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Visible-Light-Promoted Oxo-Sulfonylation of Ynamides with Sulfonic Acids

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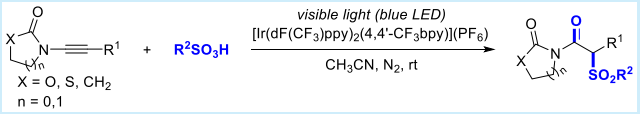
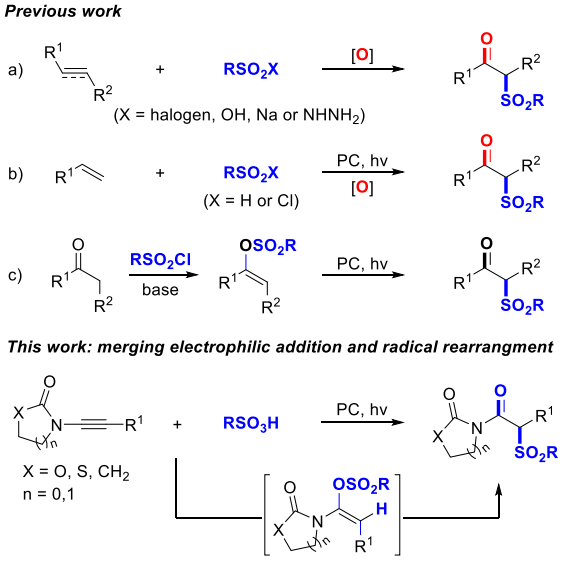
Supporting Information

ABSTRACT: A visible-light-promoted oxo-sulfonylation of ynamides with sulfonic acids is reported, giving rise to a collection of functionalized α-sulfonylated amides in a straightforward manner. The reaction proceeds sequentially through a cascade of electrophilic addition and photoinduced sulfonyl radical-sustained skeleton rearrangement. The high atom economy, mild reaction conditions, and wide substrate scope comprised the merits of this synthetic transformation.



α-Sulfonyl carbonyl derivatives are prevalent core structures in biologically active compounds and functional materials.[1] Therefore, the development of efficient synthetic methods for ready construction of this structural motif have aroused considerable interest from the synthetic community. To this end, conventional strategies including the acylation of α-sulfonyl carbanion intermediates,[2] S_N2 reaction of α-halocarbonyl derivatives with sulfinate,[3] and oxidation of sulfonyl alcohols or β-ketosulfides/sulfoxides were put forward.[4] However, the inevitable employment of elaborated starting materials, a stoichiometric amount of strong base/oxidant, and harsh reaction conditions pose great limitations on the compatibility as well as practicability regarding these ionic protocols. To ameliorate such drawbacks and also provide a complementary avenue, considerable attention from organic chemists has therefore been diverted to the exploitation of the synthetic potential of sulfonyl radical intermediates, targeting a more straightforward assembly of α-sulfonyl carbonyl derivatives from readily available starting materials. Specifically, by making use of sulfonyl halides/hydrazines,[5,6] sodium sulfinates,[7] and sulfinic acids[8] as the progenitors of sulfonyl radical, the oxo-sulfonylation of alkenes/alkynes were successfully implemented (Scheme 1a). With the progressive maturation of photocatalysis as a more convenient and milder way for radical generation,[9] much progress in β-ketosulfone synthesis was achieved. For example, by leveraging upon the ease of generation of sulfonyl radicals from sulfinates under photocatalysis,[10] the Wang group reported an effective protocol for the access of β-ketosulfone derivatives through oxo-sulfonylation of alkenes (Scheme 1b).[11] Also of note is the elegant work form Li's group, wherein photoinduced skeleton rearrangement of vinyltosylate provided an atom-economical access to various β- ketosulfones (Scheme 1c).[12] Despite notable advancement obtained, the need for a strong oxidant or corrosive reagent somehow eclipsed the advantage of photocatalysis. Thus, the development of more enabling synthetic protocol using readily available feedstocks for the construction of α-sulfonyl carbonyl derivatives is still highly desirable.

Scheme 1. Synthetic Strategies for the Construction of α-Sulfonyl Carbonyl Derivatives through Radical Manifold



In connection with our continuous interest in photoinduced radical coupling reactions,[13] we hypothesized that hydro-sulfonation of alkyne derivatives could be merged with photoinduced vinyl sulfonate rearrangement, thus enabling a rapid and convenient synthesis of α-sulfonylated carbonyl derivatives. Initially, we would like to focus our attention on the elaboration of ynamide as a more specific alkyne reaction partner, provided that ynamides are well-known for electrophilic

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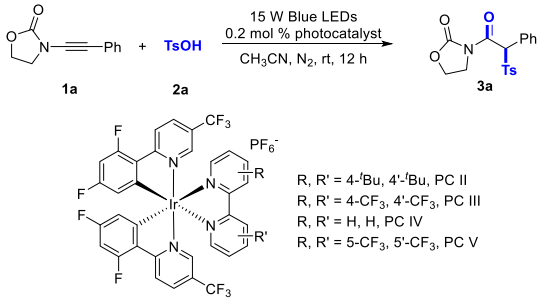
addition, leading to the corresponding adducts in high efficiency and excellent regioselectivity. Furthermore, the amide group is a versatile functionality which can be easily converted into amine, carboxylic acid, and hydroxyl groups. Compared with established methodologies,[14] we envisioned that the approach should improve reaction efficiency and practicability by (1) simplifying the reaction procedure, (2) obviating the use of an oxidant or a base, and (3) enriching the molecular complexity of α-sulfonyl carbonyl derivatives. Therefore, we would like to report a novel and efficient visible-light-promoted oxo-sulfonylation of ynamides with sulfonic acids acting as both the oxygen and sulfonyl group donors, affording a large array of functionalized α-sulfonylated amide derivatives.

We first examined the reaction between readily available ynamide (**1a**) and *p*-toluenesulfonic acid (**2a**) at room temperature. More specifically, the commercial iridium complex *fac*-Ir(ppy)$_3$ was employed as a photoredox catalyst and blue LEDs was used as the light source. The CH_3CN solution of these materials was stirred under blue light irradiation at room temperature for 12 h, and the desired product **3a** 3-(2-phenyl-2-tosylacetyl)oxazolidine-2-one was obtained in 48% yield (Table 1, entry 1). On the basis of the encouraging result, various

Table 1. Optimization of Reaction Conditions[a]



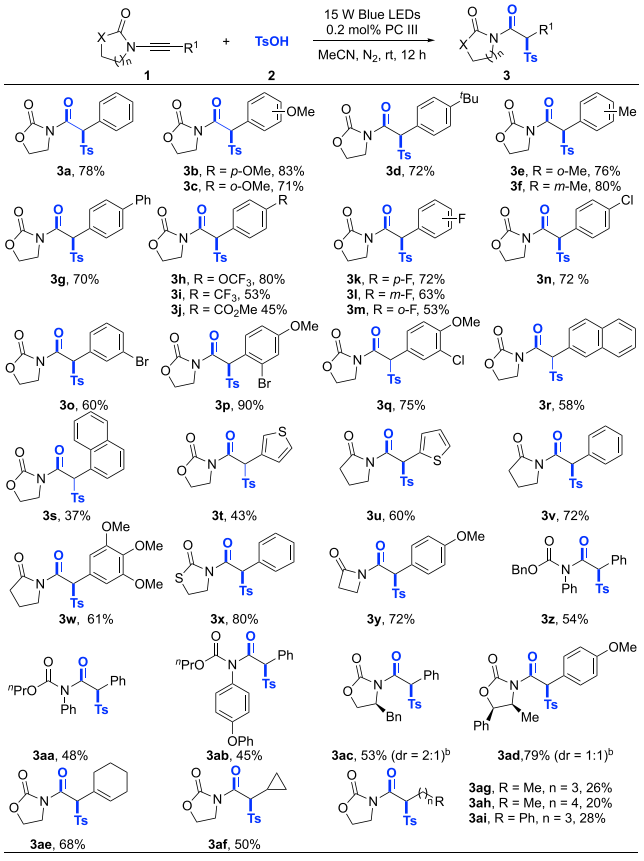
entry	photocatalyst	yield (%)[b]
1	*fac*-Ir(ppy)$_3$ PC I	48
2	PC II	55
3	PC III	64
4	PC IV	65[c]
5	PC V	55
6	9-Fluorenone PC VI	22
7	Eosin B PC VII	NDP
8	–	NR
9	PC III	NR[d]
10	PC III	67[e]
11	PC III	80[f]
12	PC III	70[g]

[a]Reaction conditions: the reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), photocatalyst (0.2 mol %) in solvent (1.0 mL), irradiating with 15 W blue LEDs under a N_2 atmosphere at room temperature for 12 h. [b]Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c]21 h. [d]Without light irradiation. [e]1.2 equiv of **2a** was employed. [f]1.2 equiv of **2a** and CH_3CN (0.33 mL) were employed. [g]The reaction was scaled up by 50 times.

iridium-based catalysts were then investigated under the same conditions (Table 1, entries 2–5). When PC II ($E^{1/2}[Ir^{IV}/*Ir^{III}]$ = −0.89 V versus SCE) which exhibits a lower reductive potential was used instead of PC I ($E^{1/2}[Ir^{IV}/*Ir^{III}]$ = −1.73 V versus SCE), the reaction efficiency was enhanced (Table 1, entry 2). Moreover, by using PC III or PC IV as the photocatalyst, the yield of **3a** was improved to 64% and 65%, respectively. Further screening of photocatalysts revealed that 9-fluorenone was less effective toward such transformation (Table 1, entry 6). Whereas Eosin B proved to be an effective catalyst for rearrangement of vinyl sulfonate by Li's group,[12] it failed to promote this reaction (Table 1, entry 7). Control experiments revealed that both the photocatalyst and light irradiation were indispensable for effective conversion (Table 1, entries 8 and 9). Since PC III showed the highest catalytic reactivity in the current system, it was used for further optimization. By fine-tuning the reaction stoichiometry, the yield of product **3a** was increased to 67% (Table 1, entry 10, and SI). Increasing the reaction concentration had a positive effect on the yield (80%, Table 1, entry 11, and SI). It is noteworthy that when the reaction was scaled up by 50 times, 1.26 g of product **3a** was obtained in 70% yield (Table 1, entry 12).

With an optimized set of conditions in hand (Table 1, entry 11), the scope of ynamides with *p*-toluenesulfonic acid was evaluated (Scheme 2). A variety of aryl ynamides were suitable

Scheme 2. Substrate Scope of Ynamides[a]



[a]See the Supporting Information for reaction details. Isolated yields were provided. [b]dr, diastereometric ratio.

substrates for this transformation (**3b–q**). Typically, ynamides that bear electron-donating groups on the phenyl ring delivered the desired products in good yields (**3b–h**). On the other hand, when aryl ynamides with electron-withdrawing groups (CF_3 and CO_2Me) were used, the corresponding products were obtained in relatively lower yields (**3i** and **3j**). Moreover, we were pleased to find that sterically demanding substrates functioned well in this reaction (**3c** and **3e**). Importantly, aryl halides (F, Cl, and Br) could be tolerated (**3k–o**), thus allowing easy further

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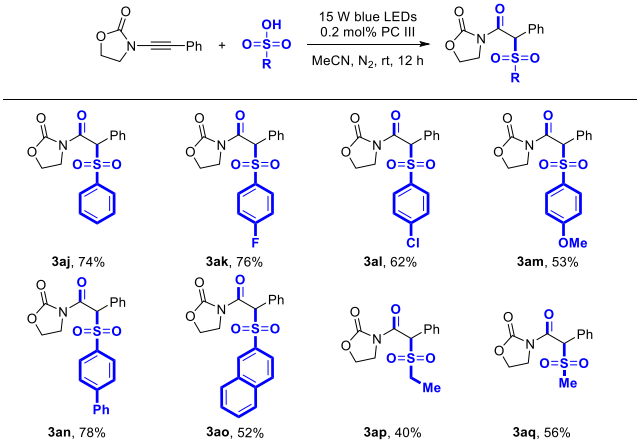
elaboration of the oxo-sulfonylation products. The aryl group decorated with multiple functional groups gave the corresponding product **3p** and **3q** in 90% and 75% yield, respectively. The reaction was also compatible with fused aromatic and heterocyclic substituents, as demonstrated by **3r**−**3u**. The amide moiety was not limited to oxazolidin-2-one; ynamides featuring pyrrolidine-2-one, thiazolidine-2-one, azetidin-2-one, and carbamate were all competent in this reaction, resulting in the desired products (**3u**−**3ab**) in moderate to good yields. An enantioselective variant of the reaction was further probed. The reaction of ynamides with chiral oxazolidin-2-one led to the desired products **3ac** and **3ad** successfully; however, only modest diastereoselectivity was achieved. Remarkably, enyne reacted smoothly in this reaction, delivering the product **3ae** in high yield, demonstrating the good chemoselectivity of this protocol. It is also worth mentioning that the reaction can be applied to cyclopropyl and alkyl ynamides, despite relatively lower yields (**3af**−**3ai**).

Next, the generality of sulfonic acids was examined with ynamide **1a**. As shown in Scheme 3, aryl sulfonic acids bearing

Scheme 3. Substrate Scope of Sulfonic Acids[a]

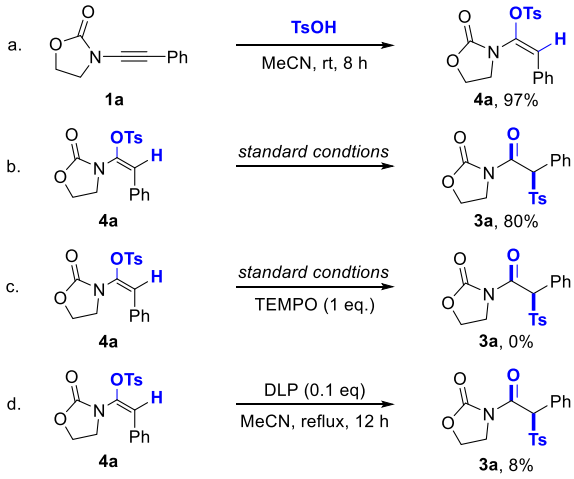


[a]See the Supporting Information for reaction details. Isolated yields were provided.

halides (F and Cl) could participate in the reaction as an oxygen and a sulfonyl source, furnishing the α-sulfonyl amides **3ak** and **3al** in 76% and 62% yields, respectively. Installation of an electron-donating group (OMe) to the phenyl ring of aryl sulfonic acid showed minimal impact on reaction yield (**3am**). Additionally, biphenyl and 2-naphthyl substituted sulfonic acids were also well tolerated as showcased in the smooth formation of **3an** and **3ao**. It is of note that alkyl sulfonic acids were also tolerated in the sulfonylation, which delivered the difunctionalization products **3ap** and **3aq** in synthetically useful yields.

To gain preliminary mechanistic insights into the reaction, the reaction progress was monitored stepwise. It was found that sulfonic acid could readily add to ynamide **1a**, giving the vinyl tosylate **4a** in nearly quantitative yield (Scheme 4a). Furthermore, the resultant vinyl tosylate can be converted into α-sulfonylated aimdes under standard conditions in high yield (Scheme 4b), thus confirming the proposed tandem reaction pathway. Moreover, the reaction of **4a** under standard conditions was completely inhibited with the addition of TEMPO as a radical scavenger, supporting a radical intermediate was involved in the rearrangement step (Scheme 4c). Of note, when the rearrangement of **4a** was performed using

Scheme 4. Control Experiments



radical initiator dilauroyl peroxide (DLP) instead of photosensitization, the oxo-sulfonylation product was also obtained, albeit in lower yield (Scheme 4d). This result further demonstrated that the radical nature of the present transformation. In addition, we performed a crossover experiment to probe whether the photoinduced rearrangement occurs through an intermolecular or intramolecular pathway. As a result, four crossover products were observed, suggesting an intermolecular mode for the sulfonyl transfer process. As shown in the Stern−Volmer quenching experiments, the excited photocatalyst could be quenched by the vinyl tosylate **4a**, rather than ynamide **1a** and tosylic acid **2a**. In order to clarify the essentially contrasting working mode of the photocatalyst (single electron transfer vs energy transfer),[15] the cyclic volatametry experiments were performed and the results showed that the reduction potential of compound **4a** ($E^{1/2}_{red} = -0.94$ V) is higher than the excited PC* ($E^{1/2}[*Ir^{III}/Ir^{IV}] = -0.51$ V), indicating that they cannot directly undergo a SET process under the standard conditions. Also, the triplet energy of **4a** and PC III were calculated to be 100.1 and 205.3 kJ/mol, respectively. Moreover, the reaction with UV sensitizer benzil delivered the desired product in 56% yield, while no product was observed when the reaction was carried out in the presence of Mn powder instead of photosensitizer.[16] These results collectively support the mechanistic rationale involving energy transfer. Remarkably, a light on/off experiment was also performed, which shows the reaction required continuous irradiation with blue LEDs. Finally, the quantum yield of the rearrangement of **4a** was determined as 10.0, suggesting a radical chain propagation process for the present reaction (see SI for details).

According to the above control experiments and prior reports, a proposed catalytic cycle for the oxo-sulfonylation is depicted in Scheme 5. Initially, electrophilic addition of sulfonic acid to ynamide **1** yields vinyl sulfonate **A** with excellent regioselectivity. Then, compound **A** is activated through the energy transfer (EnT) process from the excited PC*. The C−S bond of activated vinyl tosylate undergoes homolytic cleavage to generate an enol radical **B** as well as a sulfonyl radical **C**. Subsequently, the electrophilic *S*-centered radical **C** selectively adds to the electron-rich alkene moiety of vinyl sulfonate **A** and promotes the generation of the desired product **3** via a smooth β scission of radical intermediate **D** with the concomitantly generated sulfonyl radical **C** enabling a radical chain propagation.

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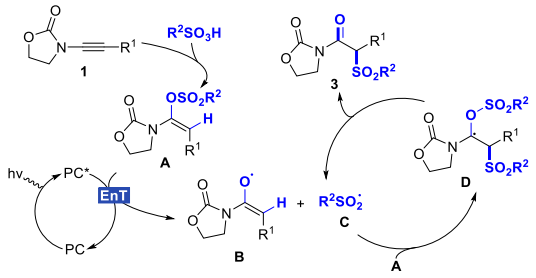
Scheme 5. Proposed Mechanism



In summary, an efficient photoinduced oxo-sulfonylation of ynamides with easily available and inexpensive sulfonic acids has been developed. A variety of α-sulfonylated amides were obtained by a tandem electrophilic addition/photoinduced radical rearrangement process. In addition, this reaction features good atom economy, mild reaction conditions, broad substrate scope, and excellent chemoselectivity. Moreover, this reaction provides an alternative strategy for α-sulfonylated amides which are important precursors in chemical transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00733.

General information, Experimental Section, mechanistic study, ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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