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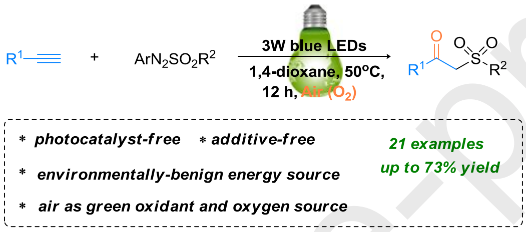

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Visible-light-promoted aerobic oxidative synthesis of β-ketosulfones under photocatalyst-free conditions

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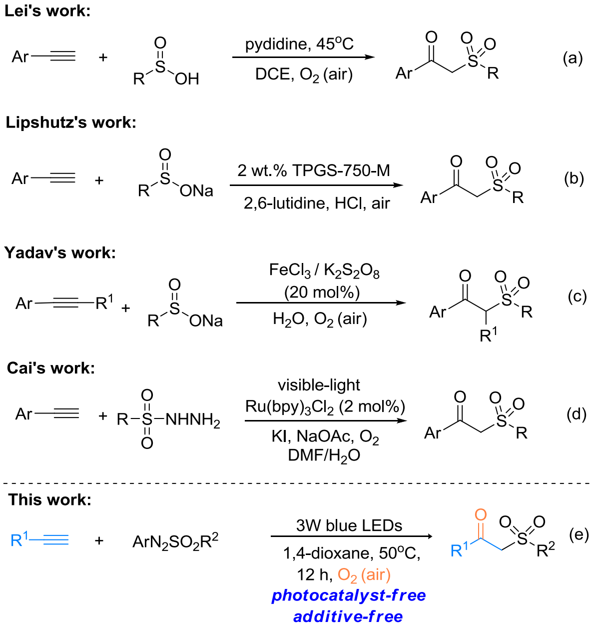
ABSTRACT

A simple and convenient visible-light-mediated method has been developed for the construction of β-ketosulfones via aerobic oxidative difunctionalization of alkynes with arylazo sulfones and dioxygen in air under photocatalyst-free conditions. The present photochemical methodology provides a facile and attractive protocol to construct a series of β-ketosulfones in moderate to good yields.

Organic sulfones have exhibited widespread applications in the organic synthesis, functionalized materials, and pharmaceutical industries.[1,2] Especially, β-ketosulfones are a highly valuable class of organic sulfones with versatile synthetic utility[3] and unique biological activity,[4] which are frequently presented in many pharmaceuticals and biologically active molecules. Given the significance of β-ketosulfones, a number of synthetic methods have been developed for the construction of β-ketosulfones during the past several decades.[5-9] Among them, the oxidative difunctionalization of alkynes with various sulfonylating agents such as sulfinic acids, sulfinates, and sulfonylhydrazides have attracted the increasingly synthetic attention of chemists due to the diversity and commercial availability of alkynes.[9] For example, in 2013, Lei and co-workers reported an elegant pyridine-mediated difunctionalization of terminal alkynes with arylsulfinic acids and dioxygen leading to β-ketosulfones (Scheme 1a).[9a] In 2014, Lipshutz demonstrated that TPGS-750-M (2 wt.%) could promote the oxysulfonylation of arylalkynes with arylsulfinate salts in the presence of dioxygen to yield β-ketosulfones in acid conditions (Scheme 1b).[9b] The same year, Yadav described an efficient $FeCl_3/K_2S_2O_8$ (20 mol%) catalyzed aerobic oxidative difunctionalization of alkynes with arylsulfinate salts in aqueous media (Scheme 1c).[9c] In 2016, Cai group reported a visible light-mediated $Ru(bpy)_3Cl_2$ catalyzed aerobic oxysulfonylation of alkynes with sulfonylhydrazides for the preparation of β-ketosulfones in the presence of 1 equiv. of KI and 4 equiv. of NaOAc (Scheme 1d).[9d] Although some significant progress has been made in this field, the development of more facile, efficient and catalyst-free synthetic strategy is still highly desirable.



Scheme 1. The methods for the synthesis of β-ketosulfones from alkynes.

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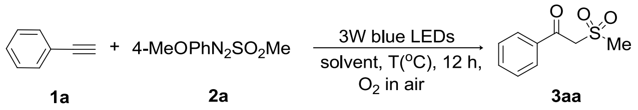
E-mail: weiweiqfnu@163.com (W. Wei); hlyue@nwipb.cas.cn (H. Yue), be readily prepared from aryldiazonium salts.[10] It is known that arylazo sulfones can undergo the photodissociation process to afford aryl radical/aryl cation and sulfonyl radical/sulfonyl anion under the irradiation of visible light.[10,11] In recent years, arylazo sulfones have been widely utilized as arylation reagents to construct various aromatic compounds in photochemical reactions in the absence of any photocatalyst (Scheme 1e).[11] Visible light as a clean and sustainable energy has been increasingly used to promote various synthetic transformations in the field of synthetic chemistry.[12] As part of our interest in developing new visible-light-mediated reactions[13] and sulfonylations,[14] herein, we report a simple and photocatalyst-free strategy for the synthesis of β-ketosulfones via visible-light-promoted oxysulfonylation of alkynes with arylazo sulfones in the presence of dioxygen in air (Scheme 1e). This reaction provides a convenient and highly attractive approach to access various β-ketosulfones in moderate to good yields under metal- and additive-free conditions.

Table 1

Screening of the reaction conditions[a]



Entry	Photocatalyst (2 mol%)	Solvent	Yield(%)[b]
1	--	CH_3CN	23
2	-	DCE	41
3	--	DMSO	14
4	--	EtOH	44
5	--	DME	46
6	--	THF	42
7	--	1,4-dioxane	51
8	--	DMF	trace
9	--	H_2O	12
10	Na_2-eosin Y (2)	1,4-dioxane	51
11	Eosin B (2)	1,4-dioxane	46
12	Rhodamine B (2)	1,4-dioxane	50
13	Eosin Y (2)	1,4-dioxane	51
14	Rose Bengal (2)	1,4-dioxane	48
15	--	1,4-dioxane	73[c]
16	--	1,4-dioxane	12[d]
17	--	1,4-dioxane	9[e]
18	--	1,4-dioxane	trace[f]

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.25 mmol), solvent (3 mL), room temperature, 3 W blue LED lamps (460-485 nm), 12h, air.

[b] Isolated yields based on **1a**.

[c] 3 W blue LED lamps, 50°C.

[d] 3 W green LED lamps, 50°C.

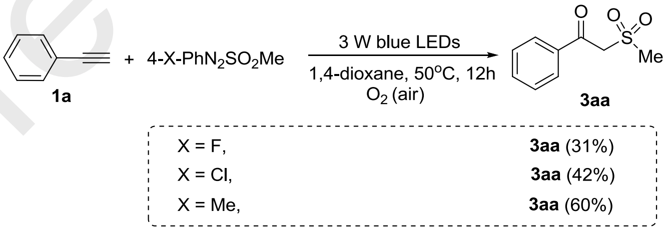
[e] 3 W white LED lamps, 50°C

[f] Without visible-light irradiation, 50°C.

Initially, phenylacetylene (**1a**) and 4-methoxyphenylazo mesylate (**2a**) were chosen as model substrates to optimize the reaction conditions under the irradiation of 3 W blue LED lamps in air. When the model reaction was conducted in CH_3CN at room temperature in the absence of photocatalyst, the desired

Encouraged by this result, we further examined a variety of solvents (Table 1, entries 2-9). Among a number of solvents tested, 1,4-dioxane was found to be the best reaction medium for this oxysulfonylation reaction, and the desired product was obtained in 51% yield (Table 1, entry 7). Only a trace amount of product was obtained in DMF (Table 1, entry 8). When reaction was conducted in H_2O, the product **3aa** was only isolated in 12% yield (Table 1, entry 9). Further investigation found that the yield of **3aa** was not increased obviously by the addition of a series of photocatalysts such as Na_2-eosin Y, Eosin B, Rhodamine B and Eosin Y (Table 1, entries 10-14). Pleasingly, the product **3aa** could be isolated in 73% yield when the reaction was conducted at 50°C under the irradiation of 3 W blue LED lamps (Table 1, entry 15). The low reaction efficiency was observed by replacing of 3 W blue LEDs with 3 W green LEDs or 3 W white LEDs (Table 1, entries 16 and 17). Only a trace amount of product was detected when the model reaction was performed in the absence of light irradiation (Table 1, entry 18).

Moreover, when 4-methoxyphenylazo mesylate was replaced by other aryldiazosulfones such as 4-fluorophenylazo mesylate, 4-chlorophenylazo mesylate or 4-methylphenylazo mesylate, the present oxysulfonylation reaction would also undergo smoothly under the standard conditions, but leading to the corresponding β-ketosulfone **3aa** in a relatively lower yield (Scheme 2). This result indicated that electron rich 4-methoxy group might more efficiently promote the homolytic cleavage of C-N and N−S bonds of arylazo sulfones.

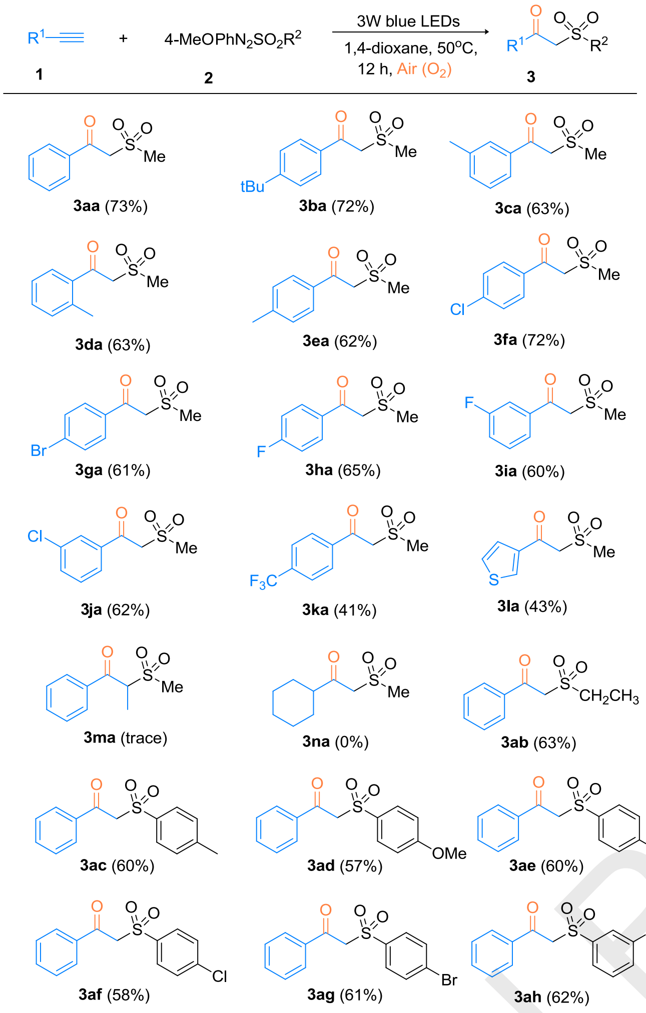


Scheme 2. The reaction of phenylacetylene (**1a**) with other aryldiazosulfones.

With the optimal conditions in hand, we moved on to examine the scope of various alkynes and arylazo sulfones (Table 2). Firstly, various aromatic alkynes bearing different substitutions were tested. In general, phenylacetylene with a series of substituents at the *ortho*-, *meta*- or *para*-position, regardless of the electron-donating (*t*Bu and Me) or electron-withdrawing (F, Cl, Br and CF_3) groups, afforded the corresponding β-ketosulfones **3ba**–**3ka** in moderate to good yields. It is noteworthy that heteroaromatic alkyne such as 3-ethynylthiophene showed favorable compatibility providing the corresponding product **3la** in 43% yield. When internal alkyne such as prop-1-ynylbenzene was used in the present reaction system, only a trace amount of desired product **3ma** was detected. Unfortunately, when alkyl alkynes were employed in the present reaction system, none of desired product **3na** was detected. Next, the scope of arylazo sulfones was evaluated. Arylazo alkylsulfone such as 4-methoxyphenylazo ethyl sulfone was also suitable substrates to give the desired product **3ab** in 63% yield. In addition, a number of arylazo arylsulfones that possessed an electron-donating or an electron-withdrawing group on the aryl rings were all well tolerated in this chemistry and thus amenable to this process to afford the corresponding products (**3ac**-**3ah**) with moderate to good yields.

Tabl

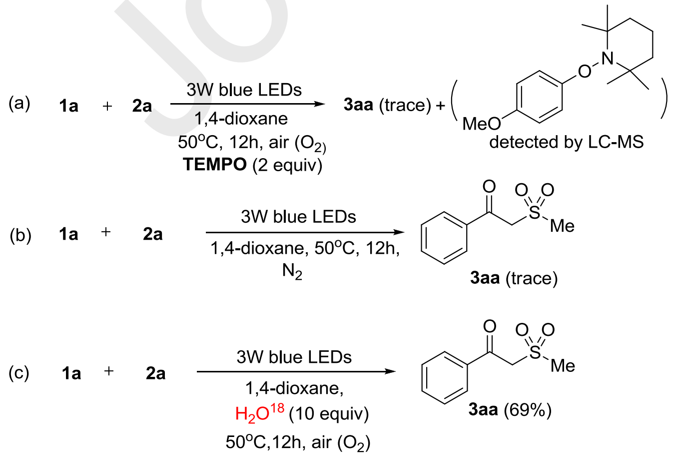
Substrate scope.[a,b]



[a] Reaction condition: **1** (0.1 mmol), **2** (0.25 mmol), 3 W blue LEDs, 1,4-dioxane (3 mL), 50°C, air, 12 h.

[b] Isolated yields based on **1**.

Several control experiments were carried out to probe some mechanistic insights into this reaction. The model reaction was extremely inhibited and TEMPO trapped complex (TEMPO-aryl) was detected when a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added in the model reaction system (Scheme 3a). This result indicated that the present reaction might undergo through a radical process.



Scheme 3. Control experiments.

ed when the reaction was carried out under N_2, suggesting that dioxygen in air is essential for this reaction (Scheme 3b). Moreover, ^{18}O labeling experiment using $H_2{}^{18}O$ showed that the carbonyl oxygen atom of product **3aa** came from dioxygen in air (Scheme 3c). Further investigations on the reaction mechanism of this protocol are currently under way in our laboratory.

In conclusion, a simple and photocatalyst-free visible-light-mediated strategy has been successfully developed for the preparation of β-ketosulfones from alkynes, arylazo sulfones and dioxygen in air. The present oxysulfonylation reaction of alkynes offers a facile and attractive approach to synthesize various β-ketosulfones without metal catalysts and additives.

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- Visible-light-promoted oxidative synthesis of β-ketosulfones
- Photocatalyst-free
- Air as the green oxidant and oxygen source
- A radical process

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: