. For example, Xiao and co-workers reported a visible-light-driven cascade reaction of oxime esters, styrenes, and boronic acids to generate various diversely 1,1-diarylmethane-containing alkylnitriles.[7] MacMillan group reported an enantioselective α-cyanoalkylation of aldehydes by photoredox organocatalysis using a cheap bromoacetonitrile as the cyanoalkyl source.[8] Despite much progress has been paid in this field, establishing more straightforward methods as well as developing environmentally friendly reaction conditions to generate diverse cyano-containing compounds remains an area of synthetic interest.

Figure 1. Pharmaceutical scaffolds including benzoxazines.



Scheme 1. Synthesis of 4-Cyanoethylated Benzoxazines.



On the other hand, 4-substituted-4H-1,3-benzoxazine scaffolds occur frequently in many pharmaceutically active molecules, such as anticancer, antibacterial, anticonvulsant, and HIV protease inhibitory activities (Figure 1),[9] and they are also useful synthetic intermediates in organic synthesis. As a result, several elegant methodologies have been developed to access such frameworks.[10] Firstly, the construction of 4-substituted-4H-1,3-benzoxazine derivatives by tandem radical addition to olefinic amides followed by cyclization is the most common method.[11] Nevertheless, to date, the synthesis of 4-cyanoethylated

benzoxazines requires stoichiometric oxidants and high temperature[12] (Scheme 1 eq. 1). Herein, we envisioned that the construction of these compounds from olefinic amides and commercial available bromoacetonitrile through a visible-light-driven domino radical addition/ oxidation/ cyclization cascade reactions (Scheme 1 eq. 2). This novel reaction featured with diverse functional group tolerance and mild reaction conditions.

Table 1. Selected results for screening the optimized reaction conditions.[a]

1a 2 3a

entry	catalyst	base	solvent	yield[b] (%)
1	*fac*-Ir(ppy)$_3$	K_2CO_3	MeCN	43
2	[Ir(ppy)$_2$(dtbbpy)]PF_6	K_2CO_3	MeCN	N.R.
3	Ru(bpy)$_3$Cl$_2$.6H$_2$O	K_2CO_3	MeCN	12
4	eosin Y	K_2CO_3	MeCN	N.R.
5	4CzIPN	K_2CO_3	MeCN	N.R.
6	*fac*-Ir(ppy)$_3$	Na_2CO_3	MeCN	46
7	*fac*-Ir(ppy)$_3$	$NaHCO_3$	MeCN	53
8	*fac*-Ir(ppy)$_3$	DABCO	MeCN	20
9	*fac*-Ir(ppy)$_3$	K_3PO_4	MeCN	78
10	*fac*-Ir(ppy)$_3$	K_3PO_4	DMF	63
11	*fac*-Ir(ppy)$_3$	K_3PO_4	DCE	51
12	*fac*-Ir(ppy)$_3$	K_3PO_4	DMSO	32
13	*fac*-Ir(ppy)$_3$	K_3PO_4	MeCN	0[c]
14	*fac*-Ir(ppy)$_3$	--	MeCN	0
15	*fac*-Ir(ppy)$_3$	K_3PO_4	MeCN	36[d] 72[e]

[a] Reaction conditions: **1a** (0.1 mmol), bromoacetonitrile (0.15 mmol), photocatalyst (0.002 mmol, 2 mol%), base (0.2 mmol) in indicated solvent (1.0 mL) was irradiated with a 16 W white LED for 24 h in a sealed Schlenk tube, unless otherwise noted. [b] Isolated yield. [c] without photocatalyst or in dark. [d] bromoacetonitrile (0.1 mmol), [e] bromoacetonitrile (0.2 mmol).

Initially, we selected N-(2-(prop-1-en-2-yl)phenyl)benzamide **1a** and bromoacetonitrile **2** as model substrates to optimize the reaction conditions. As anticipated, the reaction indeed took place in the presence of 2 mol % *fac*-Ir(ppy)$_3$ as the photocatalyst and 2 equiv. of K_2CO_3 as a base under 16 W white light-emitting diode (LED) strip irradiation in CH_3CN at room temperature and gave the oxycyanomethylation product **3a** in 43% yield (Table 1, entry 1). Then, other photocatalyst such as [Ir(ppy)$_2$(dtbbpy)]PF_6, Ru(bpy)$_3$Cl$_2$.6H$_2$O, eosin Y, 4CzIPN were tested, however, all gave inferior results than that of *fac*-Ir(ppy)$_3$ (Table 1, entries 1-5). Subsequently, other bases such as Na_2CO_3, $NaHCO_3$, DABCO, K_3PO_4 were tested to further increase the efficiency of this reaction, and K_3PO_4 was the best, the desired product could be isolated in 78% yield in the presence of 2 equivalents of K_3PO_4 (Table 1, entries 1, 6-9). Among the solvents tested, MeCN was the best choice (Table 1, entries 9-12). Under the control experiments, it was found that this reaction did not work in the absence of each reaction parameters (Table 1, entries 13-14). Additionally, decrease or improve the amount of bromoacetonitrile used all gave inferior results (Table 1, entry 15).

With the optimized reaction conditions in hand, the scope and limitation of substrates was investigated, as shown in Scheme 2. Generally, the reaction tolerated olefinic amides bearing both electron-donating and electron-withdrawing groups. However, the substrates bearing electron-withdrawing groups gave inferior results than those bearing electron-donating groups. For example, methyl, methoxyl substituted olefinic amides could afford the desired products **3a-3e** in good yields (60%-78%). However, the analogues bearing electron-withdrawing groups could generate the desired products **3f-3n** in only 33%-57% yields. It was found that 2,6-dichloro-N-(2-(prop-1-en-2-yl)phenyl)benzamide **1j** only could afford the desired product **3j** in only 33% yield, which would be attributed to the steric hindrance effect. Notably, some functional groups such as, chloro, bromo, iodo, nitro, esterand cyano groups, which were suitable for potentially further functionalization, survived in these reactions. Moreover, aliphatic substrates **1q-1s** also could react smoothly with bromoacetonitrile to give the desired products **3q-3s** in good yields (60%-64%).

Importantly, the diversity of the product was further increased as this procedure allow to access 2-(1-naphthyl) (**3o**, 43%), 2-thienyl (**3p**, 51%), 2-cinnamenyl (**3t**, 32%) of 4H-1,3-benzoxazines in moderate yields. Subsequently, *α*-aryl olefinic amide **2u** also could react smoothly under the standard conditions to generate **3u** in 53% yield.

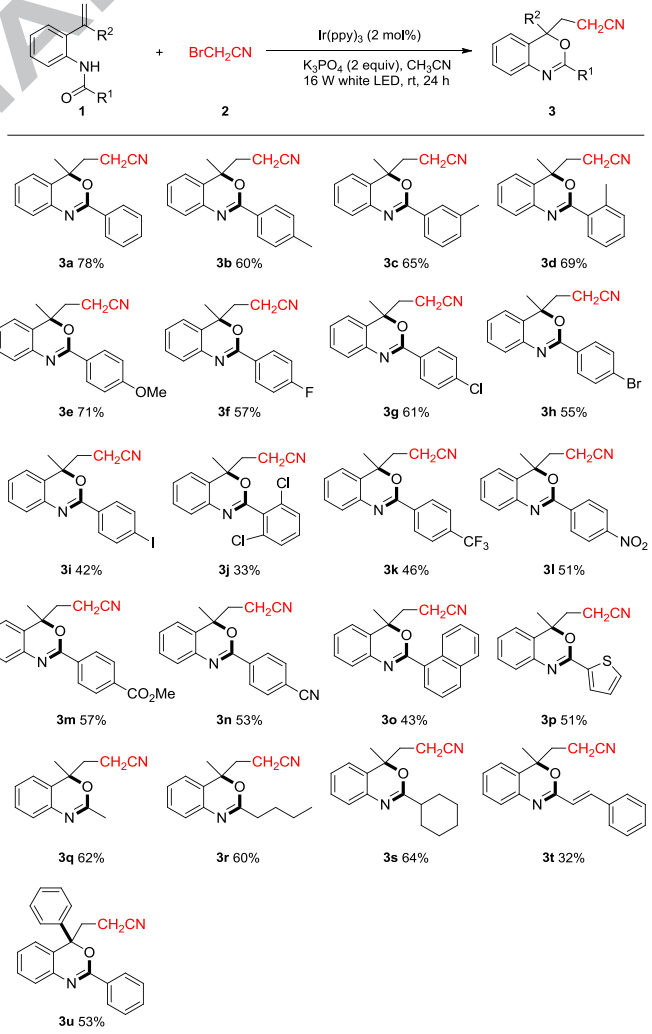
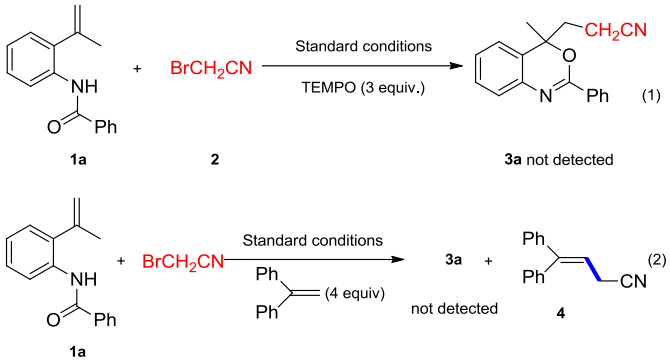


Figure 2. The substrate scope of olefinic amides [a] Reaction conditions: **1** (0.1 mmol), bromoacetonitrile **2** (0.15 mmol,), photocatalyst (0.002 mmol, 2 mol%), K_3PO_4 (0.2 mmol) in CH_3CN (1.0 mL) was irradiated with a 16 W white LED for 24 h in a sealed Schlenk tube, unless otherwise noted

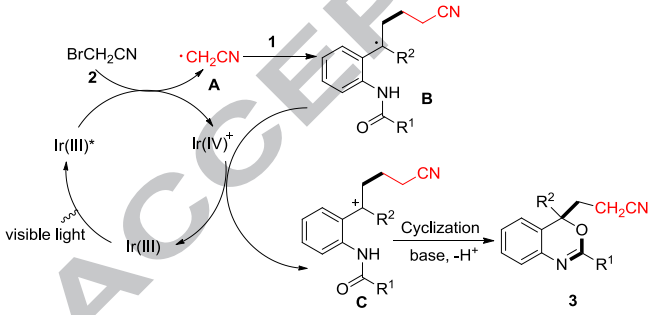
Some control experiments were conducted to get some insights into this transformation. Firstly, when 3 equivalents of radical scavenge 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added, the reaction was totally inhibited, which suggested that the reaction probably proceeded via a radical pathway (Scheme 3, eq. 1). To further confirm the involvement of radical in this transformation, another radical scavenge 1,1-diphenylethenewas used to trap the cyanomethyl radical. As expected, the formation of product **3a** was suppressed, and the coupling product 4,4-diphenylbut-3-enenitrile (**4**) was obtained (Scheme 3, eq. 2).

Scheme 2. Mechanistic study



On basis of the above discussion and some relative previous works, a tentative mechanism[13] is outlined in Scheme 4. First, the excited state [*fac*-Ir(III)(ppy)$_3$*] is formed under light irradiation, which is next oxidized by bromoacetonitrile **2** to generate a [*fac*-Ir(IV)(ppy)^3]$^+$ complex and a CH_2CN radical species **A**. The difluoromethyl radical attacks the C–C double bond of olefinic amides **1** to generate the radical intermediate **B**. The radical intermediate **B** is then oxidized by [*fac*-Ir(IV)(ppy)$_3$]$^+$ to form the carbocation intermediate **C** with the concurrent regeneration of [*fac*-Ir(III)(ppy)$_3$]. Subsequent cyclization reaction of intermediate **C** followed by deprotonation assisted by a base give the difluoromethylated product **3**.

Scheme 3. A Tentative mechanism



In conclusion, we have developed a *fac*ile and efficient protocol for the visible-light-promoted radical oxycyanomethylation of olefinic amides with bromoacetonitrile has been developed, affording a series of benzoxazine derivatives in moderate to excellent yields. The reaction featured with diverse functional group tolerance and mild reaction conditions.

Acknowledgments

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