Visible-light initiated direct oxysulfonylation of alkenes with sulfinic acids leading to β-ketosulfones†

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Visible light along with 1 mol% eosin Y catalyzed the direct oxysulfonylation of alkenes with sulfinic acids *via* a photoredox process which has been developed at room temperature under transition-metal-free conditions. The present reaction provides a highly efficient approach to diverse β-ketosulfones in moderate to good yields. It should provide a promising synthesis candidate for the formation of diverse and useful β-ketosulfone derivatives in the fields of synthetic and pharmaceutical chemistry.

Introduction

β-Ketosulfones, one of the most valuable sulfur-containing compounds, have been widely used as an important synthetic intermediate in the construction of natural products, vinyl sulfones, polyfunctionalized 4H-pyrans, quinolines, allenes, ketones, and vinylsulfones.[1] Besides this, β-ketosulfone derivatives are well-known to possess various useful biological and medicinal properties. For example, they can be used in antibacterial and antifungal drugs, and are also potent non-nucleoside inhibitors.[2] As a consequence, extensive efforts have been devoted to the discovery of efficient and useful methods for β-ketosulfone synthesis and functionalization. The conventional methods for the preparation of β-keto-sulfones mainly focus on the direct alkylation of sodium sulfinates with phenacyl halides.[3] Nevertheless, the not easily available precursors and prolonged reaction times could limit their wide applications. In 2014, Jiang *et al.* reported an elegant copper-catalyzed coupling of oxime acetates with sodium for the construction of β-ketosulfones (Scheme 1a).[4]

Recently, as one of the promising synthesis strategies, direct difunctionalization of alkenes or alkynes has attracted considerable attention because of its high efficiency in the cascade formation of carbon–carbon or carbon–heteroatom bonds.[5] In this field, some excellent difunctionalization reactions leading to β-ketosulfones have been significantly

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Scheme 1 Methods for the synthesis of β-ketosulfones.

disclosed.[6–10] In 2013, Lei and co-workers developed a highly efficient aerobic oxidative difunctionalization of alkynes leading to β-ketosulfones in the presence of 4 equiv. of pyridine under a dioxygen atmosphere (Scheme 1b).[6] In the same year, our group also reported a copper-catalyzed oxysulfonylation reaction of alkenes with sulfonylhydrazides for the synthesis of β-keto-sulfones (Scheme 1c).[7] In 2014, Yadav *et al.* demonstrated a highly efficient synthetic approach to β-ketosulfones *via* AgNO₃-catalyzed oxysulfonylation of alkenes with thiophenols (Scheme 1d).[8] Yadav and co-workers also developed a direct approach to β-ketosulfones *via* AgNO₃/K₂S₂O₈ catalyzed aerobic oxysulfonylation of alkenes with arenesulfinate salts (Scheme 1d).[9] However, challenges still remain, but it is still highly desirable to develop more efficient, environmentally-benign, and sustainable methods for the construction of β-ketosulfones.

According to the principles of green chemistry, the development of some green reaction media, catalysts, and reaction

conditions is still challenging in the current chemistry.[11] Visible light can be considered as an ideal reaction promoter for organic transformations because it is non-toxic, inexpensive, abundant, and renewable, and generates no waste. As an alternative, visible-light photoredox transformations have been successfully introduced by MacMillan, Stephenson, Yoon, and other research groups.[12] Recently, tremendous progress has been made in this respect since it opens a new avenue for the formation of C–C and C–heteroatom bonds. In comparison to iridium, ruthenium or copper complexes, organic dyes have shown better prospect in visible light-induced organic transformations owing to their cheapness and non-toxicity. Until now, eosin Y, eosin B, fluorescein and rose bengal have been proven to be efficient catalysts in different visible-light-promoted reactions.[13] For example, König et al. demonstrated an elegant eosin Y and visible light-catalyzed method for the synthesis of vinyl sulfones from aryl sulfinates.[14] On the other hand, arylsulfinic acids are more readily available in some cases and are easy to store and handle. Importantly, sulfinic acids as a sulfonylating source have been employed for constructing sulfone-containing compounds via visible-light initiated organic transformations. In 2013, Lei and co-workers developed a highly efficient oxysulfonylation method to construct β-hydroxysulfones with readily available sulfinic acids.[15] In 2014, Wang and Miao reported a novel and efficient visible light-induced synthesis of sulfonated oxindoles from N-arylacrylamides and arylsulfinic acids.[16] In 2015, Wang et al. also developed an excellent visible-light initiated oxidative cyclization of phenyl propiolates with sulfinic acids for the formation of coumarin derivatives.[17] Nevertheless, to the best of our knowledge, visible-light initiated direct oxysulfonylation of alkenes with sulfinic acids to form C–S bonds has never been exploited. Inspired and encouraged by these pioneering studies and as part of our continuing interest in sulfur-containing organic compound synthesis,[18] we herein wish to describe a new visible-light initiated direct oxysulfonylation of alkenes with sulfinic acids leading to β-ketosulfones under mild conditions (Scheme 2).

Results and discussion

Initially, styrene (**1a**) and benzenesulfinic acid (**2a**) were chosen as the model substrates to optimize reaction conditions including the photoredox catalysts, oxidants and solvents under a nitrogen atmosphere. As shown in Table 1, six photoredox catalysts such as eosin Y, Na$_2$-eosinY, rose bengal,
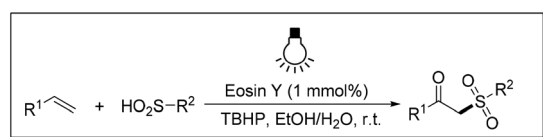
Scheme 2 Strategy for β-ketosulfones via visible-light initiated direct oxysulfonylation of alkenes with sulfinic acids.

Table 1 Optimization of the reaction conditions[a,b]

Structures of Photocatalysts:

Entry	Photoredox catalyst	Oxidant	Solvent	Yield[b] (%)
1	Eosin Y	TBHP	EtOH	70
2	Na$_2$-eosinY	TBHP	EtOH	14
3	Rose bengal	TBHP	EtOH	54
4	Eosin B	TBHP	EtOH	59
5	Rhodamine B	TBHP	EtOH	61
6	Acridine Red	TBHP	EtOH	38
7	Eosin Y	TBHP	CH$_3$CN	37
8	Eosin Y	TBHP	H$_2$O	6
9	Eosin Y	TBHP	THF	67
10	Eosin Y	TBHP	DCE	44
11	**Eosin Y**	**TBHP**	**EtOH/H$_2$O**	**75**
12	Eosin Y	DTBP	EtOH/H$_2$O	65
13	Eosin Y	H$_2$O$_2$	EtOH/H$_2$O	34
14	Eosin Y	K$_2$S$_2$O$_8$	EtOH/H$_2$O	55
15	Eosin Y	TBHP	EtOH/H$_2$O	N.R.[c]
16	Eosin Y	TBHP	EtOH/H$_2$O	75[d]
17	Eosin Y	TBHP	EtOH/H$_2$O	71[e]

[a] Reaction conditions: under a nitrogen atmosphere, **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (1.0 mol%), oxidant (3.0 equiv.), solvent 2 mL, EtOH/H$_2$O (v$_1$/v$_2$ = 4 : 1), at room temperature for 24 h. [b] Isolated yield. [c] In the dark. [d] 11 W green LED. [e] In air. N.R. = no reaction. TBHP = 5.5 M tert-butyl hydroperoxide solution in decane. DTBP = di-tert-butyl peroxide.

eosin B, acridine red, and rhodamine B were tested in EtOH under irradiation of an 11 W white-light-emitting diode (LED) for 24 h at room temperature by using 3.0 equiv. of tert-butyl hydroperoxide TBHP (relative to the amount of **1a**) as the oxidant, and eosin Y gave the highest yield (70%) (entries 1–6, Table 1). It should be noted that, when Na$_2$-eosin Y was used as the catalyst, only 14% of the desired product was obtained. We supposed that the Na$_2$-eosin Y might not be completely converted into eosin Y under the standard conditions, and the coexistence of Na$_2$-eosin Y and eosin Y in the reaction system might affect the conversion efficiency. Furthermore, solvents, including CH$_3$CN, H$_2$O, THF, DCE and EtOH/H$_2$O, were tested by using eosin Y as the photoredox catalyst at room temperature, and EtOH/H$_2$O (v$_1$/v$_2$ = 4 : 1) was superior to the others (compare entries 7–11, Table 1). Also, we attempted to use different oxidants such as H$_2$O$_2$, DTBP, and K$_2$S$_2$O$_8$, and TBHP was found to be more suitable for this reaction (compare entries 11–14, Table 1). It should be noted that no reaction

could proceed in the absence of light (entry 15, Table 1). Interestingly, the green LED also gave the same yield (entry 16, Table 1). In addition, when the reaction was performed in air, it gave a slightly lower yield (entry 17, Table 1). After the optimization process for catalysts, oxidants, and solvents, various β-ketosulfones were synthesized under our standard conditions: 1.0 mol% of eosin Y as the photoredox catalyst, 3.0 equiv. of TBHP as the oxidant, and 2.0 mL of EtOH/H$_2$O (v$_1$/v$_2$ = 4 : 1) as the solvent at room temperature under a nitrogen atmosphere.

With the optimum reaction conditions in hand, we turned our attention to investigating the scope of the substrates for the visible-light initiated direct oxysulfonylation of alkenes (1) with sulfinic acids (2) leading to β-ketosulfones (3). As shown in Table 2, a variety of alkenes, bearing either electron-donating groups (R = OMe, Me) or electron-withdrawing groups (R = Cl, Br, CN, NO$_2$) on the aryl ring, reacted smoothly with sulfinic acids, affording the corresponding β-ketosulfones 3a–3v in moderate to good yields. Notably, alkenes bearing a strong electron-withdrawing group such as nitro and cyano were also compatible with the domino sequence (3q, 3r, 3s, and 3t). Additionally, a naphthyl group could also participate in this transformation with a good reactivity (3d, 3h, 3k, 3o, 3u and 3v). Furthermore, the effects of the substituent on alkenes were also investigated. The catalytic efficiency was not obviously affected by the steric hindrance in alkenes, and gave the corresponding 3l in 51% yield (Table 2, 3l). Unfortunately, aliphatic alkenes, such as but-1-ene, did not work in the reaction (Table 2, 3w). The visible-light initiated domino reactions could tolerate some functional groups such as alkyl, ether and cyano groups and C–Cl bonds and C–Br bonds, which could be used for further modifications at the substituted positions.

In order to gain some more information on the reaction mechanism, several control reactions were performed as shown in Scheme 3. When the reaction of 1a with 2a was carried out in the presence of a stoichiometric amount of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, a well-known radical-capturing species), the present reaction was completely suppressed [eqn (1), Scheme 3]. This result suggested that a radical process might be involved in this transformation. To further probe the original source of the oxygen atom incorporated into the β-ketosulfones, the reaction between 1a and 2a under H$_2$O^{18} was carried out under the standard conditions for 24 h, and 52% ^{18}O-3a and 48% ^{16}O-3a were detected, indicating that the carbonyl oxygen atom of the β-ketosulfones came from both TBHP and H$_2$O [eqn (2), Scheme 3, HRMS, see the ESI†]. Moreover, treatment of prop-1-en-2-ylbenzene 4 with 4-methylbenzenesulfinic acid 2b under the standard conditions led to 2-phenyl-1-tosylpropan-2-ol 5 in 72% yield [eqn (3), Scheme 3]. Additionally, the reaction of 1a with sodium benzenesulfinate 6b was tested under the standard conditions. As expected, no conversion was observed [eqn (4), Scheme 3]. Furthermore, an energy transfer process between eosin Y and TBHP was confirmed by fluorescence quenching experiments (see the ESI† for detail). In order to verify the effect of photo-irradiation, an on/off visible light irradiation experiment was

**Table 2** Substrate scope of the visible-light initiated direct oxysulfonylation of alkenes with sulfinic acids^{a,b}
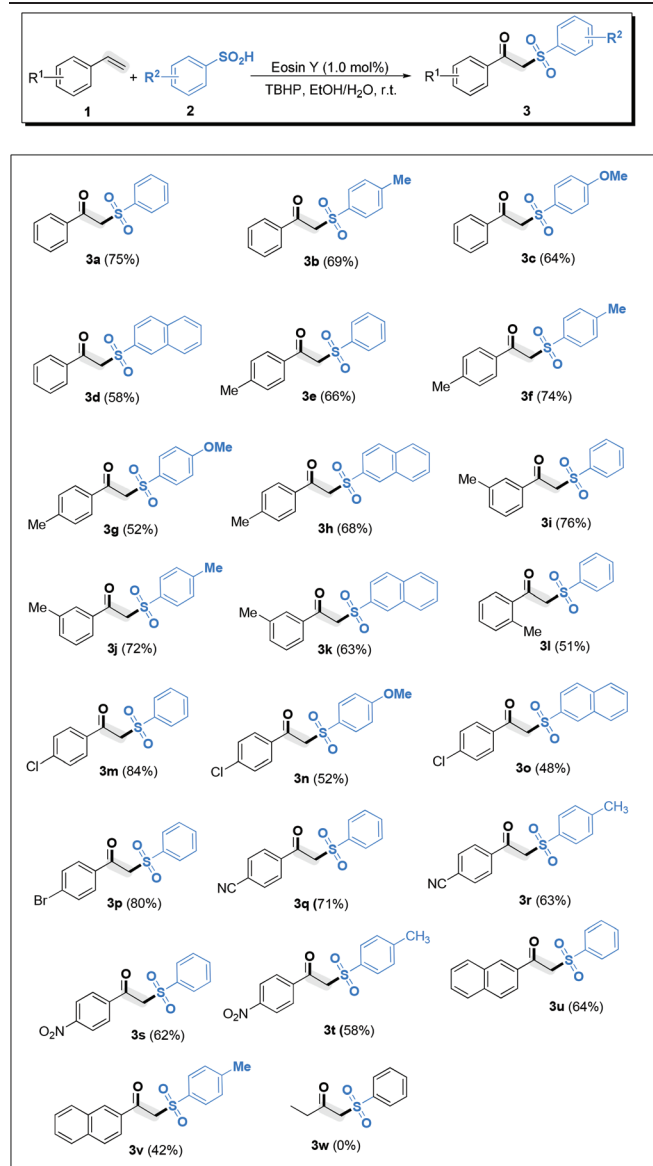
^{a} Reaction conditions: under a nitrogen atmosphere, 1a (0.2 mmol), 2a (0.3 mmol), eosin Y (1.0 mol%), TBHP (3.0 equiv.), solvent 2 mL, EtOH/H$_2$O (v$_1$/v$_2$ = 4 : 1), at room temperature for 24 h. ^{b} Isolated yield.

performed. The graph preliminarily shows that the present transformation required continuous visible light irradiation (Scheme 3). Besides this, the quantum yield in the reaction of 1a with 2a was estimated to be 0.144, which is supporting evidence for the proposed mechanism. However, the possibility of the radical chain process is not completely excluded, further investigations on the more detailed mechanism are underway in our laboratory.
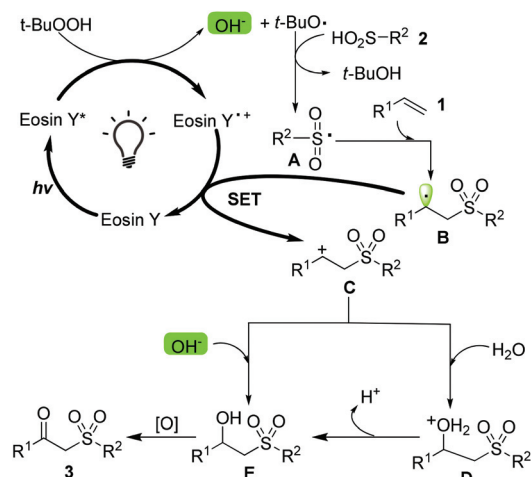
On the basis of these preliminary results above, a proposal mechanism would be herein presented (Scheme 4). Under the visible-light irradiation, eosin Y was converted to the excited eosin Y*. A single electron transfer between eosin Y* and

(1)

(2)

(3)

(4)
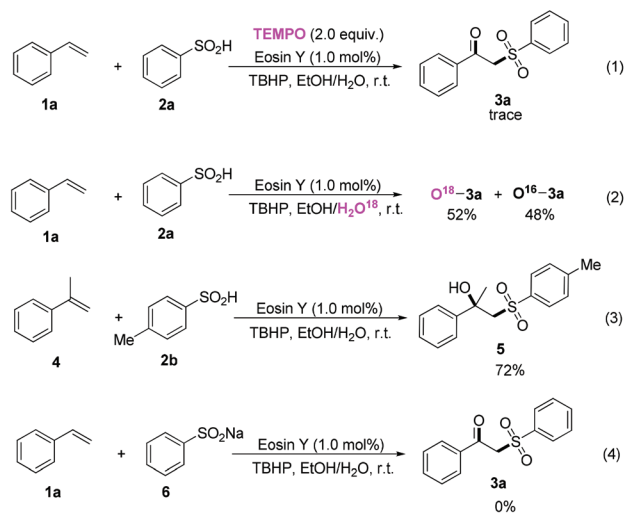
• visible light irradiation on/off experiment
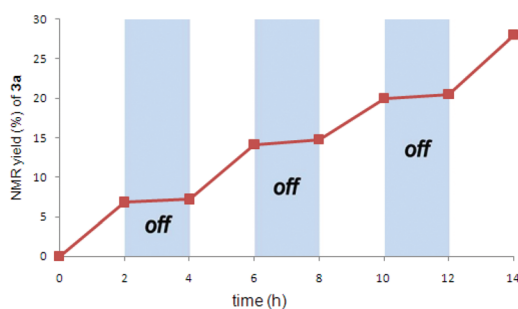
Scheme 3 Control experiments.

Scheme 4 A proposed mechanism for the direct transformation.

TBHP afforded a *tert*-butoxyl radical and a hydroxyl anion. Then sulfinic acids **2** reacted with a *tert*-butoxyl radical to furnish the corresponding sulfonyl radical **A**. Subsequent radical addition of **A** to alkenes **1** produced the carbon-centered radical **B**, which could be further transformed into

the carbocation intermediate **C** through single electron transfer (SET) with eosin Y$^{•+}$. Subsequently, the nucleophilic attack of the hydroxyl anion and H$_2$O on the carbocation intermediate produced the intermediate **E**, which was transformed into the desired product **3** under the oxidative conditions. Further investigations on the more detailed mechanism are ongoing in our laboratory.

Conclusions

In summary, we have developed an efficient eosin Y-catalyzed, visible light-initiated direct oxysulfonylation of alkenes with arylsulfinic acids to access β-ketosulfones. A wide range of functional groups can be tolerated well under the reaction conditions, and the corresponding β-ketosulfones were obtained in moderate to good yields. This method can enjoy the following advantages: (a) commercially available eosin Y as the photoredox catalyst; (b) ethanol and water as the solvent; (c) no addition of any base, ligand or additive; (d) easy workup procedure; (e) at room temperature; (f) outstanding tolerance of functional groups. With these merits meeting the requirements of green and sustainable synthesis chemistry, the developed synthesis approach would extend the scope of synthetic methods for diverse β-ketosulfones in the academic and industrial fields. Further investigation on the practical application of this method is in progress.

Acknowledgements

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