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External photocatalyst-free C-H alkylation of *N*-sulfonyl ketimines with alkanes under visible light

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ABSTRACT

A simple, practical and eco-friendly visible light-induced alkylation of *N*-sulfonyl ketamine under metal-, additive-, external photocatalyst-free conditions was developed. This photocatalytic method utilized low cost and abundant alkanes as the atom economy alkyl sources with H_2O_2 as the environmentally beneficial oxidant, allowing for the efficient construction of diverse valuable 4-alkylated sulfonyl ketamines. The *N*-sulfonyl ketamine played a dual role of reactant and photocatalyst, thus simplifying the reaction system.

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Visible light photosynthesis has emerged as an indispensable powerful tool in green organic synthesis, which utilizes light as a source of clean energy to promote carbon-carbon/heteroatom bond formation under eco-friendly and mild conditions [1–5]. A broad range of photocatalytic organo-functional group transformations have been established over the past years [6–22]. However, most of these processes depended heavily on precious ruthenium(II)/iridium(III) complexes or elaborate organic dyes [23], which not only increased manufacture costs but also caused environmental concerns. As a consequence, it is highly desirable to develop sustainable visible-light induced reactions without harmful photocatalysts.

Cyclic *N*-sulfonyl ketamine and its derivatives are broadly distributed in numerous bioactive molecules and synthetic pharmaceuticals [24,25]. They also serve as versatile and powerful building blocks and synthetic intermediates in organic synthesis [26–31]. Consequently, their synthesis and functionalization have given rise to much interest from the synthetic community [32–38]. Among various known *N*-sulfonyl ketamine derivatives, 4-alkylated sulfonyl ketamine has attracted widespread attention due to their diverse biological activities and pharmacological properties. In 2021, Liu and co-workers developed the $AgNO_3$-catalyzed decarboxylative alkylation of sulfonyl ketamine with aliphatic carboxylic acids for the synthesis of 4-alkylated sulfonyl ketamines (Scheme 1a) [39]. Although this method exhibited its individual advantages, excess inorganic oxidant and transition-metal catalyst are required, causing the problem of the removal of inorganic salts/residual transition metal in the terminal products which limits their applications in pharmaceutical synthesis and fine chemicals. Therefore, developing a metal-free and practical methodology for the synthesis of 4-alkylated sulfonyl ketamines is highly desired.

Alkanes are widely exiting in nature and regarded as the most attractive alkyl source for alkylation reactions. Given the environmental friendliness of photocatalysis, a series of visible-light induced alkylations with alkanes have been developed over the past years [40–49]. Despite these remarkable advances, however, the efficiency and practicability of these methods are compromised by the required additional photocatalysts and/or stoichiometric additives. Hydrogen peroxide (H_2O_2) is a low cost, convenient and suitable green alternative to traditional oxidizing agents [50]. In the oxidative reactions, H_2O_2 is reduced to environmentally benign water, which does not complicate product isolation [51–56]. As part of our continued efforts on green organic synthesis, we herein report an efficient and green approach for the synthesis of 4-alkylated sulfonyl ketamines through visible light-indecued alkylation of *N*-sulfonyl ketamines with alkanes in the presence of H_2O_2 as the sole oxidant under transition metal-, external photocatalyst- and additive-free conditions (Scheme 1b).

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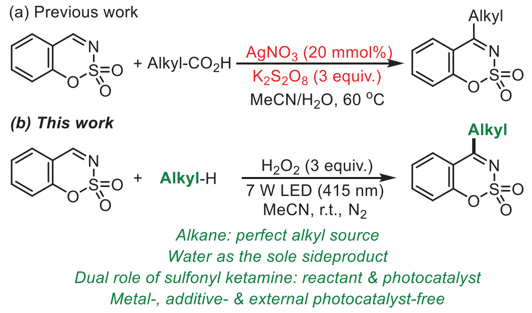
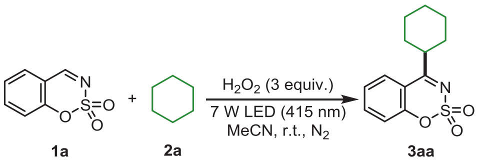


Scheme 1. Synthesis of 4-alkylated *N*-sulfonyl ketamines.

Table 1
Optimization of reaction conditions.[a]



Entry	Variation from the standard conditions	Yield (%)[b]
1	None	92
2	THF instead of MeCN	N.R.
3	DCM instead of MeCN	N.R.
4	DMF instead of MeCN	N.R.
5	DMSO instead of MeCN	N.R.
6	EtOH instead of MeCN	trace
7	EtOAc instead of MeCN	trace
8	405 nm instead of 415 nm	70
9	425 nm instead of 415 nm	59
10	Air instead of N_2	N.D.
11	Without H_2O_2 or light	N.R.

[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), H_2O_2 (0.6 mmol), MeCN (2 mL), 7 W LED (415 nm), N_2, room temperature. N.R. = no reaction.

[b] Estimated by GC–MS using dodecane as the internal reference.

At the outset of our investigations, *N*-sulfonyl ketamine (**1a**) and cyclohexane (**2a**) were chosen as model substrates to optimize the reaction conditions. To our delight, conducting the reaction with H_2O_2 (3 equiv.) as the sole oxidant in MeCN with a 415 nm LED (7 W) irradiation under nitrogen gave the desired product **3aa** in 92% yield. The solvent effect played an important role in the photocatalytic process. Changing the solvent from MeCN to THF, DCM, DMF or DMSO led to the decomposition of **1a** (entries 2–5). EtOH or EtOAc gave a trace amount of **3aa** and the starting material **1a** was nearly recovered (entries 6 and 7). Changing the LED light source with different wavelengths diminished the reaction yield (entries 8 and 9). The reaction gave an unidentified complex mixture under an air atmosphere (entry 10). Without H_2O_2 or light, no reaction was observed (entry 11).

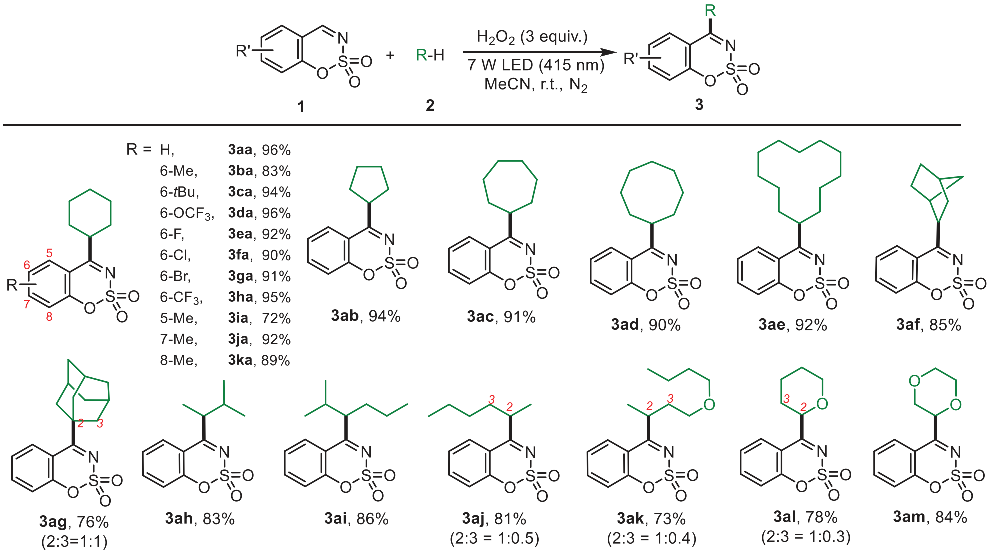
With the optimum reaction conditions established (Table 1, entry 1), the scope of the photocatalytic alkylation with respect to both *N*-sulfonyl ketimines (**1**) and alkanes (**2**) was evaluated. As shown in Scheme 2, good to excellent isolated yields were obtained for *N*-sulfonyl ketimines containing electron-neutral (**3aa**), electron-rich (**3ba-3da**) and electron-deficient groups (**3ea-3ha**) on the phenyl ring. In addition, the methyl substituent at each position of the benzene ring of substrates **1** had no significant influence on the reaction outcome, producing the desired products (**3ia-3ka**) in high yields. The reactions with five-membered or seven-membered cyclic aldimine as the substrates led to no formation of the desired products and the majority recovery of the cyclic aldimine substrates. Subsequently, the scope of this alkylation with respect to alkanes was explored. A series of cycloalkanes reacted with **1a** to deliver the target products (**3ab-3ae**) in good yields. Pleasingly, both bulky sterically norbornane and adamantane underwent the transformation smooth to provide products **3af** and **3ag** in 85% and 76% yields, respectively. The linear alkanes were also suitable substrates for this transformation, delivering the desired products (**3ah-3ak**) in good yields. The regiomeric ratios of alkylated products at different positions of alkanes were also investigated, and the results showed that the regioselectivities depended on stabilities of the corresponding generated carbon radicals and quantities of hydrogens with a same chemical environment. Furthermore, ether compounds, such as tetrahydro-2*H*-pyran and 1,4-dioxane, also underwent the alkylation reaction, generating product **3al** and **3am** in 78% and 84% yields, respectively. However, no desired product was detected with tetrahydrofuran as the alkyl source.

To prove the practicability of the photocatalytic alkylation reaction, a gram-scale reaction was performed by employing substrate **1a** (5 mmol) and alkane **2a** under the modified reaction conditions. Pleasingly, a good isolated yield (87%, 1.15 g) comparable to that of the small-scale experiment was obtained (Scheme 3).

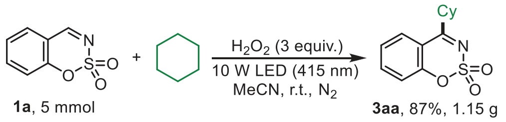
To gain more insight into the reaction mechanism, the radical-trapping experiments, kinetic isotope effect (KIE) experiments, visible-light on/off experiments and UV–vis absorption analysis were carried out. Firstly, the current reaction was completely inhibited with TEMPO or 1,1-diphenylethylene as the radical scavenger under standard conditions. Both the cyclohexyl-TEMPO adduct **4aa** and cyclohexyl-diphenylethylene adduct **4ab** were detected by GC-MS (Scheme 4a), confirming that the cyclohexyl radical was the key intermediate in this reaction. Second, KIE was investigated with regards to the $C(sp^3)$–H/D bonds for the cyclohexane. A clear KIE value of 2.8 was detected in a 1:1 mixture of **2a** and **2a-d$_{11}$** (Scheme 4b), indicating that cleavage of the $C(sp^3)$–H bond in alkane **2** might be the rate-limiting step. The result of turn-on/off light irradiation experiment suggested that the continuous visible-light irradiation was indispensable for this transformation. In addition, a low quantum yield (1.05%) was obtained through chemical actinometry (for details see Supporting information), excluding the possibility of radical propagation pathway. The results of UV–vis absorption spectra (for details see Supporting information) revealed that the substrate **1a** and product **3aa** could absorb visible light and serve as the photosensitizer [57].

Inspired by these observations and previous reports [39,40,58], a possible mechanism for the external photocatalyst-free visible light-induced alkylation was depicted in Scheme 5. Photoexcitation by 415 nm light endowed ground-state *N*-sulfonyl ketamine (**1a**) with highly reducing potential in its excited state [**1a**]*, allowing for single-electron reduction of H_2O_2 to form a hydroxyl radical ($OH^\bullet$), a hydroxyl anion (OH^-) along with generation of **1a** radical cation [**1a**]$^{\bullet+}$. Subsequently, a hydrogen atom transfer from cyclohexane (**2a**) to $OH^\bullet$ led to the formation of cyclohexyl radical ($Cy^\bullet$), which attacked **1a** to form the N-center radical **IM1**, followed by 1,2-H shift to deliver the C-center radical **IM2**. The [**1a**]$^{\bullet+}$ oxidized the intermediate **IM2** to give the carbocation intermediate **IM3** along with the re-generation of ground-state **1a**. Ultimately, the desired product **3aa** was obtained by the deprotonation of **IM3** with the assistance of OH^-. In addition, the product **3aa** could also serve as the photocatalyst to participate the photo-catalytic cycle.

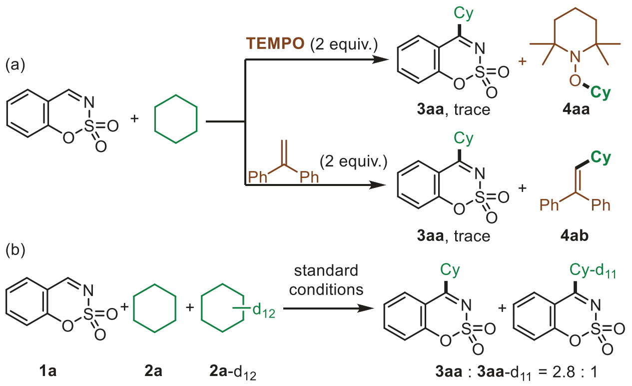
To summarize, a simple, practical and sustainable method for the synthesis of alkylated sulfonyl ketamines though visible-light induced alkylation of *N*-sulfonyl ketamine with alkanes in the presence of H_2O_2 as the sole oxidant was first developed. In sharp contrast to the previous protocol, the present reaction usedvisible light as the clean energy source and cheap alkanes as the atom economy alkylating agent, proceeding without any metal, additive or external photocatalyst and generating environmentally benign water as the sole side-product. Due to the natural abundance of cheap alkanes, good to excellent yields, strong scalability and simple opera-



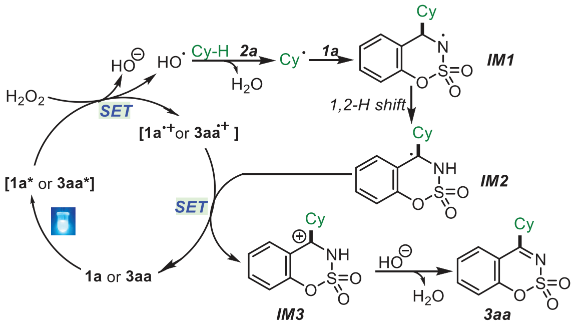
Scheme 2. Reaction scope. Conditions: **1** (0.2 mmol), **2** (0.6 mmol), H_2O_2 (0.6 mmol), MeCN (2 mL), 7 W LED (415 nm), N_2, room temperature.



Scheme 3. Gram-scale synthesis of **3aa**.



Scheme 4. Mechanistic investigations.



Scheme 5. Plausible reaction mechanism.

tion procedures, clean and mild conditions, the current reaction is expected to be widely applied in pharmaceutical industry (Fig. 1).

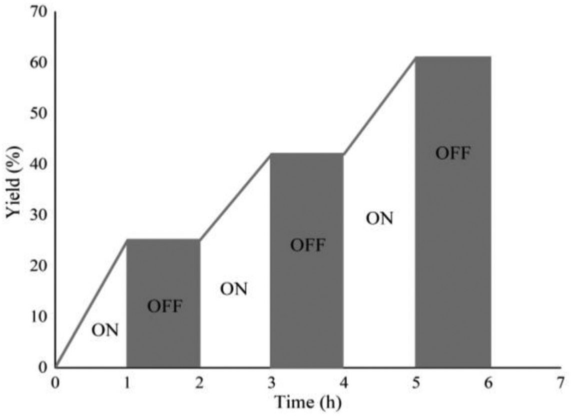


Fig. 1. Turn-on/off light irradiation experiment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108509.

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