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Photoredox-catalyzed sulfonylation of diaryliodonium salts with DABSO and silyl enolates involving the insertion of SO_2†

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A versatile photoredox-catalyzed three-component sulfonylation of diaryliodonium salts with DABSO and silyl enolates involving the insertion of SO_2 was developed. Moreover, by employing β-alkyl substituted silyl enolates as substrates, the sulfonylation would give α-alkyl substituted β-keto sulfones, which are difficult to accessed by previous method involving the insertion of SO_2.

β-Keto sulfones are privileged frameworks in many pharmaceuticals and display remarkable biological activities and pharmacological properties such as anti-bacterial, anti-fungal, anti-hepatitis, and non-nucleoside inhibition (Fig. 1).[1] Additionally, β-keto sulfones are utilized as versatile intermediate synthons in diverse synthetic transformations due to the simultaneous existence of multiple functional groups including carbonyl, sulfonyl and active methylene moieties.[2] Therefore, there is high demand for developing efficient synthesis methods to construct β-keto sulfones.

Conventional approaches for the synthesis of β-keto sulfones include oxidation of 2-oxo-sulfides with strong oxidants[3] and the sulfonylation of α-halo-ketones with preinstalled sulfonyl-containing segments,[4] which have several drawbacks, such as the employment of poorly accessible and smelly organosulfur compounds as starting materials, limited substrate applicability, and harsh conditions. In recent years, sulfonylation involving the insertion of sulfur dioxide *via* a radical process has emerged as a powerful method to access sulfone derivatives,[5] in which various SO_2 surrogates, like DABSO, metabisulfites, rongalite reagents and SOgen, are employed instead of SO_2 gas.[6] Outstanding contributions to synthesize diverse β-keto sulfones from silyl enolates *via* sulfur dioxide insertion have been made by Wu's groups using aryldiazonium tetrafluoroborates,[7] aryl/alkyl halides,[8] and thianthrenium salts[9] as active radical precursors in some cases. These transformations proceed with good tolerance of functional groups, easily enabling the incorporation of various sulfonyl skeletons into ketones.

On the other hand, diaryliodonium salts can participate in various transformations as a type of versatile, easily available, non-toxic, environmentally, and air stable solid arylating reagent.[10] So far, diaryliodonium salts as active radical precursors in multi-component sulfonylation reactions involving the insertion of sulfur dioxide has been developed initially. Jiang and coworkers reported a straightforward protocol for the synthesis of diverse functionalized diarylannulated sulfones through SO_2/I exchange of iodonium(III) salts. In this reaction, the aryl radical generated from diaryliodonium salt was captured by $Na_2S_2O_5$ to form a SO_2 radical anion, which served as the key intermediate to realize the exchange strategy (Scheme 1a).[11] In 2018, Manolikakes[12] and Zhang[13] demonstrated that visible-light-induced reduction of diaryliodonium salts would generate aryl radicals, which could undergo cascade cyclization in combination with SO_2 for the synthesis of sulfonylated coumarins (Scheme 1b) and 3-arylsulfonylquinoline derivatives, respectively. Very recently, Piguel and coworkers established the first visible-light photoredox catalyzed C–H sulfonylation of imidazopyridines with diaryliodonium salts and DABSO for the straightforward synthesis of novel C-3

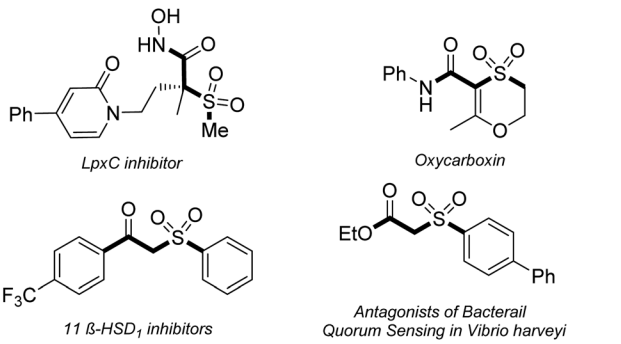

Fig. 1 Examples for β-keto sulfones and related sulfones with biological activities.

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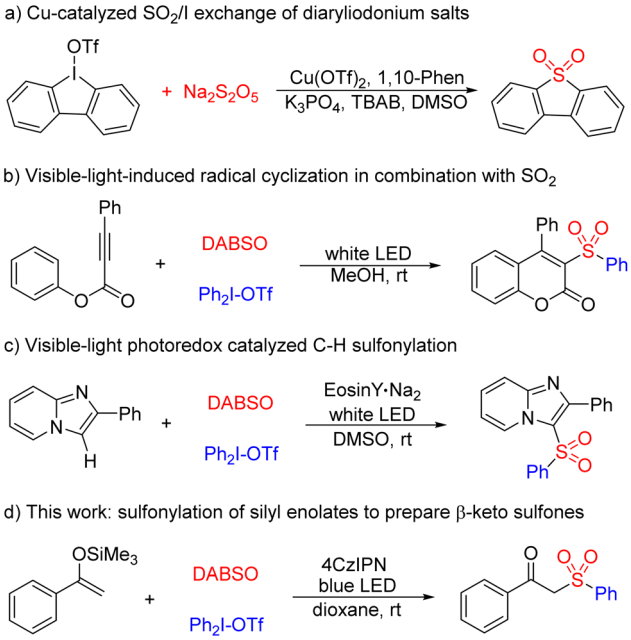
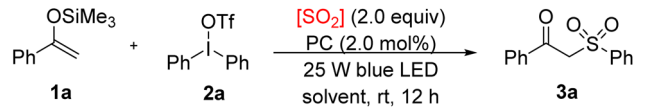


Scheme 1 Diaryliodonium salts as active radical precursors in the insertion of sulfur dioxide.

sulfonylated imidazoheterocycles (Scheme 1c).[14] Herein, we would like to report a novel 4CzIPN-catalyzed three-component sulfonylation of diaryliodonium salts with DABSO and silyl enolates *via* a radical process involving SO_2 insertion. This photoredox catalysis with the assistance of visible light represents a green and sustainable approach for the synthesis of β-keto sulfones (Scheme 1d).

Trimethyl((1-phenylvinyl)oxy)silane **1a**, diphenyliodonium triflate **2a** and 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) were selected as starting materials to optimize the sulfonylation conditions. Initially, irradiation of all three reaction partners in 1,4-dioxane with blue LED (25 W) at room temperature for 12 hours under N_2 led to the desired β-keto sulfone **3a** in 47% yield (Table 1, entry 1). Other SO_2 surrogates such as $K_2S_2O_5$, $Na_2S_2O_5$, $Na_2S_2O_4$ displayed lower activity (Table 1, entries 2–4). A variety of solvents were examined. 1,4-Dioxane proved to be superior to tetrahydrofuran (THF), acetonitrile, 1,2-dichloroethane (DCE), *N*,*N*-dimethylformamide (DMF) and toluene (Table 1, entries 1 and 5–10). When SO_2-MeCN solution was used as SO_2 source instead of DABSO, the reaction mixture in MeCN gave **3a** in a slightly increased yield (Table 1, entries 6 and 7). Next, a range of experiments were carried out under various light sources such as blue LED (10 W, 25 W, 30 W), white LED (24 W), compact fluorescent lamp (CFL, 18 W), Kessil light (390 nm) and UV (600 W). As a result, 25 W of blue LED has the best performance (Table S1 in ESI†). Despite extending the time to 24 h, only 55% yield of **3a** can be obtained (Table S1,† entry 8). The addition of photoredox catalysts was beneficial for the transformation. For example, the yield of **3a** sharply rose to more than 80% when 2.0 mol% of either $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ or 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) was added (Table 1, entries 11 and 14). Considering cost and availability

Table 1 Optimization of three-component sulfonylation[a]

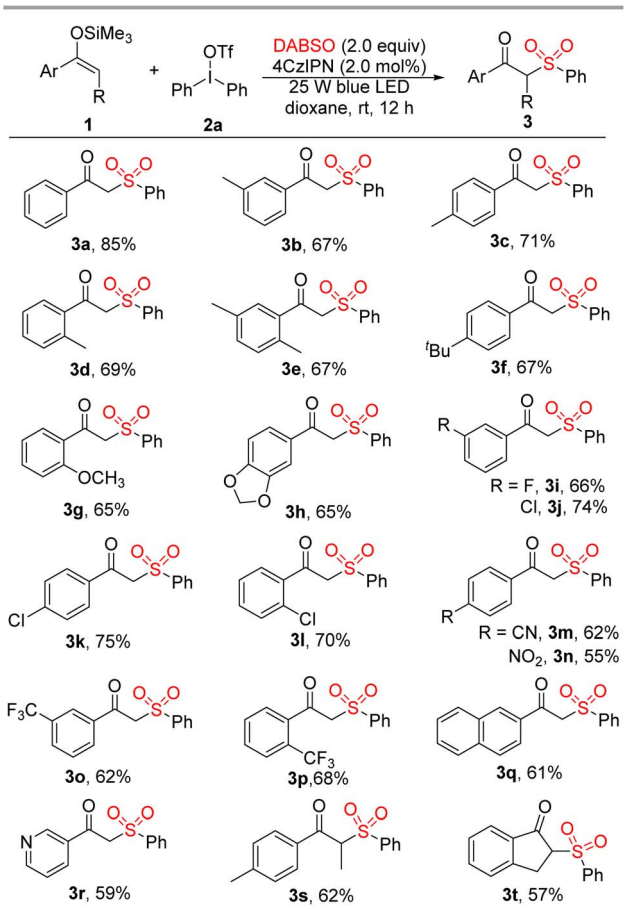


Entry	$[SO_2]$	PC	Solvent	Yield[b] (%)
1	DABSO	—	1,4-Dioxane	47
2	$K_2S_2O_5$	—	1,4-Dioxane	35
3	$Na_2S_2O_5$	—	1,4-Dioxane	24
4	$Na_2S_2O_4$	—	1,4-Dioxane	0
5	DABSO	—	THF	34
6	DABSO	—	MeCN	45
7	SO_2 solution	—	MeCN	50
8	DABSO	—	DCE	37
9	DABSO	—	PhMe	0
10	DABSO	—	DMF	0
11	DABSO	**Ir-1**	1,4-Dioxane	84
12	DABSO	**Ru-1**	1,4-Dioxane	Trace
13	DABSO	Eosin Y	1,4-Dioxane	56
14	DABSO	4CzIPN	1,4-Dioxane	85
15[c]	DABSO	4CzIPN	1,4-Dioxane	60
16[d]	DABSO	4CzIPN	1,4-Dioxane	0

[a] Reaction conditions: **1a** (2.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), $[SO_2]$ (2.0 equiv.), PC (2 mol%), and *n*-$C_{12}H_{26}$ (10 μL) in solvent (1.0 mL) at room temperature for 12 h, irradiation with 25 W blue LED, under N_2. [b] GC yields. [c] Under air atmosphere. [d] No light. **Ir-1** = $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$, **Ru-1** = $[Ru(bpy)_3]Cl_2\cdot 6H_2O$. SO_2 solution: SO_2 solution in MeCN (~7.9 M).

factors, 4CzIPN was chosen as the optimal photocatalyst. When the reaction was carried out under air atmosphere, 60% yield of **3a** was generated (Table 1, entry 15). In addition, the three-component sulfonylation cannot proceed without light (Table 1, entry 16). In addition, the introduction of various bases, such as NaO^{t}Bu, NaOH, Na_2CO_3, $NaHCO_3$ and NEt_3, has caused the reaction yield to decrease to varying degrees (Table S2 in ESI†).

We investigated the scope of this three-component sulfonylation transformation with the optimal conditions in hand. The treatment of diverse silyl enolates **1** with diphenyliodonium triflate **2a** and DABSO afforded the corresponding β-keto sulfone derivatives in moderate to good yields (Scheme 2). Silyl enolates possessing methyl and alkoxy groups on the phenyl ring could react with **2a** and DABSO smoothly to give the desired products (**3b–3h**). Halogen atoms, especially chlorine, can be compatible under the optimal conditions (**3i–3l**), which revealed possible further transformations of the resulting halogenated products with other nucleophiles.[15] Representative electron-withdrawing groups, such as cyano, nitro, and trifluoromethyl, were also tolerated in this three-component sulfonylation transformation under the optimal conditions (**3m–3p**). When trimethyl((1-(naphthalen-2-yl)vinyl)oxy)silane was treated with **2a** and DABSO, the desired **3q** was isolated in 61% yield. In addition, heterocyclic substituted silyl enolate could also be transformed to **3r** in 59% yield. It is notable that α-substituted β-keto sulfones cannot be obtained from reported radical transformations involving the insertion of SO_2.[7–9] To our

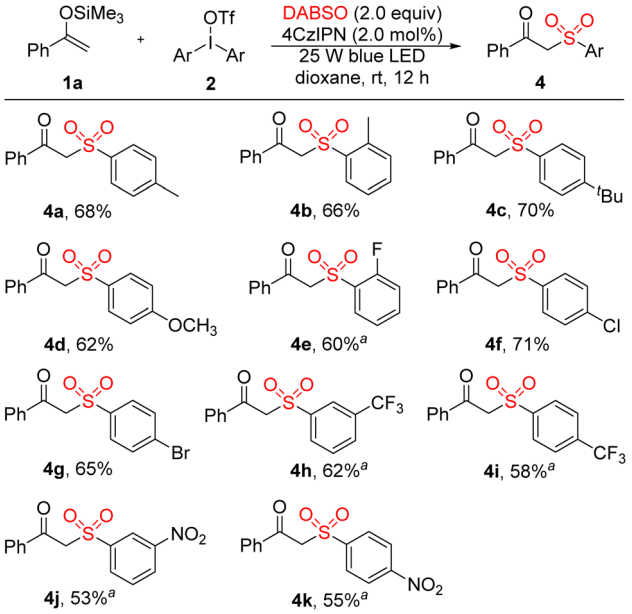


Scheme 2 The scope of silyl enolates.

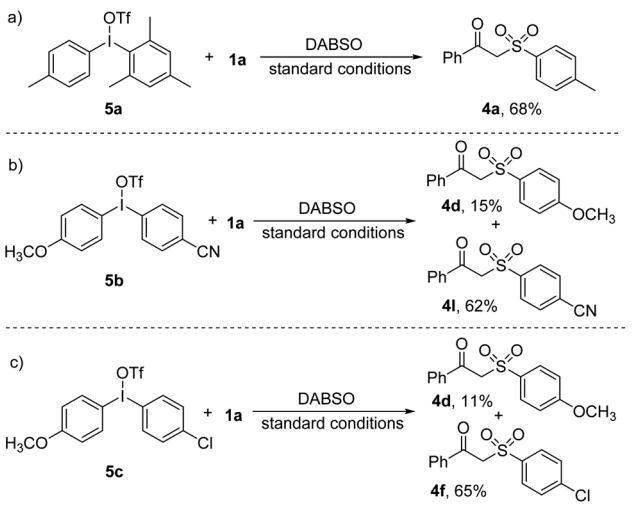
delight, β-alkyl substituted silyl enolates could work well in this three-component sulfonylation to give α-alkyl substituted β-keto sulfones **3s** and **3t** in acceptable yields.

Subsequently the scope of diaryliodonium salts was examined. As shown in Scheme 3, both diaryliodonium triflates and diaryliodonium tetrafluoroborates were suitable substrates for this photocatalytic reaction. Diaryliodonium salts bearing different functional groups, containing electron-donating methyl (**4a** and **4b**), *tert*-butyl (**4c**), methoxy (**4d**) and electron-withdrawing fluorine (**4e**), chlorine (**4f**), bromine (**4g**), trifluoromethyl (**4h** and **4i**) and nitro (**4j** and **4k**), were readily compatible in this 4CzIPN-catalyzed three-component sulfonylation.

We next investigated the 4CzIPN-catalyzed three-component sulfonylation with unsymmetrical diaryliodonium salts. When unsymmetrical salt possessing a *p*-methylphenyl and a bulky mesityl group was used, only **4a** was obtained in 68% *via* a selective transfer of the *p*-methylphenyl group (Scheme 4a). The reaction of **5b** afforded methoxy substituted sulfone **4d** and cyano substituted sulfone **4l** in 15% and 62%, respectively (Scheme 4b). When unsymmetrical diaryliodonium salt **5c** reacted with **1a** and DABSO, the β-keto sulfone **4f** was isolated as the main product in 65% with selective transfer of the electron-deficient *p*-chlorophenyl group over the electron-rich *p*-methoxyphenyl moiety (Scheme 4c). These results indicate that



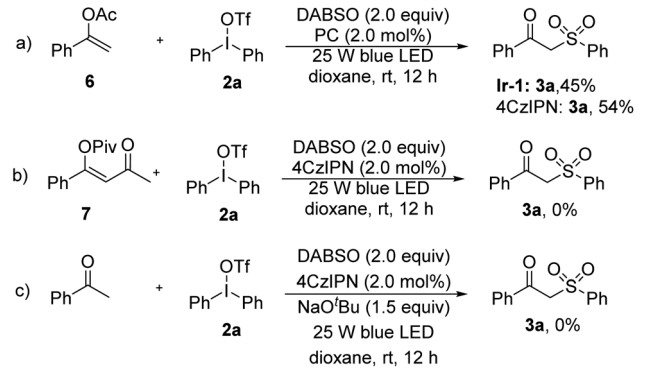
Scheme 3 The scope of diaryliodonium salts.[a] Diaryliodonium tetrafluoroborates was used.



Scheme 4 Reactions with unsymmetrical diaryliodonium salts: (a) the sulfonylation with *p*-tolyl-mesityl iodonium salt **5a**; (b) the sulfonylation with (*p*-cyanophenyl)-(*p*-methoxyphenyl) iodonium salt **5b**; (c) the sulfonylation with (*p*-chlorophenyl)-(*p*-methoxyphenyl) iodonium salt **5c**.

the electron-deficient aryl moiety is more easily reduced by photocatalyst to generate an aryl radical.

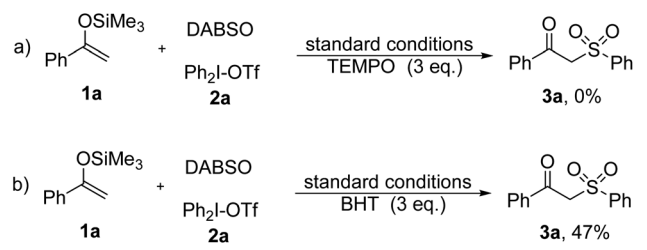
The scope of enolates in addition to silyl enolates was checked. 1-Phenylvinyl acetate **6** can afford the desired product in moderate yield in the presence of either **Ir-1** or 4CzIPN (Scheme 5a), while 1,3-diketone derived enol ester **7** was not compatible (Scheme 5b). Under the standard conditions, the combination of acetophenone and sodium *tert*-butoxide was adopted, which can generate enolate *in situ* to replace the enol silane. As a result, the generation of **3a** was not observed (Scheme 5c).



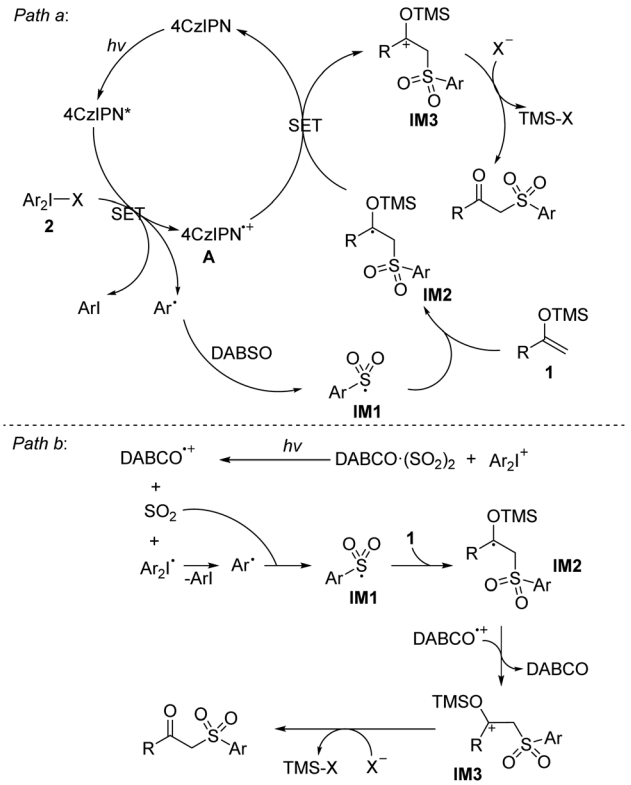
Scheme 5 The scope of other enolates: (a) the sulfonylation with 1-phenylvinyl acetate **6**; (b) the sulfonylation with 1,3-diketone derived enol ester **7**; (c) the sulfonylation with acetophenone in the presence of sodium *tert*-butoxide.

To gain more insight into the mechanism, the following radical inhibition experiments were performed. The standard sulfonylation transformation was completely restrained in the presence of 3.0 equiv. of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (Scheme 6a). At the same time, the yield of **3a** decreased to 47% when 3.0 equiv. of butylated hydroxytoluene (BHT) was added in the reaction system (Scheme 6b). These results implied that a radical process might be involved in the mechanism.

Based on the above observations and previous work, plausible mechanism of the photoredox-catalyzed sulfonylation involving the insertion of SO_2 is proposed. For the pathway in the presence of photocatalyst (Scheme 7, path a):[9] The photo-excited 4CzIPN* reduces diaryliodonium salt **2** through single electron transfer (SET) process to give an aryl radical and the oxidized photocatalyst **A**. Aryl radical is trapped by SO_2 to generate the sulfonyl radical **IM1**. Then, the addition of sulfonyl radical **IM1** into the double bond of silyl enolate **1** affords radical intermediate **IM2**, which can be oxidized to cation intermediate **IM3** by photocatalyst **A** *via* another SET along with the regeneration of the photocatalyst 4CzIPN. Finally, cation intermediate **IM3** undergoes desilylation with nucleophilic anion species to give the desired β-keto sulfone **3**. For the pathway in the absence of photocatalyst (Scheme 7, path b):[12] the interaction of iodonium salt with DABSO ($DABCO\cdot(SO_2)_2$) would produce DABCO radical cation, dioxide, and diaryl iodine radical. Fragmentation of diaryl iodine radical furnishes an aryl



Scheme 6 Parallel control experiments: (a) radical inhibition experiment with TEMPO; (b) radical inhibition experiment with BHT.



Scheme 7 Plausible mechanistic pathway.

radical, which is trapped by SO_2 to generate the sulfonyl radical **IM1**. Then, the addition of sulfonyl radical **IM1** into the double bond of silyl enolate **1** affords radical intermediate **IM2**, which can be oxidized to cation intermediate **IM3** by DABCO radical cation. Finally, cation intermediate **IM3** undergoes desilylation to give **3**.

Conclusions

In summary, a versatile strategy for the synthesis of diverse β-keto sulfones *via* photoredox-catalyzed sulfonylation of diaryliodonium salts with DABSO and silyl enolates involving the insertion of SO_2 has been established. In this reaction, blue-light-induced reduction of diaryliodonium salts afford the aryl radical, which would be trapped by SO_2 to form sulfonyl radical as the key intermediate. This novel photoredox catalysis with the assistance of visible light represents a green and sustainable approach for the synthesis of β-keto sulfones and features wide substrates scope, good reactivity, and broad functional group tolerance. In addition, by employing β-alkyl substituted silyl enolates, this three-component sulfonylation would give α-alkyl substituted β-keto sulfones, which cannot be accessed by previous method involving the insertion of SO_2.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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