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A Desulfurative Strategy for the Generation of Alkyl Radicals Enabled by Visible-Light Photoredox Catalysis

*Fei Xue,[†] Falu Wang,[†] Jiazhen Liu, Jiamei Di, Qi Liao, Huifang Lu, Min Zhu, Liping He, Huan He, Dan Zhang, Hao Song, Xiao-Yu Liu, and Yong Qin**

Abstract: *Herein, we present a new desulfurative protocol for generating primary, secondary and tertiary alkyl radicals via visible-light photoredox catalysis. A process that involves the generation of N-centered radicals from sulfinamide intermediates, followed by subsequent fragmentation, is critical to forming the corresponding alkyl radical species. This strategy has been successfully applied to conjugate addition reactions that features mild reaction conditions, broad substrate scope (>60 examples), and good functional-group tolerance.*

Radicals play a significant role in a variety of chemical transformations that have influenced and shaped the development of organic synthesis.[1] Today, one of the challenges of radical chemistry is identifying efficient ways to generate radicals under mild conditions. Methods for accessing alkyl radicals were greatly improved by the development of visible-light photoredox catalysis in the past few years.[2] Functional groups such as carboxylic acids,[3] oxalates,[4] Katritzky salts,[5] halides,[6] organoboron[7] and organosilicon compounds,[8] as well as their derivatives have proven to be good precursors for the generation of alkyl radicals under light-mediated conditions (Figure 1). The resulting alkyl radical species can be involved in an array of functionalization processes, leading to the formation of increased molecular complexity and diversity in a selective and environmentally benign manner.

Thiols and sulfides are important reagents and intermediates commonly used in organic, bioorganic, and material chemistry.[9] As mentioned above, while various functional groups have been demonstrated to serve as notable radical precursors, examples of generating alkyl radical intermediates via desulfurative approaches under visible-light photocatalytic conditions are rare. Most previous reports using sulfones,[10] sulfinates,[11] sulfonium salts,[12] or sulfonyl chlorides[13] to form carbon-centered radicals are limited to fluoroalkyl radical species, especially trifluoromethyl (CF_3) radicals (Figure 1). In 1978, Kellogg *et al.* first reported a reductive desulfuration of sulfonium salts to afford the corresponding alkanes via alkyl radical intermediates under photocatalytic conditions.[14] Very recently, the Li group developed a protocol for using sulfone compounds as alkyl radical source with UV light irradiation.[15] Knauber and co-workers have also demonstrated that sulfinate salts can be used to generate alkyl radicals and undergo photoredox cross-coupling reactions.[16] However, these known methods suffer from poor reaction generality,[14] the necessity of UV light,[15] or generally low reaction yields.[16] Thus, the development of more efficient ways to generate alkyl radicals from thiol or sulfide derivatives and the expansion of the synthetic utility of such methods remains desirable.

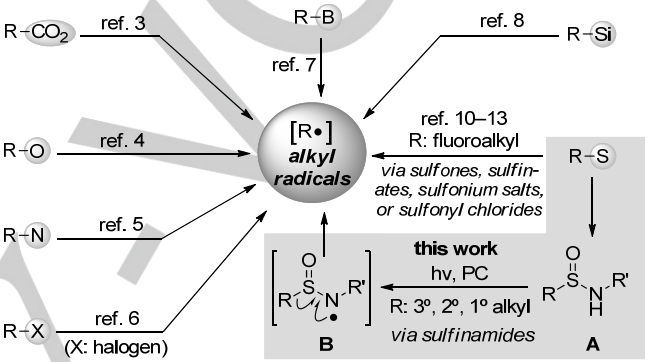

Figure 1. Visible-light photocatalytic generation of alkyl radicals from various precursors.

Recently, in our studies of *N*-centered radicals,[17] we found that *N*-acyl alkyl-sulfinamides (**A**, Figure 1) can be used to generate alkyl radicals via visible-light-mediated desulfuration. These reagents can be easily prepared from thiol or sulfide compounds.[18] As illustrated in Figure 1, upon subjection of sulfinamides (**A**) to a base and photoredox catalyst with visible light irradiation, the *N*-centered radical intermediates (**B**) would be first generated and subsequently undergo fragmentation, thus yielding the corresponding alkyl radicals. Herein, we report the synthetic utility and mechanistic insights of this unique process.

We first prepared a series of *N*-acyl *tert*-butyl-sulfinamides (Figure 1, compound **A**, R = *t*-Bu) to explore their ability to generate alkyl radicals under visible-light photocatalysis. In our initial experiments, *N*-benzoyl *tert*-butyl-sulfinamide **1** was observed to be the superior precursor among the tested sulfinamides.[18] A brief evaluation of photocatalysts showed that $[Ir(ppy)_2(dtbbpy)]PF_6$ was superior over others [e.g., $Ru(bpy)_3Cl_2 \cdot 6H_2O$, $Ir(ppy)_3$, etc]. Cyclic voltammetry (CV) of *N*-benzoyl *tert*-butyl-sulfinamide **1** demonstrated its redox potential at +0.43 V and +0.66 V, suggesting that the visible-light-excited photocatalyst $*Ir(ppy)_2(dtbbpy)^+$ ($E_{1/2}$ = +0.66 V vs SCE in MeCN) is active enough for the first single-electron transfer (SET) oxidation.[19] The conjugate addition reaction between **1** and diethyl 2-ethylidenemalonate (**2**) occurred in the presence of $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%) and K_2HPO_4 (4 equiv) in tetrahydrofuran under the irradiation of 8 W blue LED strips at 40 ºC, affording adduct **3** in 55% yield in 8 h (entry 1, Table 1). A survey of different light sources (entries 2–4) indicated that the reaction was more effective and showed an improved yield of

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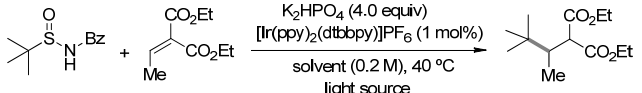
74% within 3 h when using 34 W blue LEDs (entry 4). Solvent screening indicated that acetone was the best solvent and gave the highest yield of 90% (entries 5–9). Reducing the equivalents of base (K_2HPO_4) from 4.0 equiv to 2.0 equiv required a longer reaction time (48 h) and resulted in a decreased yield (65% yield, entry 10). Additionally, the equivalents of **1** also influenced the reaction results (entries 9, 11–13); slightly reducing the loading of **1** to 1.8 equiv delivered comparable efficacy (88%, entry 11) to that obtained when using 2.0 equiv (90%, entry 9), whereas using 1.2 equiv led to significantly diminished yield (69%, entry 13).

Table 1. Optimization of the Reaction Conditions[a]



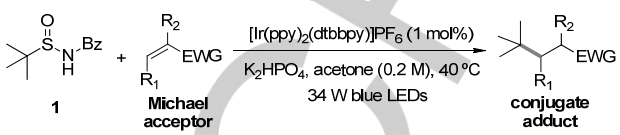
1 **2** (1.0 equiv) **3**

entry	light source	equiv of **1**	solvent	yield
1	8 W blue LEDs	2.0	THF	55%
2	15 W white LEDs	2.0	THF	56%
3	26 W CFL	2.0	THF	40%
4	34 W blue LEDs	2.0	THF	74%
5	34 W blue LEDs	2.0	CH_2Cl_2	83%
6	34 W blue LEDs	2.0	PhMe	49%
7	34 W blue LEDs	2.0	MeCN	66%
8	34 W blue LEDs	2.0	DMSO	31%
9	34 W blue LEDs	2.0	acetone	90%
10[b]	34 W blue LEDs	2.0	acetone	65%
11[c]	34 W blue LEDs	1.8	acetone	88%
12[d]	34 W blue LEDs	1.6	acetone	84%
13[e]	34 W blue LEDs	1.2	acetone	69%

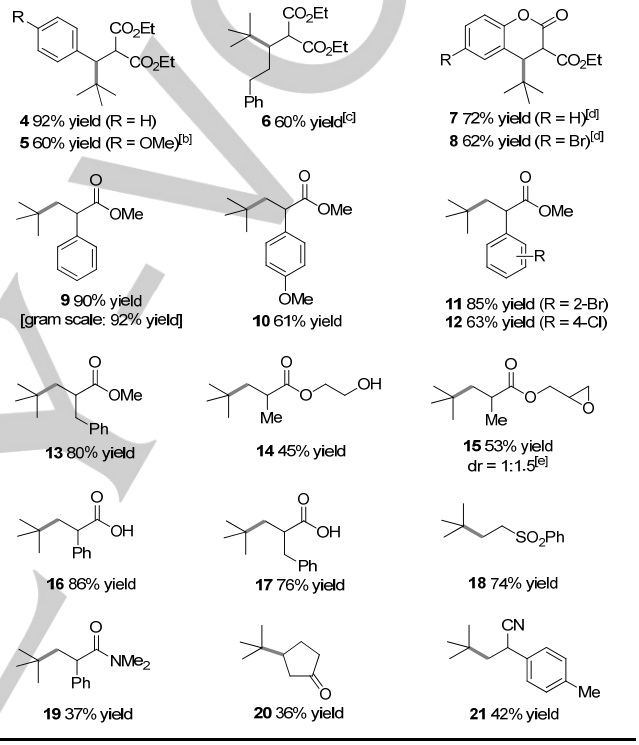
[a] Reactions were conducted on 0.4 mmol scale with 4.0 equiv of K_2HPO_4 unless otherwise stated. Yields were determined according to the isolated material. [b] 2.0 equiv of K_2HPO_4 was used. [c] Carried out with 3.6 equiv of K_2HPO_4. [d] Carried out with 3.2 equiv of K_2HPO_4. [e] Carried out with 2.4 equiv of K_2HPO_4.

With the optimized reaction conditions in hand (1 mol% $[Ir(ppy)_2(dtbbpy)]PF_6$, 4.0 equiv of K_2HPO_4, 1.8 equiv of **1**, and 34 W blue LEDs at 40 ºC, acetone), we then focused our attention on evaluating the scope of Michael acceptors for this new desulfurative conjugate addition (Table 2). Gratifyingly, we found that a wide array of electron-deficient alkenes can be used as acceptors in the Michael addition reaction. β-Aryl and β-alkyl substituted methylenemalonates, including coumarin derivatives, afforded the corresponding alkylation products in good to excellent yields (**4**–**8**, 60–92% yield). Various acrylates with α-aryl and α-alkyl groups also proved to be effective reaction partners (**9**–**15**). Notably, varying the electronic nature of the aromatic ring in α-aryl acrylates had no significant effects on the results of the reaction (**9**–**12**, 61–90% yield). Functional groups such as a free alcohol and an epoxide moiety, were well-tolerated in the photocatalytic Michael addition reactions (**14** and **15**). In addition, α,β-unsaturated carboxylic acids furnished corresponding conjugate adducts **16** and **17** in 86% and 76% yield, respectively. Moreover, other Michael receptors containing sulfone, amide, ketone, and nitrile functional groups could also be employed in this addition reaction (**18**–**21**, 36–74% yield), although some of them were less efficient.[20] Of note, the reaction of methyl phenylacrylate with **1** could be conducted on a gram scale with no decrease in the yield (**9**).

Table 2. Desulfurative Conjugate Addition: Michael Acceptor Scope[a]



1 **Michael acceptor** **conjugate adduct**

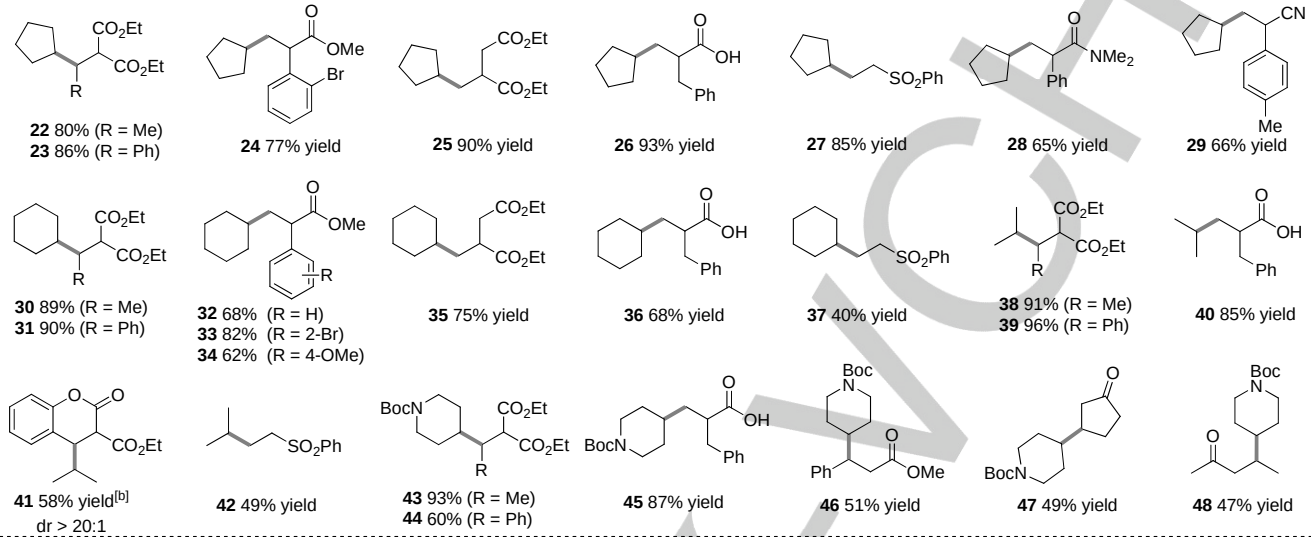


[a] Reactions were run on 0.4 mmol scale with 1.8 equiv of sulfinamide **1** and 3.6 equiv of K_2HPO_4 unless otherwise stated. Yields were determined according to the isolated material. [b] 4.0 equiv of **1** was used. [c] 5.0 equiv of **1** was used. [d] The dr value was more that 20:1. Isolated as *cis* isomer. [e] The dr value was determined by ^{1}H NMR of the crude mixture of **15**.

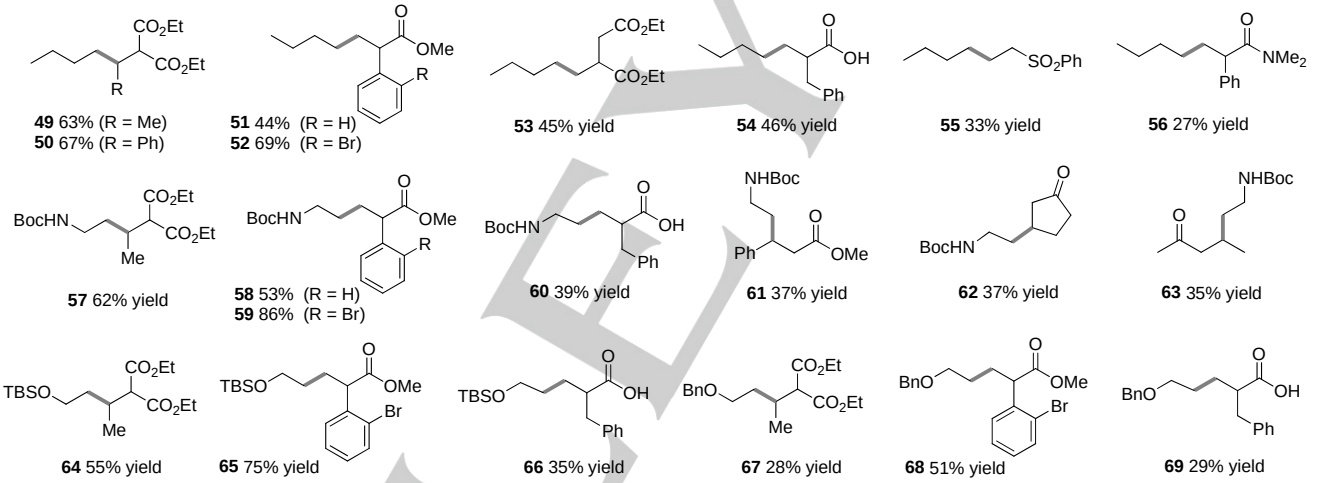
Next, we investigated the generation of secondary and primary alkyl radicals and the scope of the Michael addition reactions. As illustrated in Table 3A, subjecting secondary radical precursors to this desulfurative process typically afforded the desired adducts with good yields. As a representative example, *N*-benzoyl cyclopentyl-sulfinamide reacted with a variety of Michael acceptors, including α,β-unsaturated ester, carboxylic acid, sulfone, amide, and nitrile substrates, to efficiently generate the corresponding products (**22**–**29**, 65–93% yield). The ring expanded cyclohexyl-sulfinamide (corresponding products **30**–**37**) showed similar reactivity to that of its cyclopentyl counterpart. Moreover, the addition reactions of acyclic sulfinamides (e.g., *N*-benzoyl isopropyl-sulfinamide) occurred smoothly to yield corresponding products with good levels of efficacy (**38**–**42**, 49–96% yield). Although the free

Table 3. Desulfurative Conjugate Addition with Secondary and Primary Alkyl *N*-Benzoyl Sulfinamides[a]

A) secondary alkyl radical products



B) primary alkyl radical products



[a] Reactions were run on 0.4 mmol scale with 1.8 equiv of sulfinamide **1** and 3.6 equiv of K_2HPO_4 unless otherwise stated. Yields were determined according to the isolated material. [b] Isolated as *cis* isomer.

amine functionality was not tolerated, *N*-Boc protected sulfinamides could be used successfully (**43**–**48**, 47–93% yield).

Reported methods for generating primary alkyl radicals and for utilizing these reactive species under photocatalytic conditions are limited.[21] With this new protocol in hand, we explored the desulfurative conjugate addition of different primary alkyl radical precursors (Table 3B). Generally, the reactions of primary alkyl radicals were less efficient than those of the tertiary and secondary radicals. However, most of these *N*-benzoyl sulfinamides were well-tolerated in this reaction, affording the desired products under the optimal reaction conditions. For instance, *N*-benzoyl *n*-butyl-sulfinamide smoothly underwent the conjugate addition with various Michael acceptors to deliver the corresponding adducts (**49**–**56**).[22] Moreover, functional groups including NHBoc, OTBS, and OBn were all tolerated in this conjugate addition with primary alkyl radicals (**57**–**69**). Notably, among the few reported reactions of primary alkyl radicals through the desulfurative strategy,[15,16] our method has revealed superior functional-group compatibility and comparable efficiency.

To further understand the reaction mechanism, control experiments were carried out. Evidently, each component (e.g., visible light, base, and photocatalyst) was essential for the

desired conjugate addition (Figure 2A). Moreover, adding TEMPO to the reaction mixture greatly suppressed the formation of conjugate addition product **3**, and instead, the reaction produced TEMPO-alkyl radical adduct **70** as the major product. This result suggested the reaction occurs via an alkyl radical intermediate, which encouraged us to propose the plausible mechanism shown in Figure 2B. Initial deprotonation of an acidified N–H bond occurs in the presence of base to provide amidyl anion **I**. The photoexcited Ir^{III} complex then oxidizes **I** via SET, yielding nitrogen-centered radical **II**. This alkylsulfinamide-associated radical species automatically undergoes fragmentation during the reaction, resulting in the generation of *N*-sulfinylbenzamide (**III**)[23] and corresponding alkyl radical **IV**. The former is hydrolyzed to benzamide, which could be isolated after reaction workup,[24] while the latter participates in the subsequent Michael addition. Thus, alkyl radical **IV** adds to an electron-deficient alkene to furnish carbon radical **V**. After intermediate **V** accepts one electron from the reductive Ir^{II} complex, the resulting carbon anion **VI** is then protonatd to afford the final product. Meanwhile, the ground state Ir^{III} photocatalyst is regenerated, thus completing the catalytic cycle.

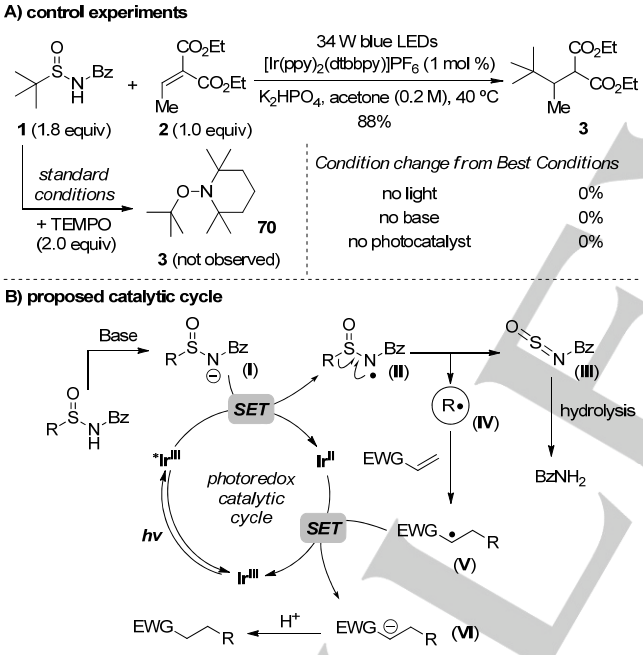


Figure 2. A) Control experiments and B) proposed catalytic cycle

In conclusion, we have developed a photocatalytic desulfurative method to generate primary, secondary and tertiary alkyl radicals using *N*-acyl alkyl-sulfinamides as radical precursors. These alkylation reagents are bench-stable, easy-to-handle solids that can be readily accessed from thiol or sulfide compounds. Central to the success of this novel protocol is the generation of alkyl radicals from *N*-centered radical intermediates via subsequent fragmentation processes. This strategy, with the successful application in conjugation addition, has provided new synthetic utility of *N*-acyl alkyl-sulfinamides as alkyl radical precursors and complements the existing approaches. Studies concerning the utilization of the alkyl radical species in other synthetic transformations are ongoing in our laboratory and will be reported in due course.

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Keywords: alkyl radical • catalysis • conjugate addition • desulfuration • photoredox

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[18] For more details, see the Supporting Information.

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[20] Note that the relatively low yielding of the conjugate adduct **20** might be due to its high volatility.

[21] For selected examples, see: refs. 6e, 7g, 7m, 8a, 8b, 8e, and 15.

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[24] Recycle of benzamide was performed in the gram-scale reaction (product **9**, Table 2). See the Supporting Information for details.

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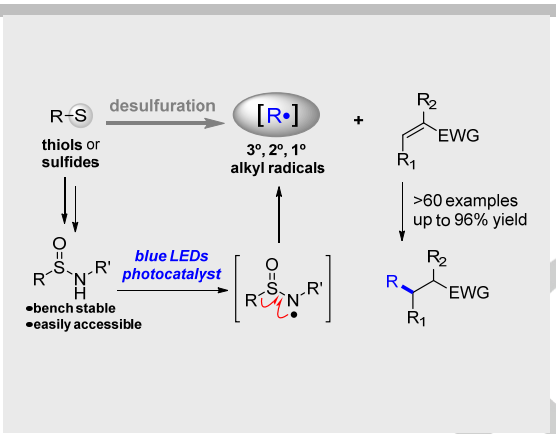
A new desulfurative protocol for generating primary, secondary and tertiary alkyl radicals via visible-light photoredox catalysis is reported. The key process for forming the alkyl radical species involves the generation of *N*-centered radicals from sulfinamide intermediates, followed by subsequent fragmentation.



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