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Visible-Light-Promoted Oxidative Difunctionalization of Alkenes with Sulfonyl Chlorides to Access β -Keto Sulfones under Aerobic Conditions

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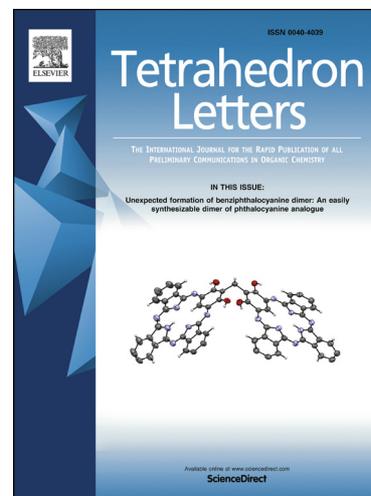
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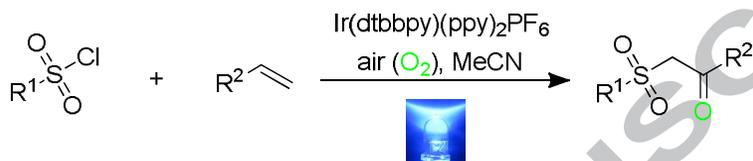
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ABSTRACT

A mild, practical and efficient strategy to prepare β -keto sulfones has been developed by visible light promoted reactions. This reaction involves Ir(ppy)₂(dtbbpy)PF₆ catalyzed direct functionalization of alkenes with sulfonyl chlorides under mild conditions. Air was used as oxidant without any additives. The transformation affords the corresponding products in moderate to high yields.

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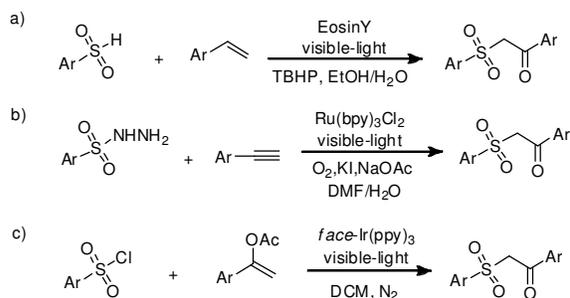
The oxidative difunctional of alkenes or alkynes to access difunctional ketone derivatives is of significant interest to organic chemists.¹ Among them β -keto sulfones have received much more reasonable attention for its widespread presence in pharmaceuticals, agrochemicals and biologically active compounds. For example, β -keto sulfones derivatives could be used in antifungal and antibacterial drugs, and are also potent nonnucleoside inhibitors.² Moreover, these motifs are valuable building blocks for the construction of a variety of other chemicals, especially biologically active heterocyclic compounds, such as polyfunctionalized 4H-pyrans and quinolines.³ Thus, a number of approaches have been employed to build these structures.

Traditional methods for the synthesis of β -keto sulfones involve the direct alkylation of sodium sulfinates with phenacyl halides.⁴ However, the precursors are not easily available. Alternatively, difunctionalization of alkenes or alkynes with sulfonic acids,⁵ sulfonylhydrazides,⁶ arenesulfinate salts,⁷ sulfonyl chlorides⁸ as well as thiophenols⁹ are also useful routes to synthesize β -keto sulfones. Although these methods provided the desired products in attractive routes, a simple and efficient way to synthesize β -keto sulfones is still highly desirable.

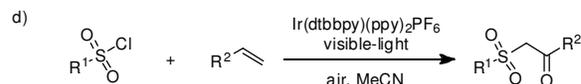
In recent years, visible light promoted oxidative difunctionalization of alkenes and alkynes has become a powerful tool in synthetic difunctional ketone derivatives because of its mild conditions, high efficiency, and convenient workup.¹⁰ Recently, tremendous progress has been made in this respect for the formation of C–S and C–O bonds. For example, in 2016, Yang and co-workers developed a visible light promoted oxysulfonylation reaction of alkenes with sulfonic acids by using

tert-butyl hydroperoxide (TBHP) as oxidant for the synthesis of β -keto sulfones (Scheme 1, a).¹¹ Consequently, Cai *et al.* demonstrated a visible light-induced aerobic oxidative difunctionalization of alkynes and sulfonylhydrazides with 4 equiv. of NaOAc and 1 equiv. of KI as additives (Scheme 1, b).¹² Utilizing oxygen for oxidative difunctionalization is more cheaper and environment friendly. It is well know that, sulfonyl chlorides are common, inexpensive and readily available sulfonylating source, which have been extensively employed for constructing sulfone-containing compounds. In this context, Yu

Previous work



This work



Scheme 1 Methods for the synthesis of β -keto sulfones by visible-light-promoted reaction.

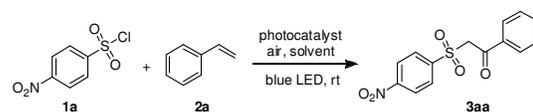
and zhang reported a visible-light-promoted directed sulfonylation with enol acetates and sulfonyl chlorides (Scheme 1, c).¹³ Give the importance of β -keto sulfones, and in continuation of our interest in photoredox difunctionalization reactions,¹⁴ herein we reported a Ir(ppy)₂(dtbbpy)PF₆-catalyzed visible-light-induced oxidative difunctionalization of alkenes with sulfonyl chlorides using air under mild conditions without any other additives (scheme 1d).

In an initial attempt, 4-nitrobenzenesulfonyl chloride **1a** and styrene **2a** were chosen as the model substrates. To our delight 58% yield of desired product **3aa** was obtained in the presence of Ru(bpy)₃Cl₂·6H₂O in MeCN at ambient temperature under air after 8 hours (Table 1, entry 1). In order to obtain the optimum yield, a wide variety of photocatalysts were screened. The typical metal photocatalysts Ir(ppy)₃ showed less catalytic activities (Table 1, entry 2). However, trace amount of **3aa** was obtained when organic photocatalysts such as Eosin Y, 9-mesityl-10-methylacridinium, Rhodamine B and Eosin B were used (Table 1, entries 3–6). The best result was obtained when Ir(ppy)₂(dtbbpy)PF₆ was used which provided **3aa** in 80% yield (Table 1, entry 7). Reducing the amount of Ir(ppy)₂(dtbbpy)PF₆ to 1 mol% led to a similar yield (Table 1, entry 8). Thus 1 mol% of Ir(ppy)₂(dtbbpy)PF₆ was used as the photocatalyst. Furthermore, different solvents including MeOH, DMSO, DMF and CH₂Cl₂ were tested, and the results showed that MeCN was the best choice (Table 1, entries 9–12). No improvement of the yield was observed when the reaction was carried out under oxygen instead of air (Table 1, entry 13). It was worth noting that the reaction did not occur in the absence of the photocatalyst or visible light (Table 1, entries 14 and 15).

With these results in hand, the scope and generality of the present method were then examined. As shown in the Table 2, diverse terminal aryl alkenes bearing a variety of electron-donating and electron-withdrawing substituents were employed to react with 4-nitrobenzenesulfonyl chloride **1a** under the optimized reaction conditions (**3aa-3ao**). Most of them delivered the corresponding β -keto sulfone derivatives **3** smoothly in moderate to high yields (52–88%, **3aa-3ao**). The electronic property of the substituents on the aryl rings of alkenes had a slight influence on the reaction except substrate **2i** which provided the product **3ai** in excellent yields (88%). Steric hindrance for alkenes were not significant, and aryl alkenes with *para*-, *meta*- or *ortho*-fluorine substituent were successfully converted into the corresponding products in 71%, 68% and 62%, respectively (**3ad-3af**). Aliphatic alkenes such as 1-hexene and vinylcyclohexane afford the corresponding β -ketosulfone in 62% and 68% yields respectively (**3al** and **3am**). Notably, heterocyclic alkene also survived as well in this transformation, and the corresponding product **3an** was obtained in moderated yield. However, internal alkene such as 2-phenyl-1-propene was not tolerated to give the desired product **3ao**.

The scope of various sulfonyl chlorides was then investigated. As can be seen in Table 3, sulfonyl chlorides with a strong electron-withdrawing substituted group were suitable for the present reaction conditions, affording the desired products in moderate to good yield (**3ba-3ea**). The steric hindrance of the substituents had a significant influence on the reaction, and the 2-nitrobenzenesulfonyl chloride gave relatively lower yield (**3ca**, 41%). The heterocyclic aromatic sulfonyl chloride worked well and afforded the corresponding product in moderate yield (**3fa**, 56%). However, alkyl sulfonyl chlorides were inert toward this transformation (**3ga** and **3ha**). Besides, substrates contains only halogen and strong electron-donating group were also unsuitable for the present reaction conditions, providing a trace amount of the desired products (Table 3, **3ia** and **3ja**).

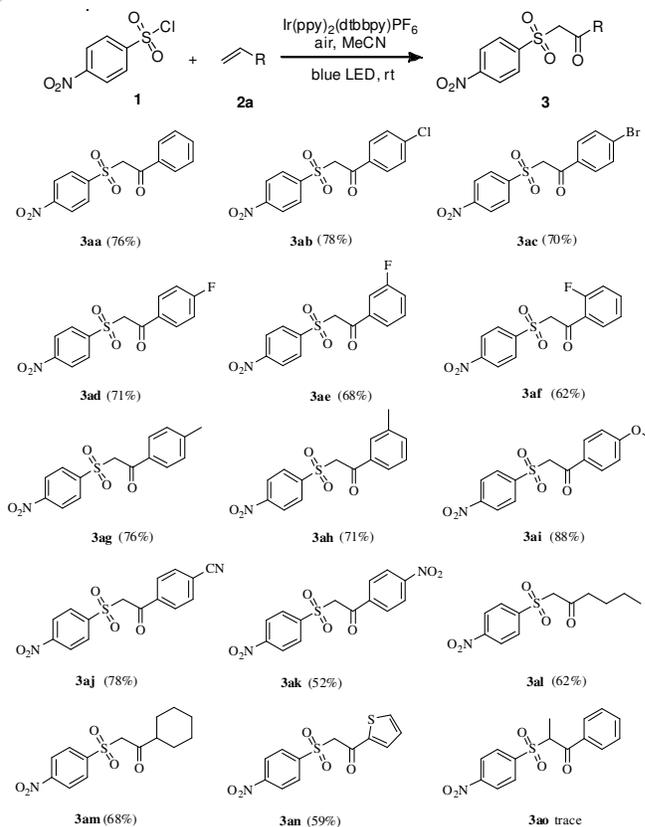
Table 1. Screening of the Reaction Conditions.^a



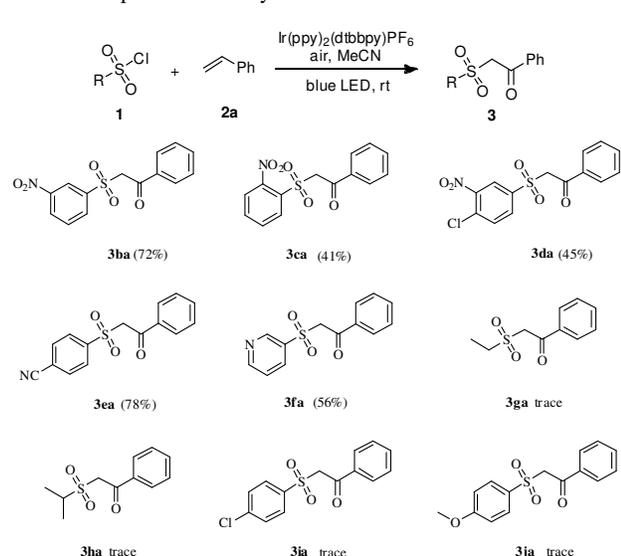
Entry	Photocatalyst (mol%)	Solvent	Yield(%) ^b
1	Ru(bpy) ₃ Cl ₂ ·6H ₂ O (2)	MeCN	58
2	Ir(ppy) ₃ (2)	MeCN	35
3	Eosin Y (3)	MeCN	trace
4	9-Mesityl-10-methylacridinium(2)	MeCN	trace
5	Rhodamine B (3)	MeCN	trace
6	Eosin B(3)	MeCN	trace
7	Ir(ppy) ₂ (dtbbpy)PF ₆ (2)	MeCN	80
8	Ir(ppy) ₂ (dtbbpy)PF ₆ (1)	MeCN	76
9	Ir(ppy) ₂ (dtbbpy)PF ₆ (1)	MeOH	50
10	Ir(ppy) ₂ (dtbbpy)PF ₆ (1)	DMSO	trace
11	Ir(ppy) ₂ (dtbbpy)PF ₆ (1)	DMF	trace
12	Ir(ppy) ₂ (dtbbpy)PF ₆ (1)	CH ₂ Cl ₂	32
13 ^c	Ir(ppy) ₂ (dtbbpy)PF ₆ (1)	MeCN	76
14	no	MeCN	NR ^d
15 ^e	Ir(ppy) ₂ (dtbbpy) PF ₆ (1)	MeCN	NR

^aReaction conditions: **1a** (0.5 mmol), **2a** (0.6mmol) and photocatalyst in indicated solvent (2 mL) were irradiated with a 5 W blue LED at rt for 8 h under open air. ^b isolated yield. ^c reaction was carried out under oxygen. ^d no reaction. ^e In the dark.

Table 2 Scope of the alkenes ^a



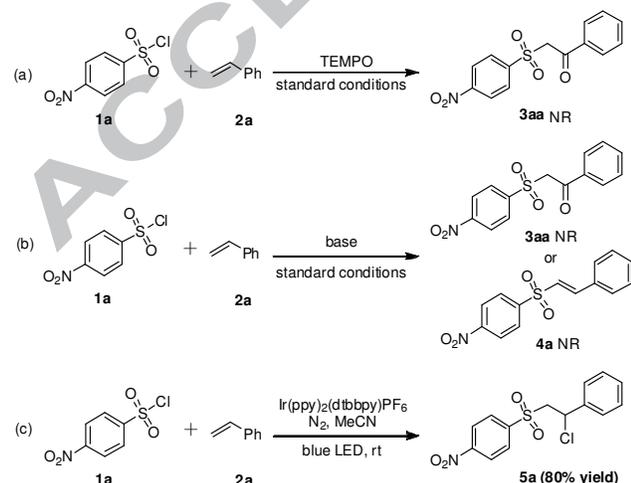
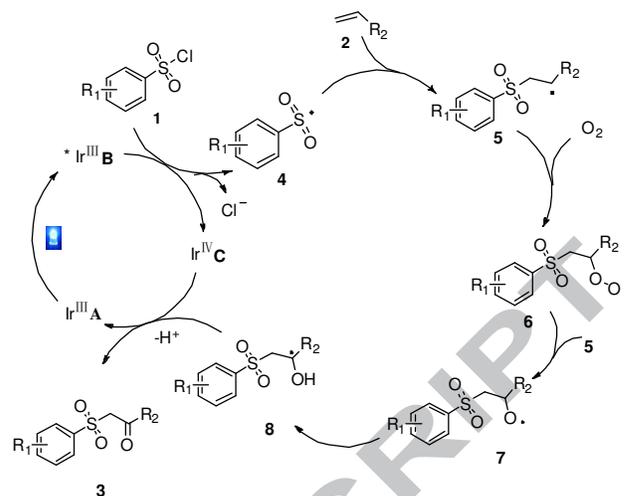
^a Reaction conditions: **1a** (0.5 mmol), **2** (0.6mmol), Ir(ppy)₂(dtbbpy)PF₆ (1 mol%) and MeCN (2 mL), irradiated with a 5 W blue LED at rt for 8 h under open air; isolated yield.

Table 3 Scope of the sulfonyl chlorides ^a

^a Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ (1 mol%) and MeCN (2 mL), irradiated with a 5 W blue LED at rt for 8 h under open air; isolated yield.

In order to further get insight into the reaction mechanism, some control experiments were carried out under the standard conditions (Scheme 2). First, 2 equivalents of free radical scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyl oxyl), was added, and the reaction was absolutely inhibited (Scheme 2, a). The result indicated that a radical route might be involved in this transformation. When the reaction was carried out in the presence of a base (Na_2CO_3 , K_2HPO_4 , Et_3N or DIPEA), no oxidation product **3aa** or coupling product **4a** were observed, suggesting that structures **4a** was excluded from our transformations as a plausible intermediate (Scheme 2b). It was worth noting that 80% yield of **5a** was obtained under nitrogen conditions, which suggested that both free radical addition and electrophilic addition might be involved (Scheme 2c).

According to the above control experiments and previous reports^{11,12,13} a plausible mechanism net for the present reaction was depicted in Scheme 3. Initially, upon the visible light irradiation, the ground-state photocatalyst $\text{Ir}(\text{ppy})_2(\text{dtbbpy})^+$ (**A**) was transferred to the excited state $^*\text{Ir}(\text{ppy})_2(\text{dtbbpy})^+$ (**B**). Oxidation of $^*\text{Ir}(\text{ppy})_2(\text{dtbbpy})^+$ (**B**) to $\text{Ir}(\text{ppy})_2(\text{dtbbpy})^{2+}$ (**C**) should be coincident with single-electron transfer (SET)

**Scheme 2** Control experiments.**Scheme 3** The proposed mechanism.

reduction of sulfonyl chloride **1**, leading to Cl^- and sulfonyl radical **4**. Then, addition of sulfonyl radical **4** to olefins **2** provides radical **5**, which is trapped by oxygen to give intermediate **6** and **7**. Ultimately, intermediate **7** undergoes 1,2-hydrogen atom shift to generate radical **8**. Subsequent SET oxidation of intermediate **8** then racemization to lose H^+ furnishes product **3**.

In summary, we have developed an effective visible-light-promoted reaction for the preparation of β -keto sulfones from simple starting materials. Compared with the previous reports,⁸ although an expensive photocatalyst was used in this protocol, only low amount of the catalyst (1 mol%) and the substrates (1 equiv of sulfonyl chlorides and 1.2 equiv of alkenes) were necessary. Importantly, air was used as the oxidant without any additives. Moreover, both aryl alkynes, aliphatic alkynes and heterocyclic alkene were tolerated well in this transformation to give the corresponding products in moderate to good yields thereby providing a potential route for both academic and industrial application.

Acknowledgments

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Supplementary Material

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The highlights of this work are list as follows:

- (1) Visible light promoted oxidative difunctionalization of alkenes
- (2) Air was used as oxidant.
- (3) Mild condition, efficient strategy and easy operation.

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