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Visible Light-Induced Metal-Free and Oxidant-Free Radical Cyclization of (2-Isocyanoaryl)(methyl)sulfanes with Ethers

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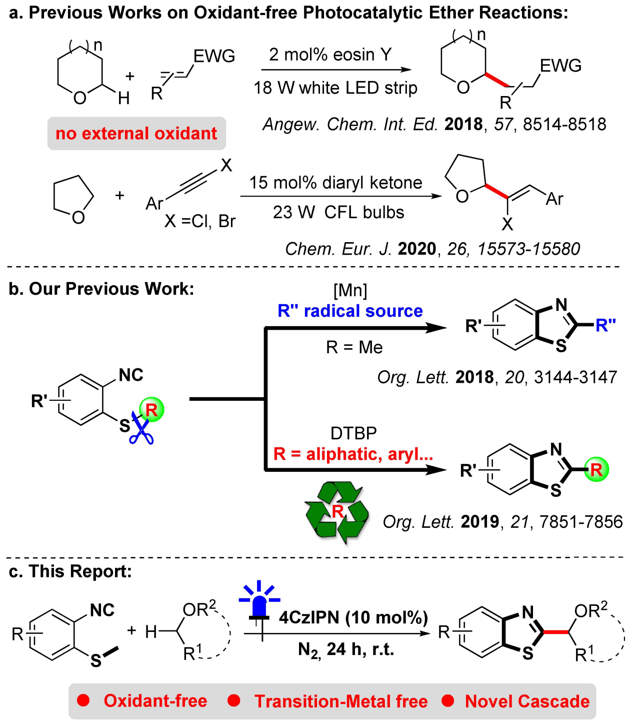
A novel cascade cyclization of (2-isocyanoaryl) (methyl)sulfanes and ethers is developed. With 4CzIPN as a photocatalyst and the irradiation of blue LED light, ether radicals are efficiently generated without adding any oxidant, endowing the strategy with features of oxidant-free, metal-free, mild reaction conditions, and operational simplicity. This strategy provides efficient approach to access various ether-containing benzothiazoles in acceptable to good yields.

Ethers, such as acyclic and cyclic, particularly for 5- and 6-membered cyclic ones, are the core scaffolds of many naturally-occurring products and synthetic pharmaceuticals with a broad spectrum of biological properties. They also serve as versatile synthons in organic synthesis and industrial processes.[1] Given the important role of ether compounds and the development of free radical chemistry, many efforts have been devoted in the way of generating ether radicals. On one hand, some research groups reported various efficient systems based on the combination of transition metal complexes and oxidants, such as Fe/TBHP, Cu/TBHP, Pd/TBHP, and Ni/DTBP.[2] On the other hand, metal-free strategies have also been established albeit using stoichiometric synthetic oxidants, such as DTBP, TBPB, TBHP, BPO, and H_2O_2.[3] These reported systems generally require high reaction temperatures along with excess amount of oxidants. Alternatively, the blooming of photocatalysis provides an efficient and mild synthetic method for the generation of ether radicals, which appealed the extensive attentions from synthetic chemists. For examples, photosensitizers of iridium/ ruthenium complexes, acridine red, and eosin Y had been utilized with organic oxidants to generate ether radicals upon visible light irradiation.[4]

Notice that, among above-mentioned protocols, ether radicals would not be produced without adding extra synthetic oxidants. It is well-known that synthetic oxidants are deemed as environmentally unfriendly and dangerous due to their instability. For limited examples of oxidant-free strategy, Doyle's and Molander's groups have independently reported nickel and iridium-based photoredox catalyzed coupling of ethers and aryl bromides/chlorides.[5] Gratifyingly, the bottleneck on using transition metals was broken by the Wu's group in 2018.[6] In their study, the coupling of ether substrates and electron-deficient olefins were enabled by an eosin Y-based photocatalytic hydrogen-atom transfer (HAT) strategy (Scheme 1a), where the direct HAT process between ether and photoexcited eosin-Y completely replaced the role of an external oxidant. In a latest case, Hashmi *et al.* found that visible light excited diaryl ketones could selectively abstract hydrogen atom from saturated ethers, which exhibited excellent reactivities toward chloro- and bromo-alkynes.[7]

Isocyanides demonstrate great synthetic potential as valuable building blocks in the preparation of biologically and pharmaceutically active nitrogen-containing molecules.[8] Since



Scheme 1. Previous Works on Oxidant-free Photocatalytic Ether Reactions (a); Our Previous Work (b); This Report (c).

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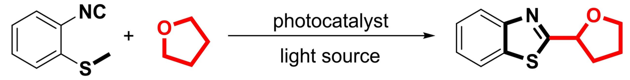
2018, our group have revealed that isocyanide moieties can be used as ideal radical acceptors in the process of radical C(sp^2/sp^3)-S cleavage mediated by manganese salt or synthetic oxidant (DTBP) (Scheme 1b).[9] Inspired by the aforementioned studies on ether functionalization, we envisioned that ether radicals generated from visible light irradiation would be ideally compatible with the imidoyl radical formation and C–S cleavage.[4f,8,9a] With our continuing interest in carbon-heteroatom bond cleavage and radical-involved reactions,[10] we herein disclosed a novel visible light-induced oxidant-free and metal-free cascade cyclization of 2-isocyanoaryl thioethers with ethers, providing an expeditious approach to access ether-functionalized benzo-thiazoles (Scheme 1c).

We commenced the exploration with (2-isocyanophenyl)(methyl)sulfane (**1a**) and THF (**2a**) as the model substrates for optimizing reaction conditions. To our delight, with eosin Y as a photocatalyst, the model reaction underwent smoothly to deliver 2-(tetrahydrofuran-2-yl)benzo[*d*]thiazole (**3a**) in 49% isolated yield after being irradiated by 3 W white LEDs for 24 h under a nitrogen atmosphere. (Table 1, entry 1). Spurred by this preliminary result, systematically screenings of the conditions were performed to enhance the efficiency. Both organic dyes and transition metal photo-sensitizers were tested as photocatalysts, including rose bengal, fluorecein, Mes-Acr$^+$, rhodamine B, *fac*-Ir(ppy)$_3$ and Ru(bpy)$_3$Cl$_2$, giving yields ranging from 0–53% (Table 1, entries 2–7). When it came to 1,2,3,5-tetrakis-(carbazol-9-yl)-4,6-dicyanobenzene (**4CzIPN**), the yield of desired product **3a** could be improved to 55% (Table 1, entry 8). Moreover, the wavelength of light sources dramatically affected the reaction efficiency. For instance, the reaction irradiated by blue LEDs delivered target product in 66% yield, green and red LEDs, however, were proved to be useless (entries 9–11). The loadings of photocatalyst were also considered as key parameters for the cascade reaction. When lower or higher dosage of catalyst were used, no competitive yields would be obtained (entries 12 and 13). It is worthy to mention that the presence of oxygen might quench an excited photocatalyst intermediates[11] thus totally inhibiting the cascade reactions either under air or oxygen atmosphere (entry 14). No conversion could be observed for reactions in the dark or with conventional heating (entry 15). The target product also can be obtained with lower yield when we attempted to reduce the amount of THF (1.0 mL) or use a cosolvent. The above results collectively indicate that blue light, **4CzIPN**, and nitrogen atmosphere are all essential to achieve the cascade reaction.

Table 1. Visible Light-Induced Cascade Reaction of (2-isocyanophenyl)(methyl) sulfane with Ether: Conditions Screening.[a]



1a **2a** **3a**

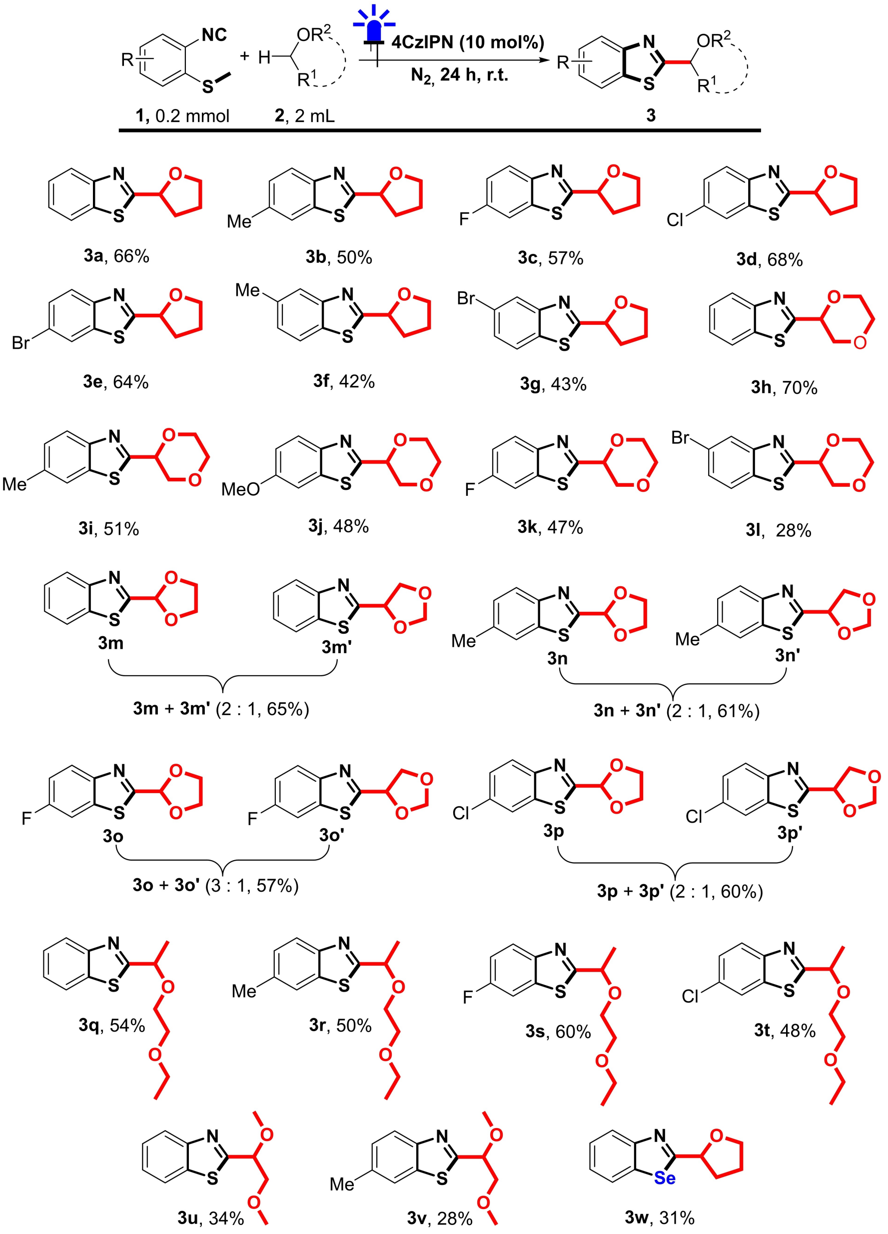
Entry	Photocatalyst	Light Source	Yield [%][b]
1	eosin Y	white LED	49
2	rose bengal	white LED	0
3	fluorecein	white LED	0
4	Mes-Acr$^+$	white LED	50
5	rhodamine B	white LED	0
6	*fac*-Ir(ppy)$_3$	white LED	53
7	Ru(bpy)$_3$Cl$_2$	white LED	13
8	4CzIPN	white LED	55
9	4CzIPN	blue LED	66
10	4CzIPN	green LED	0
11	4CzIPN	red LED	0
12	4CzIPN	blue LED	58[c]
13	4CzIPN	blue LED	60[d]
14	4CzIPN	blue LED	0[e], 0[f]
15	4CzIPN	blue LED	0[g], 0[h]

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (2.0 mL) and 10 mol% photocatalyst were irradiated by 3 W Blue LEDs (450-455 nm) under N$_2$ atmosphere for 24 h at room temperature. [b] Isolated yield. [c] 5 mol% 4CzIPN. [d] 15 mol% 4CzIPN. [e] under oxygen atmosphere. [f] under air. [g] in dark. [h] in dark and heated up to 50 °C.

After establishing the optimal conditions [**1a** (0.20 mmol), 4CzIPN (10 mol%) in 2 mL THF irradiated by 3 W blue LEDs for 24 h under N$_2$ atmosphere], we subsequently started to explore the substrate scope for the cascade cyclization reactions by examining various isocyanides **1** and ethers **2** (Scheme 2). Initially, isocyano-aryl thioethers attached with variety of functional groups were selected to react with THF and 1,4-dioxane under the optimal conditions. Both electron-rich groups (–Me, –OMe) and electron-poor groups (–F, –Cl, –Br) were well tolerated in the present reactions and smoothly led to the corresponding products (**3a**–**3k**) in medium to good yields (42–70%). Notably, halide substituent Br on both 4- and 5- positions of the phenyl rings was found to be suitable in this transformation (**3e**, **3g** and **3l**), although the former one giving relatively low yields. Moreover, the synthetic application of this methodology was further extended to 1,3-dioxolane, and a variety of substituted isocyanides performed well to afford the corresponding products in combined yields ranging from 57%–65% (**3m/m′**–**3p/p′**). To be noted, the products gave certain preferences of C2 selectivity with ratios of 2:1–3:1 over C4 position.

On the other hand, the commonly used acyclic ethers were further examined in this transformation. The reactions of ethylene glycol diethyl ether with isocyanoaryl thioether and other functionalized isocyanoaryl thioethers proceeded smoothly to give the desired products in good yields (**3q**–**3t**, 48–60%). 1,2-Dimethoxyethane also reacted in the system but impaired the efficiency a little furnishing **3u** and **3v** in 34% and 28% respectively. In addition, it was found that when the 2-position of isocyanide is substituted by selenium, it can also react with THF under the template reaction conditions to obtain the target product **3w** in 31% yield.

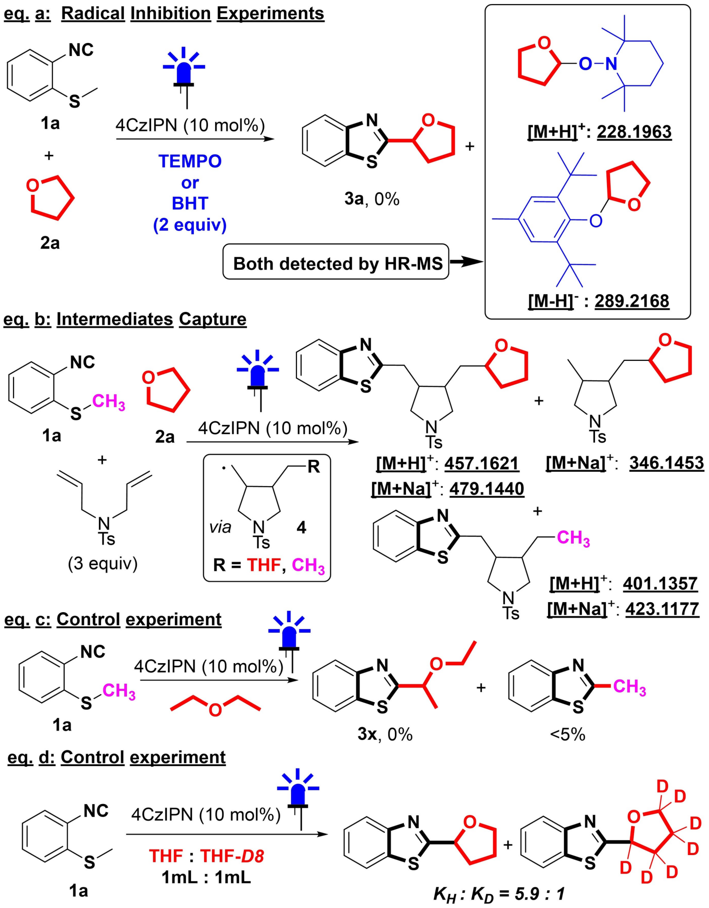
To gain further insight of the product-forming profile, several mechanistic experiments were carried out (Scheme 3). When radical scavengers of either TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol) were added into reaction mixtures under the optimized reaction conditions, the cascade cyclizations were entirely inhibited. It was indicated that the photo-induced THF radical was *in-situ* quenched by TEMPO and BHT, which could be confirmed by HR-MS analysis (eq. a, see details in the Supporting Information). In order to capture more reaction intermediates, the standard system was treated with tosylated diallylamine. As shown in eq. b, THF radical, methyl radical and benzothiazole



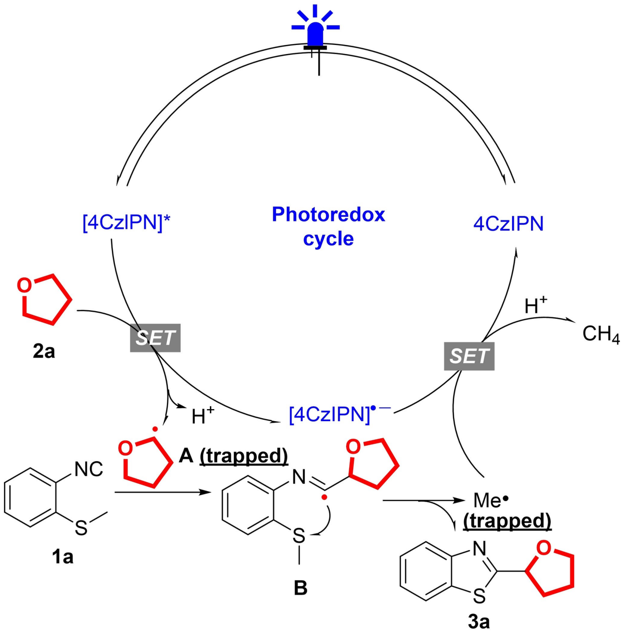
Scheme 2. Reaction conditions: **1** (0.20 mmol), **2** (2.0 mL) and 10 mol% 4CzIPN were irradiated by 3 W Blue LEDs under N_2 atmosphere for 24 h at room temperature. Isolated yields reported.

moiety were successfully trapped and the related adducts were detected by HR-MS as well. Notably, based on our previous research,[9] the capture of benzothiazole moiety does not indicate the formation of a benzo-thiazole radical, but derives from cascade cyclizations of **1 a** and intermediate **4**. A negative control experiment in ethyl ether instead of THF strongly supported that the cascade reaction should be trigged by an ether radical, while the methyl radical is lack of competitiveness (eq. c). Finally, a significant kinetic isotope effect ($K_H/K_D = 5.9$) was recorded in the process, that cleavage of α-C(sp3)–H in THF should be involved in the rate-determining step (eq. d, see details in the Supporting Information).

Based on the results of mechanistic studies and the literature reports,[4f,9,12] a cyclization mechanism was proposed in Scheme 4. First, photoexcitation of **4CzIPN** to its excited state renders **4CzIPN*** under the irradiation of visible light, after which single electron transfer (SET) from THF (**2 a**) to **4CzIPN*** produced an α-oxy radical **A** and **4CzIPN**$^{\bullet-}$. Subsequently, radical **A** reacts with **1 a** to form an imidoyl radical **B**, which undergoes intermolecular cyclization to afford the final product **3 a** along with the release of a methyl radical. Finally, the methyl radical combines with the proton to form methane radical cation, and methane radical cation to form methane under the action of the catalyst anion, and led to an oxidative quenching



Scheme 3. Mechanism Studies.



Scheme 4. Plausible Mechanism.

process to achieve the regeneration of **4CzIPN**. Notably, A small amount of byproduct 2-methylbenzo[d]thiazole is produced.

In summary, we have established a novel cascade cyclization of (2-isocyanoaryl)(methyl)sulfanes and ethers. With **4CzIPN** as a photocatalyst under the irradiation of blue LEDs light, ether radicals were efficiently generated without adding any oxidant, endowing the reaction with green features of oxidant-free, metal-free, mild reaction conditions and operational simplicity. Diverse range of ether-containing benzothiazoles were afforded in acceptable to good yields. Antifungal test of the products and further application of this strategy into the synthesis of complicated bioactive molecules is undergoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Benzothiazoles · Ether radical · Metal-free · Oxidant-free · Visible light catalysis

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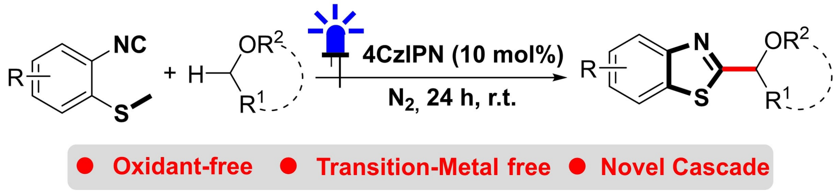

A novel visible light-induced oxidant-free and metal-free cascade cyclization of 2-isocyanoaryl thioethers with ethers has been established, which provides an expeditious approach to access ether-functionalized benzothiazoles in acceptable to good yields. The obtained products combine benzothiazole with ether and represent key structural motifs of a large of biologically active molecules in medicinal chemistry.

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Visible Light-Induced Metal-Free and Oxidant-Free Radical Cyclization of (2-Isocyanoaryl)(methyl) sulfanes with Ethers