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Visible-Light Photoredox Catalyzed Double C–H Functionalization: Radical Cascade Cyclization of Ethers with Benzimidazole-Based Cyanamides

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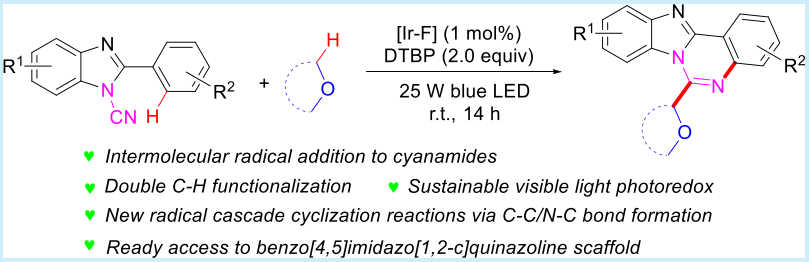

ABSTRACT: A visible-light photoredox catalyzed radical cascade cyclization of simple ethers with cyanamides is developed at room temperature. This strategy involves sequential inert C_{sp3}-H/C_{sp2}-H functionalizations through intermolecular addition reaction of oxyalkyl radicals to *N*-cyano groups followed by radical cyclization of iminyl radicals *in situ* generated with C-2 aryl rings. This method allows for efficient synthesis of tetracyclic benzo[4,5]imidazo[1,2-*c*]quinazolines. Importantly, this is the first example of an intermolecular–intramolecular radical cascade cyclization reaction of cyanamides.

Cyanamide chemistry has been increasingly attracting great interest in the chemists' community due to the versatile reactivities of cyanamides as building blocks[1] for organic synthesis. Thus, cyanamides can be used for nucleophilic additions, cycloadditions, aminocyanation, electrophilic cyanation, and radical reactions. Recently, radical cascade reactions of cyanamides have emerged as a powerful strategy to assemble polycyclic *N*-heterocycle frameworks. Malacria and co-workers pioneered the introduction of *N*-acylcyanamides as viable radical acceptors for the construction of tri- and tetracyclic quinazolinone derivatives (Scheme 1a).[2] The methods typically relied on the toxic tin-based mediators initiated radical generation from iodoaryls,[2a,b] iodovinyls,[2c] azides,[2d] and phenylselenyls.[2e] The Cui group incorporated the cyanamide moiety into unactivated alkenes to develop new radical cascade cyclizations through the alkene difunctionalization strategy using Togni's reagent,[3] phosphine oxides,[4] and 1,3-dicarbonyls[5] as radical precursors (Scheme 1b). Zhu et al. reported radical relay reactions of *N*-cyanamide alkenes to readily access functionalized γ-lactams (Scheme 1c).[6] However, these seminal works are restricted to intramolecular radical reactions of cyanamides. To the best of our knowledge, the intermolecular version of cyanamides is underexplored to date, except with thiyl radical to give a rearranged *N*-acyl isothioureas, rather than thiylated quinazolinones generated via radical cascade cyclization (Scheme 1d).

Photoredox synthesis constitutes a powerful and sustainable tool to form chemical bonds and complex organic molecular architectures.[7] The photoredox catalyzed intramolecular radical additions to the *N*-CN moiety have been disclosed.[8] Our interest in photochemistry[9] and heterocycle synthesis[10] promoted us to radical transformations of *N*-cyanobenzimidazoles. We report herein a visible-light photoredox catalyzed intermolecular radical addition to the *N*-CN part of *N*-cyanobenzimidazoles and subsequent radical cyclization of the iminyl radicals *in situ* generated. Our strategy involves a double C–H functionalization process and enables ready access to tetracyclic products, benzo[4,5]imidazo[1,2-*c*]-quinazolines. Benzimidazoles[11] and quinazolines[12] are privileged structural cores prevalent in natural compounds and bioactive molecules.

In terms of polarity matching, *N*-cyanobenzimidazoles would readily couple with nucleophilic radicals. Ethers is widely used to generate nucleophilic carbon centered radicals through oxidation.[13] We initially chose *N*-cyano-2-phenyl

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Scheme 1. Intra- and Intermolecular Radical Addition to Cyanamides

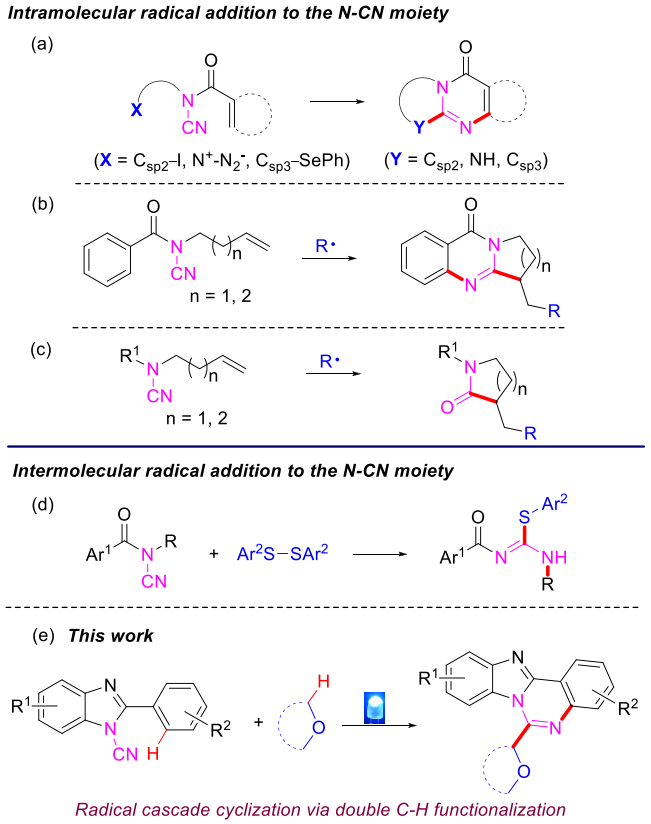
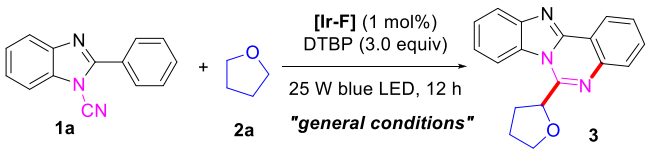


Table 1. Optimization of Reaction Conditions[a]



entry	variation from general conditions	yield (%)[b]
1	none	74
2	$[Ir(dtbbpy)(ppy)_2]PF_6$	70
3	*fac*-$Ir(ppy)_3$	62
4	Eosin Y–H_2	68[c]
5	Eosin Y–Na_2	70[c]
6	Methylene blue	68[c]
7	Riboflavin	68[c]
8	THF (0.25 mL) in DCE (0.25 mL)	62
9	THF (0.25 mL) in EtOAc (0.25 mL)	65
10	TBHP	64
11	TBPB	54
12	1.5 equiv of DTBP	68
13	2.0 equiv of DTBP	81
14	2.5 equiv of DTBP	75
15	for 14 h	85
16	w/o photocatalyst	trace
17	in dark	N.R.

[a]General conditions: **1a** (0.1 mmol), **2a** (0.5 mL), DTBP (3.0 equiv), $Ir[(dFppy)_2(dtbbpy)]PF_6$ ([**Ir–F**]) (1 mol %), r.t., 25 W blue LED (460–470 nm), 12 h. [b]Isolated yields. [c]Photocatalyst (3 mol %). DTBP = di-*tert*-butyl peroxide, DCE = 1,2-dichloroethane, TBHP = *tert*-butyl hydroperoxide (70% solution in water), TBPB = *tert*-butyl peroxyl benzoate, N. R. = no reaction.

benzimidazole (**1a**) and tetrahydrofuran (**2a**) as model substrates using 3.0 equiv of di-*tert*-butyl peroxide (DTBP) as the oxidant for photoredox transformation under irradiation by 25 W blue light LED lamp. An array of photocatalysts, including the extensively studied Ir-/Ru-based complexes and organocatalysts, were screened. All the photocatalysts tested except phenothiazine could promote this photochemical reaction (see the ESI, Table S1). The catalysts $[Ir(dFppy)_2(dtbbpy)]PF_6$ ([**Ir–F**]), $Ir(dtbbpy)(ppy)_2]PF_6$, and *fac*-$Ir(ppy)_3$ (1 mol % loading) afforded good yields of 62–74% (Table 1, entries 1–3). Likewise, the organocatalysts, like Eosin Y series, methylene blue, and riboflavin, achieved comparable efficacies with 3 mol % being used (Table 1, entries 4–7). The use of THF mixed, respectively, with DCE and EtOAc in 1:1 volume ratio, led to slight decrease in the yields (Table 1, entries 8 and 9). It is worth noting that the type of oxidant exerted a significant impact on the reaction efficiency. The peroxides, TBHP, TBPB, and DTBP, could trigger the radical cascade cyclization, with the former being less effective (Table 1, entries 10 and 11). The amount of oxidant was optimized to be 2.0 equiv, and the time of irradiation was kept for 14 h (Table 1, entries 12–15). Notably, the blue light with the wavelength ranging from 420 to 470 nm could efficiently facilitate the transformation (see the ESI, Table S5). Under the optimal conditions, 85% of compound **3** was obtained. Besides, without either photocatalyst or light irradiation, only trace or none of **3** was detected by GC-MS.

Having established the optimal reaction conditions, we turned our attention to exploring the generality of this photoredox process. As is shown in Scheme 2, all the *N*-cyanobenzimidazoles tested could smoothly undergo the visible-light initiated oxidative radical cascade cyclization, providing 6-functionalized tetracyclic benzo[4,5]imidazo[1,2-*c*]quinazolines in moderate to good yields. The substituents on the C-2 aryl rings of benzimidazoles **1**, -Me, -OMe, -F, -Cl, -Br, and $-CF_3$, could be well tolerated in this photochemical oxidative reaction. It is worthwhile to note that the electron-rich groups favored the reaction while the electron-deficient ones diminished the reaction yields. Moreover, it was found that the functional groups located at the *ortho*-, *meta*-, and *para*-position of the benzimidazolyl C-2 aryl ring afforded comparable yields (Scheme 2, for -Me, compounds **4**, **7**, and **10**; for -Cl, compounds **6**, **8**, and **14**), indicating that the steric effect imposed little influence on the reaction efficiency. Notably, this cascade cyclization possessed an excellent regioselectivity, and the *in situ* generated iminyl radicals preferentially attacked the aryl rings at the *para*- position of the substituents with the *meta*-substituted subtrates (Scheme 2, compounds **7**–**9**). Benzimidazoles **1**, with 2,4-dimethyl and 3,5-dimethyl attached at the C-2 aryl ring, reacted well under the standard conditions to furnish compounds **17** and **18** in 82% and 83% yields, respectively. Similarly, compounds **19** and **20** bearing dichloro groups were obtained in 65% and 67% yields, respectively. Furthermore, the introduction of substituents to the fused benzene ring of benzimidazoles enriched the substrate scope with respect to benzimidazoles **1**, with high reaction efficiencies (Scheme 2, compounds **21**–**23**).

Next, other ethers **2** such as 1,3-dioxolane, 1,4-dioxane, and 2-methyltetrahydrofuran, as radical precursors were also explored. To our delight, these substrates delivered their individual cyclization products **24**–**26** in 35–72% yields under

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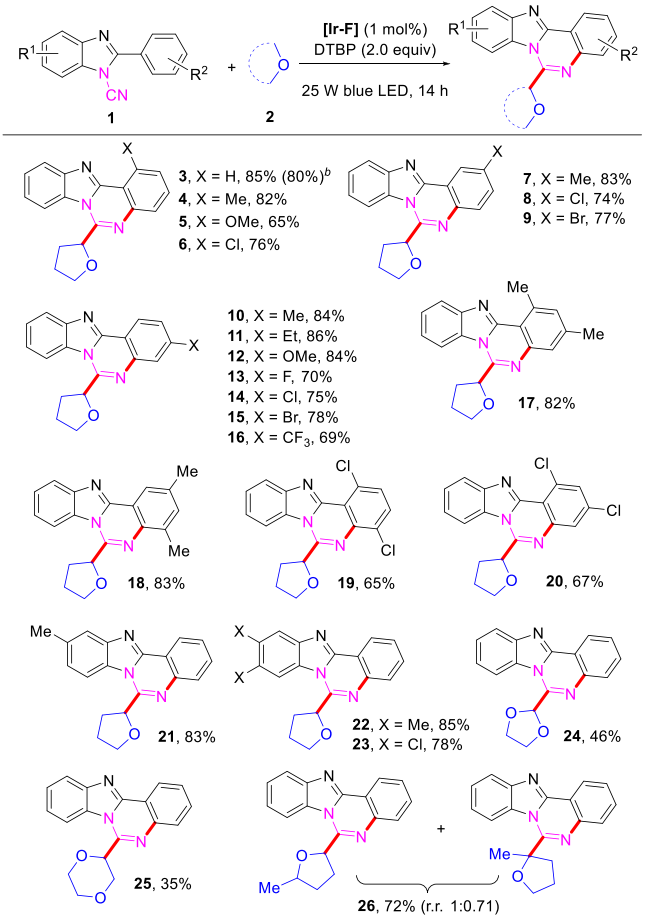
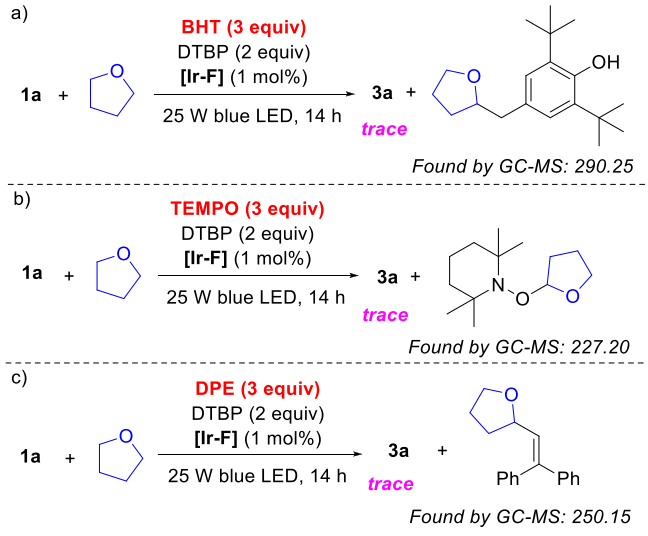
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mL), DTBP (2.0 equiv), [**Ir−F**] (1 mol %), r.t., 25 W blue LED (460−470 nm), 14 h. The r.r. (regioisomeric ratio) determined by GC. [b]Yield for 1 mmol scale.

Scheme 3. Control Experiments



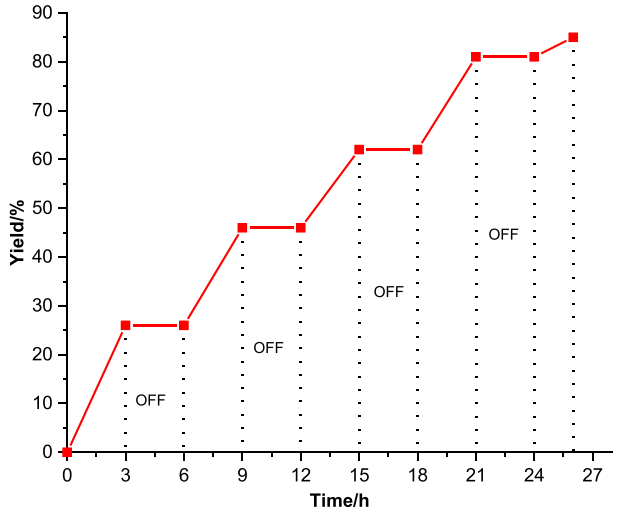


Figure 1. ON/OFF experiments.

the standard conditions. It should be noted that 2-methyltetrahydrofuran gave two inseparable regioisomeric products **26** with a 1:0.7 ratio (determined by GC). Besides, 80% yield of product **3** in a 1 mmol scale verified the applicability of this photochemical method.

To shed light on the plausible mechanism for this novel radical cascade cyclization, a series of control experiments were carried out (Scheme 3). When 3 equiv of the radical inhibitor 2,6-di(*tert*-butyl)-4-methylphenol (BHT) was added under the standard conditions, the reaction was almost completely inhibited, with the possible benzylated tetrahydrofuran being detected by GC-MS (*m*/*e* 290.25) (Scheme 3a). The addition of a commonly used radical trapper, 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, 3 equiv), to the standard reaction system led to only trace of the target product **3**, and also the adduct aminoxylated tetrahydrofuran was found by GC-MS (*m*/*e* 227.20) (Scheme 3b). Furthermore, the adduct 2-(2,2-diphenyl vinyl)tetrahydrofuran (*m*/*e* 250.15) was observed in a considerable amount[14] when the standard reaction was carried out in the presence of 1,1-diphenylethylene (DPE, 3 equiv) (Scheme 3c). These experimental results imply the involvement of radical species in the present transformation.

To preliminarily unveil the role of the photoirradiation, an on/off blue light irradiation experiment was performed (Figure 1). The result shows that continuous exposure to visible light is indispensable to the high reaction efficiency and also indicates that a radical-chain process is unlikely to be a predominant pathway, albeit can not be excluded, for the present photoredox reaction. Furthermore, fluorescence quenching experiments were conducted to ascertain whether the photocatalyst first reacted with DTBP under photoirradiation (see the Supporting Information for details).

On the basis of the above preliminary experimental results combined with the previous literatures,[13d−f,15] a plausible mechanism involved in photoredox catalysis is proposed in Scheme 4. First, the photocatalyst, [**Ir−F**], is excited by blue light irradiation to result in the formation of the excited species, [**Ir−F**]*, which would then reduce the oxidant DTBP to a *tert*-butoxyl radical and a *tert*-butoxyl anion via a single electron transfer (SET) process, along with the generation of a radical cation, $[\mathbf{Ir-F}]^{\bullet+}$. The resultant *tert*-butoxyl radical undergoes hydrogen atom transfer (HAT), selectively abstracting the most hydridic hydrogen atom from tetrahydrofuran to afford a nucleophilic ether carbon-centered radical, R·. Subsequently, the radical R· can participate in intermolecular nucleophilic addition to the cyano group of **1a** to produce an iminyl radical, **A**, which is then transformed into

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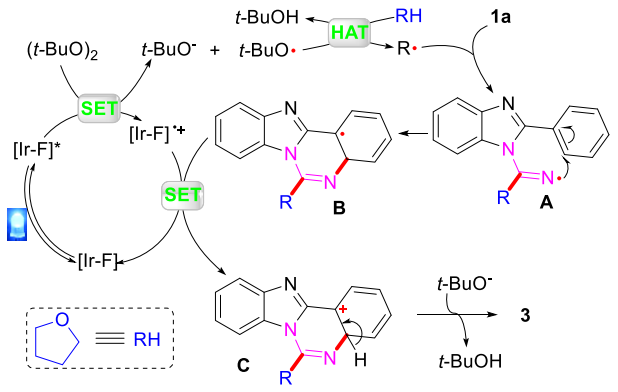
Scheme 4. Plausible Mechanism for Photochemical Radical Cascade Cyclization



the intermediate **B** through radical cyclization. The species **B** would be further oxidized by the $[\mathbf{Ir{-}F}]^{\bullet+}$ *in situ* generated through another SET reaction, thus providing an intermediary cation, **C**, and concomitantly regenerating the Ir-based photocatalyst. Finally, the intermediate **C** deprotonates by the *tert*-butoxyl anion to yield the product **3**.

In conclusion, we have disclosed a radical cascade cyclization reaction of simple ethers with benzimidazole-based cyanamides through visible light photoredox catalyzed double C−H functionalization. The protocol includes intramolecular radical addition of oxyalkyl radicals to the cyano moieties and the subsequent intramolecular cyclization of the iminyl radical *in situ* generated and allows for ready access to benzo[4,5]-imidazo[1,2-*c*]quinazolines. To the best of our knowledge, this is the first example of an intermolecular−intramolecular radical cascade cyclization reaction of cyanamides. Our method will provide an alternative strategy for the construction of imidazoquinazolines from the view of sustainable chemistry and could find its applications in medicinal research and material developments. Extensive investigation on the radical chemistry of benzimidazole-based cyanamides is under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03853.

Experimental details, characterization data for new compounds, copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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