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Visible-Light-Induced Radical Cascade Cyclization of Oxime Esters and Aryl Isonitriles: Synthesis of Cyclopenta[*b*]quinoxalines

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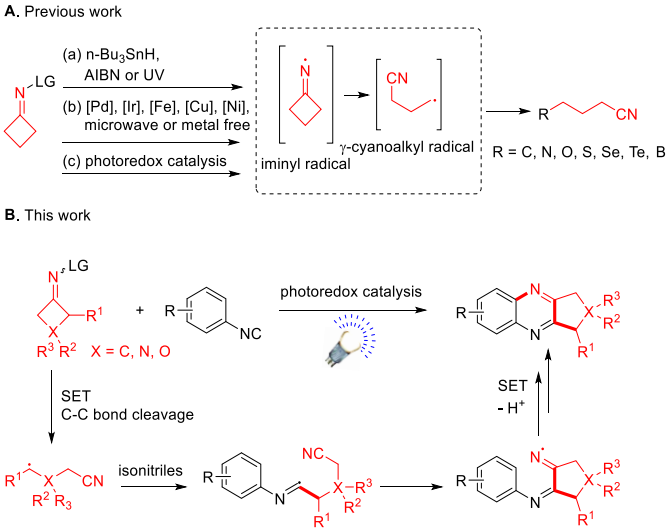
A visible-light-induced radical cascade cyclization of aryl isonitriles and cyclobutanone oxime esters for the synthesis of cyclopenta[*b*]quinoxalines has been accomplished for the first time. Key to the success of this process was the integration of the in-situ-formed nitrile radical followed by the cascade radical isonitrile/nitrile insertion-cyclization. The easy introduction of substituents for both substrates and the high functional group tolerance of the reaction make it an efficient strategy to give various quinoxaline derivatives in moderate to good yields.

Free radical reactions play an important role in organic chemistry, which establish powerful strategies for the synthesis of a diverse collection of organic molecules.[1] Therefore, developing efficient methods for the generation of free radicals is of great concern. In 1991, the Zard group pioneered the use of cyclobutanone sulfenylimines and carboxymethyl oximes as iminyl radical precursors to achieve selective C–C bond cleavage and produce γ-cyanoalkyl radicals.[2] It provided an efficient protocol to access structurally diverse nitriles, which are versatile building blocks in organic chemistry and medicinal chemistry.[3] However, stoichiometric radical initiators (*n*-Bu_3SnH or AIBN) or UV irradiation was used in this process. Later, Uemura,[4] Guo[5] and other groups[6] developed transition-metal (Pd, Ir, Fe, Cu, Ni)-catalyzed, microwave-promoted or metal free iminyl radical-involved ring-opening of cyclobutanone oximes to construct C–C and C–Y (Y = O, S, N, Se, Te, B) bonds with the synthesis of complex and multifunctionalized nitriles. Recently, visible light photoredox catalysis emerged as an effective means for the production of reactive radical intermediates.[7] In this context, Xiao,[8] Zhou,[9] Leonori,[10] Waser[11] and Wu[12] demonstrated visible-light-catalyzed iminyl radical-involved C–C bond cleavage/cross-coupling reactions of cyclobutanone oxime esters in the last two years (**Scheme 1**, **A**).

Scheme 1. Cyanoalkylation by Means of Cycloketone Oxime Esters and Reaction Design



All the reactions mentioned above realized the synthesis of various substituted nitrile compounds, which can be easily converted into other functional compounds. Our group has been interested in the visible-light-induced radical cascade cyclization with isonitriles for the synthesis of nitrogen-containing heterocyclic molecules.[13] In this work, we further exploited the radical cascade cyclization of isonitriles and the in-situ-formed nitrile radical. As depicted in Scheme **1 B**, we envision that the cyanoalkyl radicals produced from cyclobutanone oximes would undergo a radical insertion with isocyano group of aryl isonitriles. The resulting imidoyl radical containing the in-situ-formed nitrile could attach to the cyano

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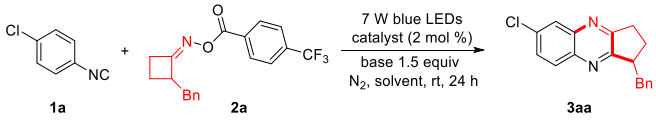
group through an intramolecular radical addition resulting in the iminyl radical. Finally, the target cyclopenta[*b*]quinoxalines would be obtained after the following intramolecular radical cyclization process.

On the other hand, quinoxaline derivatives are very important skeletons widely existed in biologically active molecules and pharmaceutical drugs.[14] Since 1990s, Nanni,[15] Curran[16] and Yu[17] groups have reported the radical cascade cyclization of aryl isonitriles and 4-iodobutanenitrile or diethyl 2-bromo-2-(2-cyanoethyl)malonate, however, those cyanide source were not so easily be obtained or modified. Given the importance of them, the C–C bond cleavage of cyclobutanone oxime esters gives a new approach to get cyanoalkyl radicals from easily available starting materials, which provide possibilities to synthesize diverse quinoxaline derivatives.

Table 1. Optimization of Reaction Conditions[a]

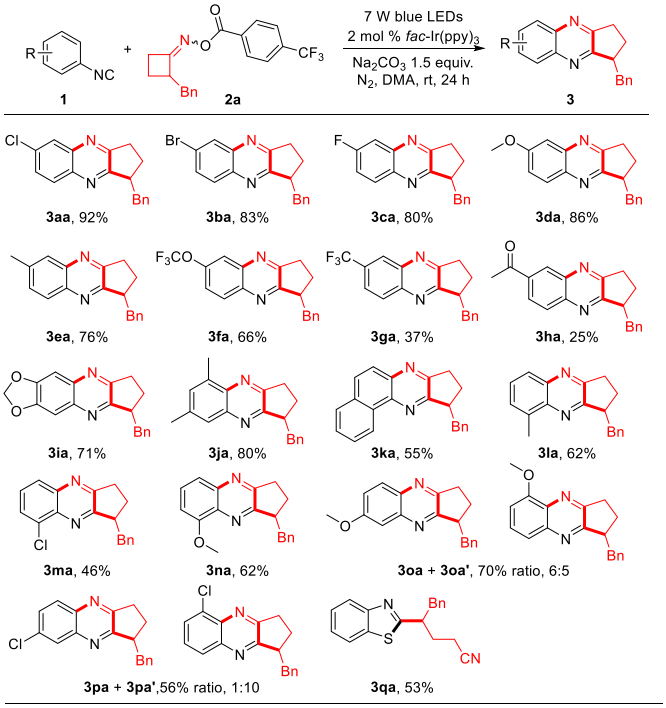


entry	catalyst	solvent	base	yield (%)[b]
1	*fac*-Ir(ppy)$_3$	DMA (3 mL)	Na_2CO_3	41
2	[Ir(ppy)$_2$dtb-bpy]PF_6	DMA (3 mL)	Na_2CO_3	4
3	Ru(bpy)$_3$(PF_6)$_2$	DMA (3 mL)	Na_2CO_3	0
4	Eosin Y	DMA (3 mL)	Na_2CO_3	trace
5	Mes-Acr$^+$$ClO_4^-$	DMA (3 mL)	Na_2CO_3	0
6	*fac*-Ir(ppy)$_3$	DMA (4 mL)	Na_2CO_3	55
7	*fac*-Ir(ppy)$_3$	DMA (5 mL)	Na_2CO_3	83
8	*fac*-Ir(ppy)$_3$	DMA (6 mL)	Na_2CO_3	92
9	*fac*-Ir(ppy)$_3$	DMA (7 mL)	Na_2CO_3	80
10	*fac*-Ir(ppy)$_3$	DMA (8 mL)	Na_2CO_3	66
11	*fac*-Ir(ppy)$_3$	DMF (6 mL)	Na_2CO_3	56
12	*fac*-Ir(ppy)$_3$	DMSO (6 mL)	Na_2CO_3	58
13	*fac*-Ir(ppy)$_3$	DCE (6 mL)	Na_2CO_3	17
14	*fac*-Ir(ppy)$_3$	CH_3CN (6 mL)	Na_2CO_3	34
15	*fac*-Ir(ppy)$_3$	DMA (6 mL)	K_2CO_3	89
16	*fac*-Ir(ppy)$_3$	DMA (6 mL)	Li_2CO_3	87
17	*fac*-Ir(ppy)$_3$	DMA (6 mL)	Na_2HPO_4	71
18	*fac*-Ir(ppy)$_3$	DMA (6 mL)	/	46
19[c]	*fac*-Ir(ppy)$_3$	DMA (6 mL)	Na_2CO_3	0
20	/	DMA (6 mL)	Na_2CO_3	0

[a] Conditions: **1a** (27.5 mg, 0.2 mmol), **2a** (138.9 mg, 0.4 mmol), photocatalyst (2 mol %), solvent, irradiation with a 7 W blue LEDs at room temperature under N_2 atmosphere for 24 h. [b] Isolated yield. [c] Reaction was carried out in the dark.

To investigate the feasibility of our design, we chose 1-chloro-4-isocyanobenzene (**1a**) and 2-benzylcyclobutan-1-one *O*-(4-(trifluoromethyl)benzoyl) oxime (**2a**) as the model substrates to study the radical cascade cyclization reaction. To our delight, the target product 1-benzyl-6-chloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline (**3aa**) was obtained in 41% yield when *fac*-Ir(ppy)$_3$ (2 mol %) was used as a photocatalyst with Na_2CO_3 (1.5 equivalents) as the base in DMA at room temperature for 24 h (**Table 1**, entry 1). A brief screening of commonly used photocatalysts showed that *fac*-Ir(ppy)$_3$ was the most efficient catalyst (**Table 1**, entries 1-5). In accordance with Xiao group's previous study,[8] cyclobutanone oxime esters involved photoreactions were very sensitive to the reaction concentration. The concentration screening of our reaction showed that a 0.03 M of substrate **1a** gave highest yield of 92% (**Table 1**, entries 6-10). Compared to DMA, other solvents such as DMF, DMSO, DCE and CH_3CN significantly diminished the yields (**Table 1**, entries 11-14). Then, we examined several inorganic bases such as K_2CO_3, Li_2CO_3, and Na_2HPO_4, however, no better results were found than with Na_2CO_3 as the base (**Table 1**, entries 15-17). Notably, the base is critical to the reaction efficiency, only a 46% yield was obtained in the absence of the base (**Table 1**, entry 18). Finally, the control experiments demonstrated the indispensability of the visible light and photocatalysts (**Table 1**, entries 19, 20). According to Xiao group's work,[8] acyl moiety on the oxime was important for the reaction and *p*-trifluoromethylbenzoate substrate was superior to its analogues. The same result was obtained in our reaction, C_6H_5CO- and *p*-$NO_2C_6H_4CO$-protected oxime was not active in this reaction.

Scheme 2. Substrates Scope of Isocyanides[a]



[a] Conditions: **1** (0.2 mmol), **2a** (138.9 mg, 0.4 mmol), Na_2CO_3 (31.8 mg, 0.3 mmol), *fac*-Ir(ppy)$_3$ (2.6 mg, 2 mol %), DMA (6 mL), irradiation with a 7 W blue LEDs under N_2 atmosphere at room temperature for 24 h.

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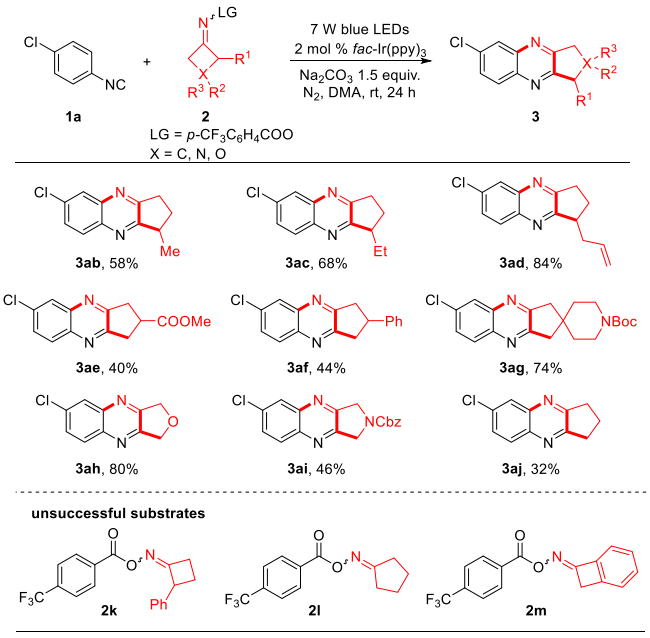
With the optimized reaction conditions in hand, we first investigated the substrate scope of the aryl isonitriles. As the results in **Scheme 2** revealed, a series of different substituted aryl isonitriles underwent this radical cascade cyclization smoothly giving the corresponding products in moderate to good yields. In addition to **3aa**, a range of aryl isonitriles bearing either halogen (Br, F) or electron-donating groups (MeO, Me, CF_3O) at the *para*-position of the phenyl ring were well tolerated, conferring the corresponding products **3ba**-**3fa** with yields in the range of 66% – 86%. However, electron-withdrawing-group-substituted aryl isonitriles had poor reaction efficiency. As a result, *para*-CF_3 and acetyl substituted aryl isonitriles gave the corresponding cyclopenta[*b*]quinoxalines **3ga** and **3ha** in 37% and 25% yields, respectively. This might be attributed to the weak nucleophilicity of this type of aryl isonitriles, which slows down the rate of the desired reaction and increases the possibility of the intermediate being quenched. Disubstituted phenyl isocyanide and naphthalene-derived isocyanides were also successful in this transformation, affording **3ia**, **3ja** and **3ka** in 71%, 80% and 55% yields, respectively. Moderate yields were obtained when 1-isocyano-2-methylbenzene (**1l**), 1-chloro-2-isocyanobenzene (**1m**) and 1-isocyano-2-methoxybenzene (**1n**) were used as substrates (**Scheme 2, 3la-3na**). For the *meta*-OMe-phenyl isocyanide involved reaction, two regioisomers **3oa** and **3oa'** were isolated in a 6:5 ratio in 70% combined yield. And for *meta*-Cl-phenyl isocyanide, **3pa** and **3pa'** were isolated in a 1:10 ratio in 56% combined yield. Interestingly, when (2-isocyanophenyl)(methyl)sulfane were subjected to this reaction, 4-(benzo[*d*]thiazol-2-yl)-5-phenylpentanenitrile (**Scheme 2, 3qa**) was isolated in 53% yield instead of the cyclopenta[*b*]quinoxaline product, indicating that the thiazole ring was much easier to be composed than the cyclopentane.

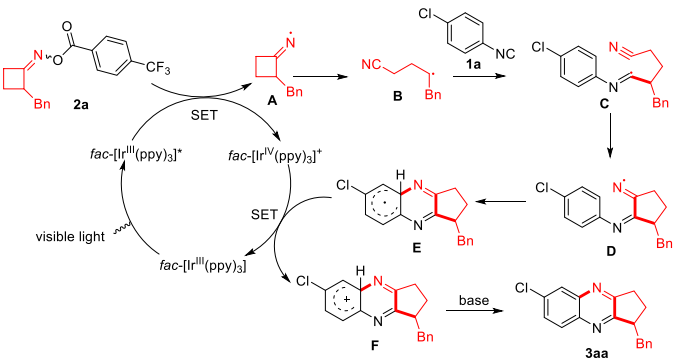
Scheme 3. Substrates Scope of Cyclobutanone Oxime Esters [a]



[a] Conditions: **1a** (27.5 mg, 0.2 mmol), **2** (0.4 mmol), Na_2CO_3 (31.8 mg, 0.3 mmol), *fac*-Ir(ppy)$_3$ (2.6 mg, 2 mol %), DMA (6 mL), irradiation with a 7 W blue LEDs under N_2 atmosphere at room temperature for 24 h.

To further evaluate the utility of this radical cascade cyclization method, a variety of cycloketone oxime esters were employed as substrates under the standard conditions. Apart from **3aa**, cyclobutanone-derived *O*-acyl oximes with methyl, ethyl and allyl groups at the 2-position proved to be compatible for this reaction, giving cyclopenta[*b*]quinoxalines in 58% - 84% yields (**Scheme 3, 3ab-3ad**). However, cyclobutanone-derived *O*-acyl oximes bearing ester group and phenyl ring at the 3-position gave the corresponding products **3ae** and **3af** in lower yields, 40% and 44%, respectively. Happily, the sterically more demanding substrates **2g** with substituent group at the 3-position had a better reaction efficiency affording **3ag** in 74% yield. Moreover, this catalytic system was also compatible for oxetan-3-one and 1-Cbz-3-azetidinone derived *O*-acyl oximes, delivering products **3ah** (80%) and **3ai** (46%), which provide possibilities for this method to synthesize complex bioactive molecules. Notably, unsubstituted cyclobutanone *O*-(4-(trifluoromethyl)benzoyl) oxime also proceeded smoothly to give the product **3aj** in 32% yield. Finally, as listed in **Scheme 3**, **2k, 2l** and **2m** were not suitable for this reaction: compound **2k** decomposed while **2l** and **2m** were inert under the reaction conditions.

Scheme 4. Proposed Mechanism



On the basis of the above experiments and relevant literature,[8, 17] a plausible mechanism is proposed in **Scheme 4**. Initially, irradiation of *fac*-[Ir^{III}(ppy)$_3$] with visible light leads to the formation of an excited state *fac*-[Ir^{III}(ppy)$_3$]* species. An SET from *fac*-[Ir^{III}(ppy)$_3$]* to cyclobutanone oxime esters **2a** results in a reductive N–O bond cleavage of **2a** with the generation of a *fac*-[Ir^{IV}(ppy)$_3$]$^+$ complex and iminyl radical **A**. Then, iminyl radical **A** undergoes a regioselective C–C bond β-scission to form cyanoalkyl radical **B**, which can be captured by aryl isonitriles **1a** to generate a new imidoyl radical **C**. Subsequently, imidoyl radical **C** attaches to cyano group through a intramolecular radical addition resulting in the iminyl radical **D**, and the following intramolecular radical cyclization onto aromatic ring gives the radical intermediate **E**. Afterwards, one-electron oxidation of radical intermediate **E** by *fac*-[Ir^{IV}(ppy)$_3$]$^+$ generates carbocation intermediate **F** and ground-state *fac*-[Ir^{III}(ppy)$_3$], completing the photocatalytic cycle. Finally,

deprotonation assisted by base yields the target product cyclopenta[*b*]quinoxalines **3aa**.

In summary, we have successfully taken the in-situ-formed nitrile (produced by oxime esters) into a visible-light-induced radical cascade cyclization with aryl isonitriles for the synthesis of cyclopenta[*b*]quinoxalines. This reaction features mild conditions, broad functional group tolerance, and a broad substrate scope, providing an efficient approach to the quinoxaline derivatives.

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Conflicts of interest

There are no conflicts to declare.

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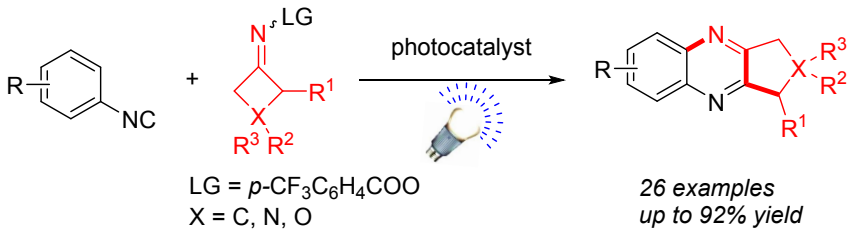

The in-situ-formed nitrile produced by oxime esters was taken into a visible-light-induced radical cascade cyclization with aryl isonitriles.