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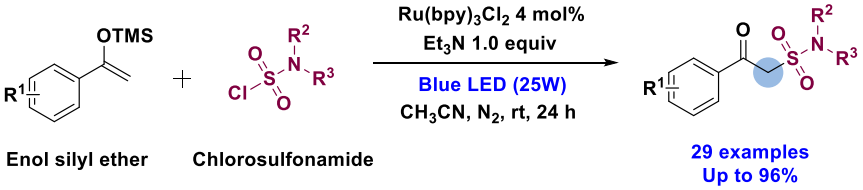
Photoredox-Catalyzed Generation of Sulfamyl Radicals: Sulfonamidation of Enol Silyl Ether with Chlorosulfonamide

Qiyu Luo,‡ Runyu Mao,‡ Yan Zhu and Yonghui Wang*

Department of Medicinal Chemistry, School of Pharmacy, Fudan University, 826 Zhangheng Road, Pudong, Shanghai 201203, China

yonghuiwang@fudan.edu.cn



ABSTRACT: A novel and practical photoredox-catalyzed generation of sulfamyl radicals followed by radical sulfonamidation of enol silyl ether has been described. Diverse functionalized *β*-ketosulfonamides were prepared in modest to excellent yields under mild and economic reaction conditions through the present catalytic protocol. Furthermore, the methodology developed provides an efficient and convenient approach to the synthesis of antiseizure drug Zonisamide.

Introduction

Sulfonamide was found to be the most important and valuable functional group in pharmaceutical and agrochemical industries.[1] In 2016, about 15% of the top 100 most prescribed drugs with a wide range of therapeutic applications such as cancer, cardiovascular, infectious and neurological diseases contain sulfonamide structure.[2] For example, Polmacoxib (**A**) is a cyclooxygenase-2 (COX-2) inhibitor used to treat osteoarthritis,[3] while Zonisamide (**B**) plays an important role in the treatment of partial seizures in adults (Figure 1).[4] Until now, although the traditional method of nucleophilic addition of amines to sulfonyl chlorides for synthesizing sulfonamides constitutes a

large proportion in organic synthesis, it still has several limitations such as poor reaction selectivity and instability during storage due to the high reactivity of sulfonyl chloride.[5] As a consequence of versatility and importance of sulfonamides, substantial attention was attracted in recent years to the development of new synthetic methods to prepare sulfonamide containing molecules. In 2018, Wu group reported a copper-catalyzed aminosulfonylation of aryldiazonium tetrafluoroborates, DABCO·$(SO_2)_2$, and N-chloroamines, affording a wide range of sulfonamides in moderate to good yields under mild conditions.[6] Later a method using calcium triflimide [$Ca(NTf_2)_2$] as a Lewis acid to activate sulfonyl fluorides toward nucleophilic addition with amines mediating the corresponding sulfonamides in good yields was described by Ball and his colleagues.[7] However, the development of a mild, effective and operationally simple approach to the synthesis of functionalized sulfonamides is still limited.

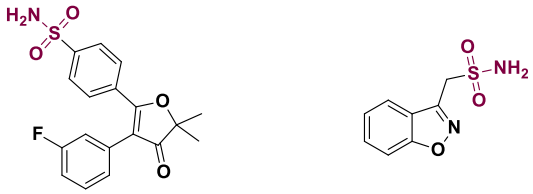
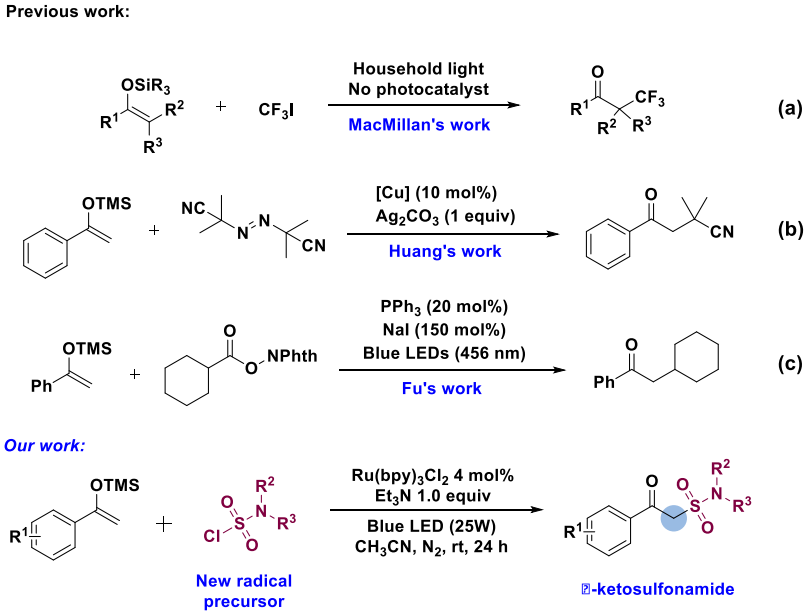


Figure 1. Biologically Active Molecules Containing Sulfonamide Core Structure

Silyl enol ethers are versatile reaction partners for constructing functionalized ketones and their derivatives in organic synthesis due to its property of reacting rapidly with the electrophilic carbon-centered radicals.[8] In 2011, MacMillan group reported a mild, operationally simple photoredox-catalyzed approach to the synthesis of α-trifluoromethyl carbonyl compounds from silyl enol ethers (Scheme 1, **a**).[9] Later a copper-catalyzed oxidative coupling of AIBN and ketone-derived enoxysilanes to γ-ketonitriles was presented by Huang group (Scheme 1, **b**).[10]

Very recently, Fu group disclosed a pioneering work on photocatalytic decarboxylative alkylations of silyl enol ethers mediated by triphenylphosphine and sodium iodide (Scheme 1, **c**).[11] Despite these progress achieved, it is particularly urgent and important to develop new methods to construct diverse functionalized ketones such as *β*-ketosulfonamides. Instead of the construction of S-N bond, installation of the whole aminosulfonyl motif would provide a better accessibility to complex sulfonamides. To that end, sulfamyl radicals have been considered as the key intermediates.[12] We were intrigued by the possibility whether chlorosulfonamide could serve as a new radical precursor to react with silyl enol ether generating highly functionalized *β*-ketosulfonamides by visible-light-mediated photoredox catalysis which was boomed as a competitive method for functional-group interconversions.[13] Herein, we report a novel and practical photoredox-catalyzed method for the generation of sulfamyl radicals from chlorosulfonamide followed by sulfonamidation of enol silyl ether, and demonstrate its application on efficient synthesis of antiseizure drug Zonisamide.

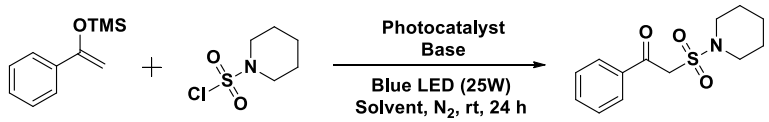
Scheme 1. Research Background and Summary of This Work



Results and Discussion

To verify the feasibility of our hypothesis, 1-phenyl-1-trimethylsiloxyethylene (**1a**) and piperidine-1-sulfonyl chloride (**2a**) were taken as representative reactants to conduct the optimization of reaction conditions under a photoredox-catalyzed system. To our delight, the reaction went smoothly generating the desired *β*-ketosulfonamide product in 23% yield using $Ru(bpy)_3Cl_2$ as photocatalyst (PC), K_2CO_3 as base and CH_3CN as solvent in blue LED (25 W) at room temperature (Table 1, entry 1). Further screening of PC revealed that no other PCs were superior to $Ru(bpy)_3Cl_2$ (Table 1, entry 2 and 3). The control experiments found that PC and light were essential in this photoredox-catalyzed system (Table 1, entry 4 and 5). Further investigation on ratio of the reactants **1a** and **2a** indicated that 45% of the product **3a** could be obtained when a ratio of **1a** and **2a** of 5:1 was applied (Table 1, entry 6-8). Base screening revealed that Et_3N was the best choice by increasing the yield to 67% (Table 1, entry 9). Obviously, the reaction couldn't occur in the absence of base (Table 1, entry 10). It is noteworthy that an excellent yield of 90% (86% isolated yield) was achieved by increasing the loading of PC to 4 mol% (Table 1, entry 11 and 12).

Table 1. Screening of the Reaction Conditions[a]



1a 2a 3a

Entry	PC (mol%)	Base	Ratio (**1a** : **2a**)	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$ (2)	K_2CO_3	2:1	23
2	*fac*-Ir(ppy)$_3$ (2)	K_2CO_3	2:1	17

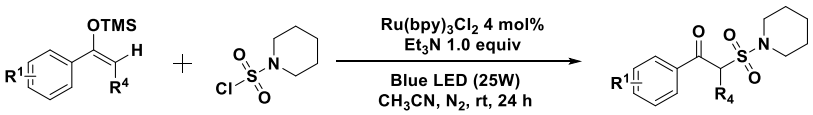
3	Eosin Y (2)	K_2CO_3	2:1	12
4	-	K_2CO_3	2:1	NR
5[c]	$Ru(bpy)_3Cl_2$ (2)	K_2CO_3	2:1	NR
6	$Ru(bpy)_3Cl_2$ (2)	K_2CO_3	3:1	26
7	$Ru(bpy)_3Cl_2$ (2)	K_2CO_3	4:1	33
8	$Ru(bpy)_3Cl_2$ (2)	K_2CO_3	5:1	45
9	$Ru(bpy)_3Cl_2$ (2)	Et_3N	5:1	67
10	$Ru(bpy)_3Cl_2$ (2)	-	5:1	NR
11	$Ru(bpy)_3Cl_2$ (3)	Et_3N	5:1	75
12	$Ru(bpy)_3Cl_2$ (4)	Et_3N	5:1	90(86[d])

[a] Reaction conditions: **1a**, **2a** (0.2 mmol), PC, base (1.0 equiv, 0.2 mmol), CH_3CN, blue LED (25 W), N_2, rt, 24 h; [b] HPLC yield; [c] No light; [d] Yield based on **2a**.

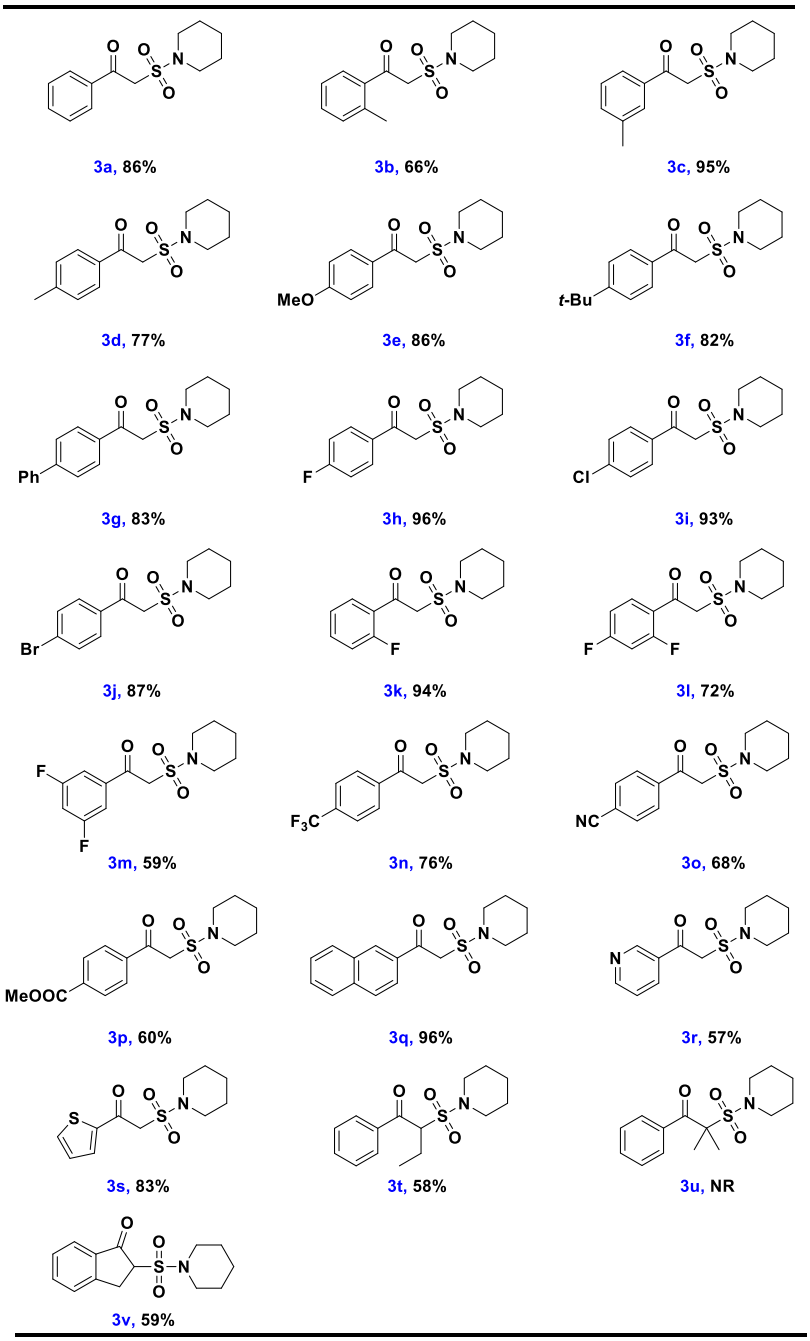
We then explored the reaction scope with a wide range of silyl enol ethers bearing multiple functional groups under the optimized reaction conditions as summarized in Table 2. It was demonstrated that the substrates with different electron-donating groups such as methyl, methoxy, *tert*-butyl and phenyl group proceeded smoothly to afford the desired *β*-ketosulfonamide products in good yields (Table 2, **3b**-**3g**). In addition, halogen substituents were found to be suitable candidates in this transformation to produce the corresponding products **3h**-**3m** in 59-96% yields. Notably the electron-withdrawing substituents such as CF_3- (**3n**), CN- (**3o**) and COOMe- (**3p**) on the *para* position of the aromatic ring were also compatible in this protocol. Furthermore,

naphthyl-substituted substrate performed well in 96% yield (Table 2, entry **3q**). Interestingly, heteroaromatic substrates were able to be efficiently converted into the desired *β*-ketosulfonamides (Table 2, **3r** and **3s**). More importantly, a moderate yield was achieved by using (*E*)-trimethyl((1-phenylbut-1-en-1-yl)oxy)silane as a substrate in this reaction (Table 2, **3t**). However, for the substrate of trimethyl((2-methyl-1-phenylprop-1-en-1-yl)oxy)silane, the reaction could hardly occur probably due to steric effect (Table 2, **3u**). To our delight, for the less reactive substrate **3v**, the reaction could occur in a satisfactory yield.

Table 2. Substrate Scope of Various Enol Silyl Ethers[a, b]



1 2a 3

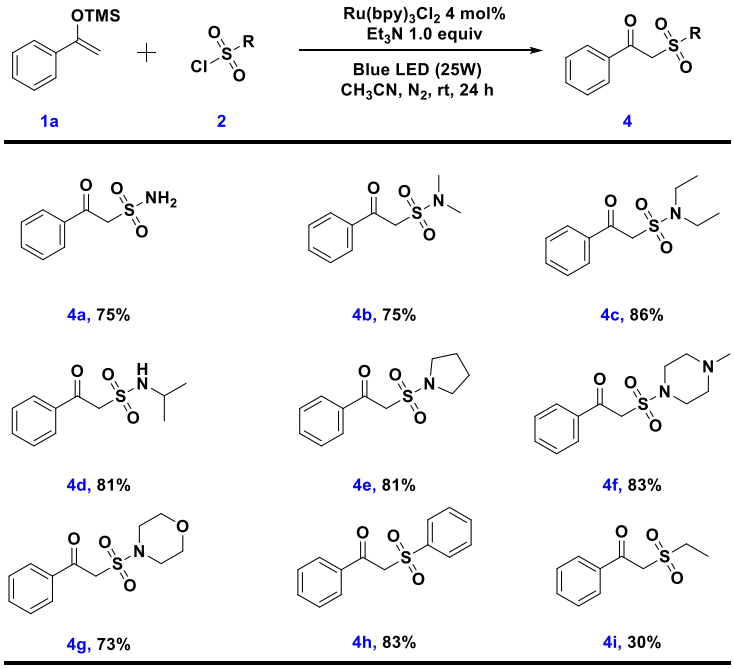


[a] Reaction conditions: **1** (5.0 equiv, 1.0 mmol), **2a** (0.2 mmol), $Ru(bpy)_3Cl_2$ (4 mol%, 0.008 mmol), Et_3N (1.0 equiv, 0.2 mmol), CH_3CN, blue LED (25W), N_2, rt, 24 h; [b] Yield based on **2a**.

Encouraged by these results, we further probe the reaction generality with respect to different chlorosulfonamides under the optimized reaction conditions as depicted in Table 3. It was interesting to learn that unsubstituted chlorosulfonamide could serves as good substrate in this

process and efficiently formed *β*-ketosulfonamide **4a** which could undergo further functionalizations in organic synthesis and have applications in pharmaceutical industry. In the meanwhile, other chlorosulfonamides bearing a mono-substituted group or di-substituted groups were all converted to the corresponding *β*-ketosulfonamides smoothly in good to excellent yields (Table 3, **4b**-**4g**). Interestingly, benzenesulfonyl chloride and ethanesulfonyl chloride (Table 3, **4h** and **4i**) were also well tolerated in our photoredox-catalyzed system.

Table 3. Substrate Scope of Various Sulfonyl Chlorides[a, b]



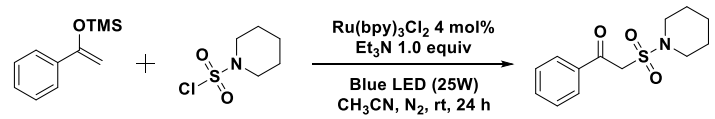
[a] Reaction conditions: **1a** (5.0 equiv, 1.0 mmol), **2** (0.2 mmol), $Ru(bpy)_3Cl_2$ (4 mol%, 0.008 mmol), Et_3N (1.0 equiv, 0.2 mmol), CH_3CN, blue LED (25W), N_2, rt, 24 h; [b] Yield based on **2**.

To demonstrate the potential application of our methodology, a gram-scale synthesis was then performed. 6.0 Mmol of **2a** was taken into the model reaction, the corresponding product **3a** was obtained in 78% yield (1.25 g, Scheme 2, **d**). Next, a one-pot synthetic protocol was attempted by

using acetophenone as the starting material without purifying the intermediate **1a**, but only 17% of the desired *β*-ketosulfonamide product **3a** was detected by HPLC (Scheme 2, **e**). Further transformations of *β*-ketosulfonamide were conducted by subjecting **4a** into copper-catalyzed coupling reaction with phenylboronic acid [14] to provide **5** in 70% yield and nucleophilic substitution reaction with 1-bromopropane [15] to mediate **6** in 52% yield (Scheme 2, **f**). To further demonstrate the utility of the method developed, we have applied it to the preparation of Zonisamide [16] (Scheme 2, **g**). Key intermediate **7c** could be easily prepared in 71% yield with our method from intermediate **7b** which was derived from commercially available 2'-fluoroacetophenone. Finally, Zonisamide was prepared from *β*-ketosulfonamide **7c** by sequential hydroxyl amination and cyclization reaction with an overall of 54% yield.

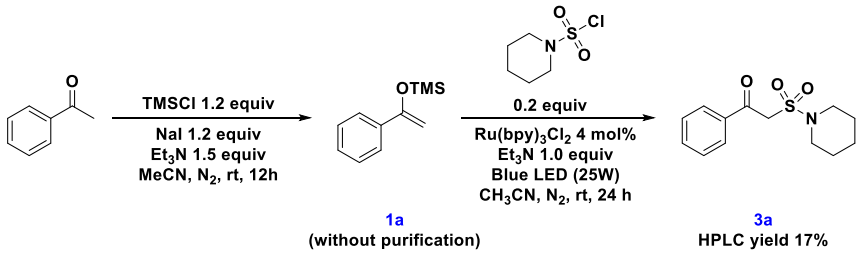
Scheme 2. Functional Group Transformation and Synthetic Application

Gram-scale synthesis:



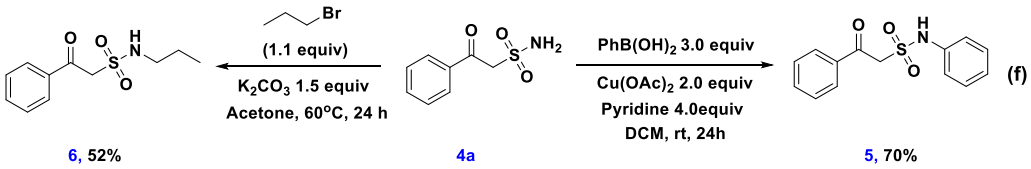
(d)

One-pot synthesis:

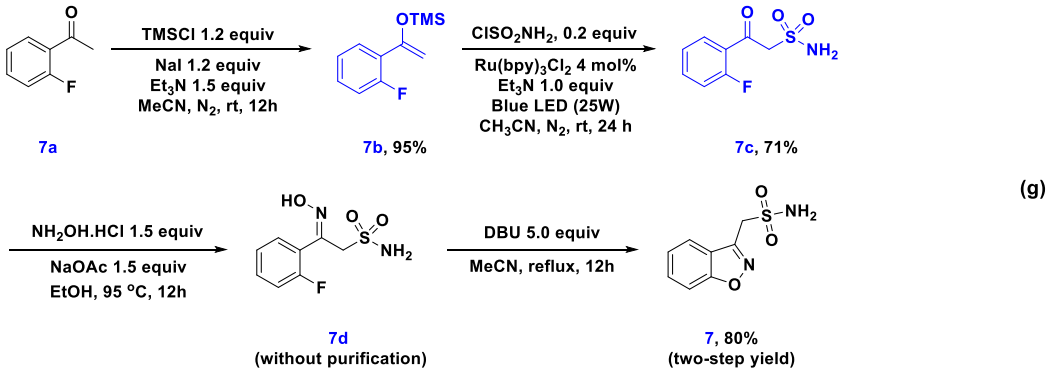


(e)

Functionalization of *β*-ketosulfonamide **4a**:

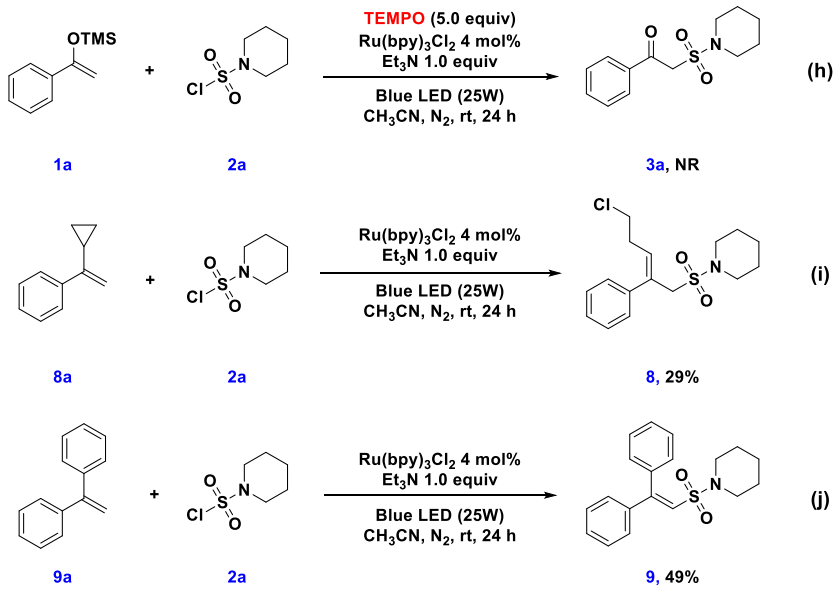


Synthesis of Zonisamide:



To validate the reaction mechanism, some experiments were designed and carried out. First, the desired transformation was completely hindered after the introduction of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (Scheme 3, **h**). Next, reaction with the radical clock precursor **8a** gave the ring-opening product **8** in 29% yield (Scheme 3, **i**). Last, radical trapping product was isolated in 49% yield by using 1,1-diphenylethylene under the standard condition (Scheme 3, **j**). All these experimental results indicated that a free-radical addition process was involved in the reaction.

Scheme 3. Mechanistic Study

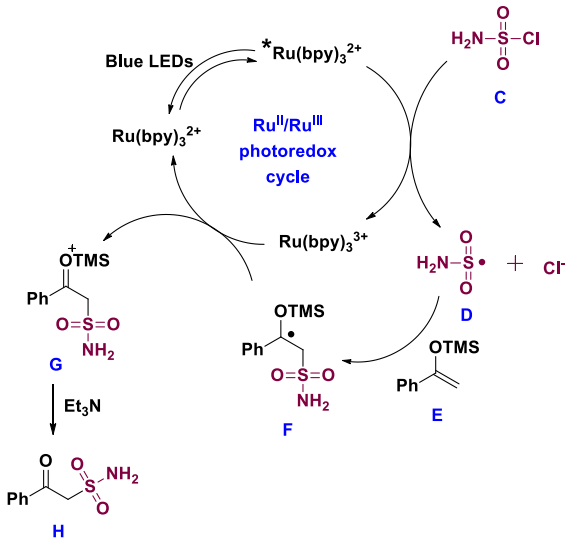


In order to understand the quenching cycle of this system, we carried out some luminescence quenching experiments. It showed that $Ru(bpy)_3Cl_2$ luminescence decreased dramatically in the presence of piperidine-1-sulfonyl chloride (**2a**), but dropped a little in the presence of trimethylamine and maintained in the presence of trimethyl[(1-phenylvinyl) oxy] silane (**1a**) (Supporting Information, Schemes S1-S3). Also we have determined the quantum yield of the photoreaction ($\Phi = 41\%$).

Based on the present experimental evidence and literature precedent, a plausible mechanism for the generation of sulfamyl radical followed by sulfonamidation of enol silyl ether was proposed in Scheme 4. Initially, irradiation of $Ru(bpy)_3Cl_2$ with visible light makes it convert into the excited-state species $Ru(bpy)_3^{2+}$*. Immediately single electron transfer (SET) oxidation of $Ru(bpy)_3^{2+}$* by electrophilic chlorosulfonamide generates $Ru(bpy)_3^{3+}$ and sulfamyl radical **D**.[17] **D** subsequently attacks 1-phenyl-1-trimethylsiloxyethylene to produce radical intermediate **F**. A second SET oxidation process of **F** then occurs, generating intermediate **G** and $Ru(bpy)_3^{2+}$.[18]

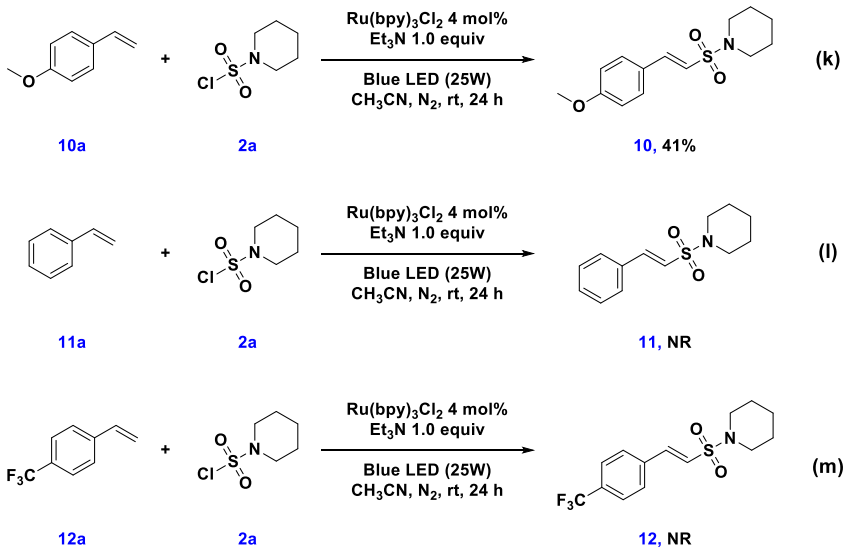
Ultimately, eliminating the proton of **G** in the presence of base gives the desired *β*-ketosulfonamide **H**.

Scheme 4. Proposed Mechanism



In an attempt to elucidate the reactivity of sulfamyl radical, substituted styrenes with different electronic properties were subjected to the optimal reaction condition. Only strong electron-donating group provided the corresponding product (Scheme 5, **k**), whereas electron-withdrawing substituent or non-substituted styrenes resulted in no reaction (Scheme 5, **l** and **m**), which indicated the electrophilic character of the sulfamyl radical. Indole was also taken as a coupling partner in the reaction, but there was no desired product obtained. The electrical selectivity of sulfamyl radical can guide us to design radical series reactions, and possibly, three component reactions can be performed.

Scheme 5. Reactivity of Sulfamyl Radical



Conclusion

In summary, we have developed a novel and practical photoredox-catalyzed generation of sulfamyl radicals from chlorosulfonamide followed by radical sulfonamidation of enol silyl ethers. A set of *β*-ketosulfonamides are synthesized with expanded substrate scope and good functional group compatibility. Besides, the excellent performance in the synthesis of antiseizure drug Zonisamide indicates that the transformation is efficient, practical and valuable in organic synthesis. Further investigation on detailed mechanism and synthetic applications are currently in progress.

Experimental Section

General Information. All commercially available reagents were used without further purification unless otherwise stated. $Ru(bpy)_3Cl_2$ was purchased from *Shanghai Bidepharm*. The reactions were monitored by thin-layer chromatography (TLC) analysis. Silica gel (200−300 mesh) was used for column chromatography. High-resolution MS (HRMS) was analyzed by a TOF analyzer.

The ion source is electrospray ionization (ESI). ^{1}H, ^{19}F NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra was recorded on 600 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of DMSO-d_6 (δ 2.50 ppm). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of DMSO-d_6 (δ 39.52 ppm) on the δ scale. The blue LED was manufactured by *Xuzhou Aijia Electronic Technology Co. Ltd.*. The power is 25 W, 15 W, 5 W and the wavelength range is from 460 nm to 465 nm. The distance from the light source to the irradiation vessel is 5 cm. The quantum yield was determined by a FZ-A irradiatometer, and the luminescence quenching experiment was recorded using a F98 Fluorospectrophotometer.

General procedure for preparation of silyl enol ethers (GP-1).[19] A round-bottom flask containing a mixture of ketone (1.0 equiv, 10 mmol), sodium iodide (1.2 equiv, 12 mmol) and dry CH_3CN (15 mL) was evacuated and filled with nitrogen three times, stirring for 5 mins at room temperature. To the resulting solution, triethylamine (1.5 equiv, 15 mmol) and chlorotrimethylsilane (1.2 equiv, 12 mmol) were added. The reaction mixture was stirred overnight at room temperature and quenched with a mixture of petroleum ether (25 mL) and saturated NH_4Cl (25 mL) at 0 °C. The organic phase was separated and the aqueous layer was extracted with petroleum ether (2 × 30 mL). The combined organic fractions were washed with ice water (25 mL) and saturated NH_4Cl (25 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by distillation under

reduced pressure to deliver silyl enol ethers **1a – 1v**.

General procedure for photoredox-catalyzed sulfamidation of silyl enol ethers (GP-2). $Ru(bpy)_3Cl_2$ (4.0 mol%, 0.008 mmol, 0.004mmol/mL) was added to a dry 10 mL Schlenk tube with a stirring bar, then air was withdrawn and backfilled with N_2 (three times). Dry CH_3CN (2 mL), silyl enol ether (5.0 equiv, 1.0 mmol) and sulfamyl chloride (1.0 equiv, 0.2 mmol) were added under N_2. The reaction mixture was stirred under the irradiation of a 25 W blue LED for 24 h at room temperature. After that, the mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (petroleum ether / ethyl acetate = 5:1 – 1:1) to provide the product **3a – 3v**, **4a – 4i**, **7c**, **8**, **9**, **10**. Two tubes were set up at the same time.

Gram-scale synthesis of 3a. $Ru(bpy)_3Cl_2$ (4.0 mol%, 0.24 mmol) was added to a dry round-bottom flask with a stirring bar, then air was withdrawn and backfilled with N_2 (three times). Dry CH_3CN (60 mL), **1a** (5.0 equiv, 30.0 mmol) and **2a** (1.0 equiv, 6.0 mmol) were added under N_2. The reaction mixture was stirred under the irradiation of a 25 W blue LED for 24 h at room temperature. After that, the mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (petroleum ether / ethyl acetate = 10:1 – 5:1) to provide the product **3a** (1.25 g, 78%) as white solid.

One-pot synthesis of 3a. Crude product of **1a** was prepared by **GP-1** without reduced pressure

distillation. $Ru(bpy)_3Cl_2$ (4.0 mol%, 0.008 mmol) was added to a dry 10 mL Schlenk tube with a stirring bar, then air was withdrawn and backfilled with N_2 (three times). Dry CH_3CN (2.0 mL), crude **1a** (5.0 equiv, 1.0 mmol) and **2a** (1.0 equiv, 0.2 mmol) were added under N_2. The reaction mixture was stirred under the irradiation of a 25 W blue LED for 24 h at room temperature. The yield was determined by HPLC, 17%.

Procedure for preparation of 2-Oxo-N, 2-diphenylethane-1-sulfonamide (5).[14] A round-bottom flask with a stirring bar contained a mixture of **4a** (1.0 equiv, 0.4 mmol, 79.6 mg), $Cu(OAc)_2$ (2.0 equiv, 0.8 mmol, 145.3 mg), phenylboronic acid (3.0 equiv, 1.2 mmol, 146.3 mg), pyridine (4.0 equiv, 1.6 mmol, 136.2 mg) and CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature overnight, then extracted with CH_2Cl_2 (10 ml×2), dried over anhydrous sodium sulfate, concentrated in vacuo, and purified by column chromatography (petroleum ether / ethyl acetate = 5:1 – 1:1) to provide the product **5** as white solid.

Procedure for preparation of 2-Oxo-2-phenyl-N-propylethane-1-sulfonamide (6).[15] A round-bottom flask with a stirring bar containing a mixture of **4a** (1.0 equiv, 0.4 mmol, 79.6 mg), 1-bromopropane (1.1 equiv, 0.44 mmol, 54.1 mg), K_2CO_3 (3.0 equiv, 1.2 mmol, 165.6 mg), acetone (4 mL). The reaction mixture was stirred at 60 ºC in an oil bath, monitored by TLC. After full conversion, concentrated in vacuo, and purified by column chromatography (petroleum ether / ethyl acetate = 5:1 – 1:1) to provide the product **6** as white solid.

Procedure for preparation of Benzo [d] isoxazol-3-ylmethanesulfonamide (7).[20]

Intermediate **7b** was prepared by following GP-1 and **7c** was obtained by following GP-2.

A mixture of **7c** (1.0 equiv, 0.3 mmol, 65.0 mg), $NH_2OH{\cdot}HCl$ (1.5 equiv, 0.45 mmol, 31.3 mg), and NaOAc (2.5 equiv, 0.75 mmol, 61.5 mg) in ethanol (1.5 mL) was placed into a 10 mL round-bottom-flask with a reflux condenser. Then the reaction flask was heated to 95 ºC in an oil bath and the reaction progress was monitored by TLC. After full conversion, the mixture was cooled to room temperature and filtered, the solution was concentrated in vacuo without further purification. Then CH_3CN (2 mL) and DBU (4.0 equiv, 1.2 mmol, 182.7 mg) were added to the crude product, the reaction mixture was refluxed in an oil bath at 85 ºC and monitored by TLC. After completion of the reaction, the resulting mixture was concentrated in vacuo, and purified by silica gel chromatography (DCM / MeOH) to provide the final product **7** as white solid and the total yield was 54%.

1-Phenyl-2-(piperidin-1-ylsulfonyl) ethan-1-one ***(3a)***.[21] 91.8 mg, yield: 86%, white solid, mp: 106.4 – 107.9 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 4.89 (s, 2H), 3.21 – 3.18 (m, 4H), 1.56 – 1.49 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.8, 136.0, 134.1, 129.2, 128.8, 55.9, 46.3, 25.1, 23.1; MS (ESI) $[M+H]^+$ 268.1.

2-(Piperidin-1-ylsulfonyl)-1-(o-tolyl) ethan-1-one ***(3b)***. 74.2 mg, yield: 66%, white solid, mp: 63.8 – 65.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.39 – 7.33 (m, 2H), 4.81 (s, 2H), 3.15 (s, 4H), 2.42 (s, 3H), 1.49 (s, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 192.7, 138.2, 136.5, 132.3, 131.7, 130.3, 125.8, 58.3, 46.2, 25.1, 23.1, 20.7; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1158, found 282.1157.

*2-(Piperidin-1-ylsulfonyl)-1-(m-tolyl) ethan-1-one (**3c**).* 106.8 mg, yield: 95%, white solid, mp: 72.8 – 75.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 – 7.84 (m, 2H), 7.52 (d, J = 6.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 4.86 (s, 2H), 3.19 (s, 3H), 2.39 – 2.37 (m, 4H), 1.56 – 1.48 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.8, 138.2, 136.0, 134.7, 129.4, 128.6, 126.6, 55.9, 46.2, 25.1, 23.1, 20.8; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1158, found 282.1157.

*2-(Piperidin-1-ylsulfonyl)-1-(p-tolyl) ethan-1-one (**3d**).* 86.5 mg, yield: 77%, white solid, mp: 73.5 – 75.3 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 6.8 Hz, 2H), 7.38 (d, J = 6.8 Hz, 2H), 4.83 (s, 2H), 3.21 – 3.17 (m, 4H), 2.39 (s, 3H), 1.56 – 1.49 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.2, 144.8, 133.6, 129.4, 129.3, 55.8, 46.3, 25.1, 23.2, 21.2; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1158, found 282.1156.

*1-(4-Methoxyphenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3e**).* 102.2 mg, yield: 86%, white solid, mp: 95.6 – 97.3 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 4.79 (s, 2H), 3.86 (s, 3H), 3.20 – 3.17 (m, 4H), 1.56 – 1.48 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 187.9, 163.9, 131.8, 129.0, 114.0, 55.8, 55.7, 46.3, 25.1, 23.2; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{20}NO_4S$ 298.1108, found 298.1106.

*1-(4-(Tert-butyl) phenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3f**).* 105.9 mg, yield: 82%, white solid, mp: 155.7 – 156.8 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 4.84 (s, 2H), 3.21 – 3.18 (m, 4H), 1.56 – 1.51 (m, 6H), 1.31 (s, 9H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.2, 157.3, 133.5, 129.3, 125. 6, 55.9, 46.2, 34.9, 30.7, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{17}H_{26}NO_3S$ 324.1628, found 324.1629.

*1-([1,1'-Biphenyl]-4-yl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3g**).* 113.9 mg, yield: 83%, white solid, mp: 109.8 – 110.9 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 4.92 (s, 2H), 3.23 – 3.21 (m, 4H), 1.58 – 1.50 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.3, 145.4, 138.6, 134.8, 123.0, 129.1, 128.6, 127.1, 126.9, 56.0, 46.3, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{22}NO_3S$ 344.1315, found 344.1318.

*1-(4-Fluorophenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3h**).* 109.4 mg, yield: 96%, white solid, mp: 132.2 – 133.5 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 – 8.12 (m, 2H), 7.43 – 7.39 (m, 2H), 4.89 (s, 2H), 3.20 – 3.18 (m, 4H), 1.56 – 1.49 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 188.4, 165.6 (d, J = 255.0 Hz), 132.7, 132.4 (d, J = 9.5 Hz), 132.4, 155.9, 115.9 (d, J = 21.8 Hz), 56.0, 46.3, 25.1, 23.1; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ -104.41 – -104.38 (m, 1F); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{17}FNO_3S$ 286.0908, found 286.0907.

*1-(4-Chlorophenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3i**).* 112.0 mg, yield: 93%, white solid, mp: 148.4 – 150.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 4.89 (s, 2H), 3.21 – 3.17 (m, 4H), 1.56 – 1.50 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 188.9, 139.1, 134.6, 131.1, 128.9, 56.1, 46.2, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{17}ClNO_3S$ 302.0612, found 302.0611.

*1-(4-Bromophenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3j**).* 120.1 mg, yield: 87%, white solid, mp: 158.8 – 161.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 4.90 (s, 2H), 3.20 – 3.18 (m, 4H), 1.56 – 1.50 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz,

DMSO-d_6) δ 89.1, 134.9, 131.8, 131.2, 128.4, 56.1, 46.2, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{17}BrNO_3S$ 346.0107, found 346.0106.

*1-(2-Fluorophenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3k**).* 107.2 mg, yield: 94%, white solid, mp: 82.7 – 84.1 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 – 7.90 (m, 1H), 7.73 – 7.71 (m, 1H), 7.40 – 7.36 (m, 2H), 4.79 (s, 2H), 3.19 – 3.16 (m, 4H), 1.56 – 1.49 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 187.4, 160.9 (d, J = 254.4 Hz), 136.0 (d, J = 9.3 Hz), 131.0, 124.8, 117.0 (d, J = 22.8 Hz), 59.2, 46.2, 25.1, 23.1; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ -110.63 – -110.57 (m, 1F); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{17}FNO_3S$ 286.0908, found 286.0905.

*1-(2,4-Difluorophenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3l**).* 87.3 mg, yield: 72%, white solid, mp: 106.4 – 107.6 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (dd, J = 8.4 Hz, 1H), 7.47 (t, J = 10.3 Hz, 1H), 7.28 (t, J = 8.8 Hz, 1H), 4.78 (s, 2H), 3.19 – 3.17 (m, 4H), 1.56 – 1.50 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 186.2, 165.5 (dd, J = 254.0 Hz, 12.8 Hz), 161.9 (dd, J = 257.7 Hz, 13.2 Hz), 133.4 (d, J = 10.4 Hz), 121.8 (d, J = 10.2 Hz), 112.4 (d, J = 21.6 Hz), 105.4 (t, J = 26.6 Hz), 59.1, 46.2, 25.1, 23.1; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ -110.81 – -110.71 (m, 1F), -105.22 – -105.13 (m, 1F); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{16}F_2NO_3S$ 304.0813, found 304.0812.

*1-(3,5-Difluorophenyl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3m**).* 71.5 mg, yield: 59%, white solid, mp: 101.4 – 103.4 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 6.1 Hz, 2H), 7.67 (t, J = 8.7 Hz, 1H), 4.96 (s, 2H), 3.21 – 3.18 (m, 4H), 1.56 – 1.50 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 188.0, 162.4 (dd, J = 246.8 Hz, 12.2 Hz), 138.9 (t, J = 8.0 Hz), 112.4 (d, J = 21.3 Hz), 109.4 (t, J = 25.6 Hz), 56.3, 46.2, 25.1, 23.1; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ -108.31

(t, J = 7.5 Hz, 2F); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{16}F_2NO_3S$ 304.0813, found 304.0814.

*2-(Piperidin-1-ylsulfonyl)-1-(4-(trifluoromethyl) phenyl) ethan-1-one (**3n**).* 101.8 mg, yield: 76%, white solid, mp: 109.4 – 110.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H), 4.99 (s, 2H), 3.22 – 3.19 (m, 4H), 1.56 – 1.51 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.5, 139.00, 133.2 (q, J = 32.0 Hz), 130.0, 125.7, 123.6 (q, J = 271.0 Hz), 56.4, 46.2, 25.1, 23.1; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ - 61.72 (s, 3F); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{17}F_3NO_3S$ 336.0876, found 336.0873.

*4-(2-(Piperidin-1-ylsulfonyl) acetyl) benzonitrile (**3o**).* 79.4 mg, yield: 68%, white solid, mp: 134.1 – 137.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 8.2 Hz, 2H), 8.07 (d, J = 8.2 Hz, 2H), 4.98 (s, 2H), 3.21 – 3.18 (m, 4H), 1.56 – 1.49 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.4, 138.9, 132.7, 129.7, 118.0, 115.9, 56.3, 46.2, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{14}H_{16}N_2O_3SNa$ 315.0774, found 315.0774.

*Methyl 4-(2-(piperidin-1-ylsulfonyl) acetyl) benzoate (**3p**).* 78.0 mg, yield: 60%, white solid, mp: 92.4 – 94.1 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 8.3 Hz, 2H), 8.11 (d, J = 8.3 Hz, 2H), 4.96 (s, 2H), 3.90 (s, 3H), 3.21 – 3.18 (m, 4H), 1.56 – 1.51 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.7, 165.4, 139.2, 133.9, 129.4, 129.4, 56.3, 52.6, 46.2, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{20}NO_5S$ 326.1057, found 326.1056.

*1-(Naphthalen-2-yl)-2-(piperidin-1-ylsulfonyl) ethan-1-one (**3q**).* 121.7 mg, yield: 96%, white solid, mp: 109.0 – 111.3 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.05 – 8.02 (m, 3H), 7.71 – 7.68 (m, 2H), 5.03 (s, 2H), 3.24 – 3.22 (m, 4H), 1.54 – 1.49 (m,

6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.7, 135.3, 133.3, 132.1, 132.0, 129.8, 129.2, 128.4, 127.7, 127.2, 123.8, 56.0, 46.3, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{17}H_{20}NO_3S$ 318.1158, found 318.1160.

*2-(Piperidin-1-ylsulfonyl)-1-(pyridin-3-yl) ethan-1-one (**3r**).* 61.1 mg, yield: 57%, white solid, mp: 100.3 – 102.1 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.85 (d, J = 4.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.0, 4.0 Hz 1H), 4.98 (s, 2H), 3.21 – 3.19 (m, 4H), 1.56 – 1.51 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.4, 154.1, 150.3, 136.5, 131.3, 123.9, 56.4, 46.2, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{12}H_{17}N_2O_3S$ 269.0954, found 269.0952.

*2-(Piperidin-1-ylsulfonyl)-1-(thiophen-2-yl) ethan-1-one (**3s**).* 90.6 mg, yield: 83%, white solid, mp: 135.4 – 137.5 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 4.0 Hz, 1H), 8.14 (d, J = 4.0 Hz, 1H), 7.31 (t, J = 4.0 Hz, 1H), 4.81(s, 2H), 3.21 – 3.18 (m, 4H), 1.55 – 1.52 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 182.1, 143.3, 137.1, 136.5, 129.0, 56.6, 46.3, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{11}H_{16}NO_3S_2$ 274.0566, found 274.0564.

*1-Phenyl-2-(piperidin-1-ylsulfonyl) butan-1-one (**3t**).* 68.4 mg, yield: 58%, white solid, mp: 105.3 – 107.1 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 6.9 Hz, 1H), 7.58 (t, J = 6.7 Hz, 2H), 5.49 – 5.46 (m, 1H), 3.15 – 3.13 (m, 4H), 2.20 – 2.12 (m, 1H), 1.99 – 1.92 (m, 1H), 1.43 – 1.40 (m, 6H), 0.83 (t, J = 6.0 Hz, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 193.1, 137.1, 134.0, 128.8, 66.6, 46.7, 25.5, 23.1, 21.4, 10.9; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{15}H_{22}NO_3S$ 296.1315, found 296.1315.

*2-(Piperidin-1-ylsulfonyl)-2,3-dihydro-1H-inden-1-one (**3v**).* 65.8 mg, yield: 59%, white solid, mp: 93.9 – 95.8 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 – 7.70 (m, 2H), 7.66 (d, J = 7.6 Hz, 1H),

7.49 (t, *J* = 7.3 Hz, 1H), 4.68 (dd, *J* = 8.0, 2.7 Hz, 1H), 3.60 – 3.54 (m, 1H), 3.44 – 3.39 (m, 1H), 3.33 – 3.23 (m, 4H), 1.51 – 1.49 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 195.8, 152.7, 135.8, 135.5, 128.1, 126.9, 123.8, 64.9, 46.6, 29.2, 25.4, 23.2; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{18}NO_3S$ 280.1002, found 280.1004.

*2-Oxo-2-phenylethane-1-sulfonamide (**4a**)*. 59.7 mg, yield: 75%, white solid, mp: 152.7 – 154.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, *J* = 7.9 Hz, 2H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.17 (s, 2H), 4.81 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 190.0, 135.9, 133.9, 129.2, 128.7, 61.8; HRMS (ESI-TOF) m/z $[M-H]^-$ calcd for $C_8H_8NO_3S$ 198.0230, found 198.0230.

*N, N-dimethyl-2-oxo-2-phenylethane-1-sulfonamide (**4b**)*.[22] 68.1 mg, yield: 75%, white solid, mp: 81.6 – 82.8 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 4.93 (s, 2H), 2.83 (s, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.9, 135.9, 134.1, 129.2, 128.8, 54.8, 37.4; MS (ESI) $[M+H]^+$ 228.1.

*N, N-diethyl-2-oxo-2-phenylethane-1-sulfonamide (**4c**)*.[23] 87.7 mg, yield: 86%, white solid, mp: 56.6 – 58.4 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 4.90 (s, 2H), 3.24 – 3.19 (m, 4H), 1.12 – 1.09 (t, *J* = 6.0 Hz, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.7, 135.9, 134.0, 129.2, 128.7, 58.2, 42.2, 14.6; MS (ESI) $[M+H]^+$ 256.2.

*N-isopropyl-2-oxo-2-phenylethane-1-sulfonamide (**4d**)*. 78.1 mg, yield: 81%, white solid, mp: 81.7 – 84.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 7.9 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 1H), 4.85 (s, 2H), 3.55 – 3.47 (m, 1H), 1.11 (d, *J* =

6.5 Hz, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.9, 136.0, 133.9, 129.3, 128.7, 59.7, 45.5, 23.6; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{11}H_{15}NO_3SNa$ 264.0665, found 264.0666.

*1-Phenyl-2-(pyrrolidin-1-ylsulfonyl) ethan-1-one (**4e**)*.[24] 82.0 mg, yield: 81%, white solid, mp: 99.0 – 101.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 6.9 Hz, 2H), 7.70 (t, J = 6.8 Hz, 1H), 7.57 (t, J = 6.7 Hz, 2H), 4.97 (s, 2H), 3.31 – 3.28 (m, 4H), 1.86 – 1.83 (m, 4H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 190.1, 136.0, 134.1, 129.3, 128.8, 55.1, 47.8, 25.3; MS (ESI) $[M+H]^+$ 254.1.

*2-((4-Methylpiperazin-1-yl) sulfonyl)-1-phenylethan-1-one (**4f**)*. 93.7 mg, yield: 83%, white solid, mp: 60.4 – 62.1 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 7.5 Hz, 2H), 7.71 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 4.95 (s, 2H), 3.23 (t, J = 6.1 Hz, 4H), 2.36 (t, J = 6.0 Hz, 4H), 2.19 (s, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.7, 135.9, 134.2, 129.2, 128.8, 55.9, 54.0, 45.4, 45.3; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_3S$ 283.1111, found 283.1113.

*2-(Morpholinosulfonyl)-1-phenylethan-1-one (**4g**)*.[25] 78.5 mg, yield: 73%, white solid, mp: 135.1 – 137.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 7.8 Hz, 2H), 7.71 (t, J = 7.9 Hz, 1H), 7.58 (t, J = 8.1 Hz, 2H), 5.00 (s, 2H), 3.63 (t, J = 6.3 Hz, 4H), 3.23 (t, J = 6.1 Hz, 4H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.7, 135.9, 134.2, 129.2, 128.8, 65.8, 55.7, 45.6; MS (ESI) $[M+H]^+$ 270.1.

*1-Phenyl-2-(phenylsulfonyl) ethan-1-one (**4h**)*.[26] 86.3 mg, yield: 83%, white solid, mp: 95.8 – 97.1 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 7.2 Hz, 2H), 7.91 (t, J = 7.6 Hz, 2H), 7.73 (t, J = 6.6 Hz, 1H), 7.69 – 7.62 (m, 3H), 7.52 (t, J = 6.8 Hz, 2H), 5.37 (s, 2H); ^{13}C {^{1}H} NMR (150

MHz, DMSO-d_6) δ 189.1, 139.5, 135.7, 134.2, 134.0, 129.2, 129.0, 128.7, 128.0, 62.1; MS (ESI) $[M+H]^+$ 260.9.

*2-(Ethylsulfonyl)-1-phenylethan-1-one (**4i**).*[27] 25.5 mg, yield: 30%, colourless liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.5 Hz, 2H), 5.11 (s, 2H), 3.31 (q, J = 7.3 Hz, 2H), 1.29 (t, J = 7.4 Hz, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 190.2, 136.0, 134.5, 129.3, 129.0, 58.5, 48.2, 6.2; MS (ESI) $[M+H]^+$ 213.0.

*2-Oxo-N, 2-diphenylethane-1-sulfonamide (**5**).* 77.0 mg, yield: 70%, white solid, mp: 97.6 – 100.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.00 (d, J = 7.1 Hz, 2H), 7.68 (t, J = 6.9 Hz, 1H), 7.54 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.0 Hz, 2H), 7.25 (d, J = 7.3 Hz, 2H), 7.12 (t, J = 6.8 Hz, 1H), 4.92 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 189.2, 137.7, 135.8, 134.1, 129.2, 128.7, 124.1, 120.2, 57.8; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{14}NO_3S$ 276.0689, found 276.0688.

*2-Oxo-2-phenyl-N-propylethane-1-sulfonamide (**6**).*[28] 50.1 mg, yield: 52%, white solid, mp: 101.8 – 103.4 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 5.6 Hz, 1H), 4.86 (s, 2H), 2.97 – 2.92 (m, 2H), 1.48 – 1.43 (m, 2H), 0.85 (t, J = 6.1 Hz, 3H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 188.9, 134.9, 132.9, 128.2, 127.7, 57.6, 43.5, 21.8, 10.1; MS (ESI) m/z $[M-H]^-$ 240.2.

*((1-(2-Fluorophenyl) vinyl) oxy) trimethylsilane (**7b**).* 840.0mg, yield: 95%, colorless liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (t, J = 8.0 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.22 (t, J = 9.7 Hz, 2H), 4.93 (s, 1H), 4.68 (s, 1H), 0.23 (s, 9H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 159.4 (d, J = 248.1 Hz), 150.0, 130.0 (d, J = 8.6 Hz), 128.5, 124.9 (d, J =11.0 Hz), 124.1, 115.9 (d, J = 23.0 Hz),

96.8 (d, J = 10.7 Hz), 0.2; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ -113.39 – -113.33 (m, 1F); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{11}H_{16}FOSi$ 211.0949, found 211.0944.

*2-(2-Fluorophenyl)-2-oxoethane-1-sulfonamide (**7c**)*. 122.4 mg, yield: 71%, white solid, mp: 155.0 – 155.7 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (t, J = 8.0 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.42 – 7.31 (m, 2H), 7.20 (s, 2H), 4.75 (s, 2H).; ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 187.7, 161.6 (d, J = 254.4 Hz), 135.9 (d, J = 8.7 Hz), 131.1, 124.8, 116.9 (d, J = 22.7 Hz), 65.1; ^{19}F {^{1}H} NMR (376 MHz, DMSO-d_6) δ -110.48 – -110.42 (m, 1F); HRMS (ESI-TOF) m/z $[M-H]^-$ calcd for $C_8H_7FNO_3S$ 216.0136, found 216.0139.

*Benzo [d] isoxazol-3-ylmethanesulfonamide (**7**)*.[29] 52.0 mg, yield: 54%, white solid, mp: 163.9 – 165.4 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.28 (s, 2H), 4.85 (s, 2H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 162.8, 150.7, 130.4, 123.8, 123.3, 121.0, 109.6, 50.8; MS (ESI) m/z $[M-H]^-$ 211.0.

*(E)-1-((5-Chloro-2-phenylpent-2-en-1-yl) sulfonyl) piperidine (**8**)*. 37.9 mg, yield: 29%, white solid, mp: 106.4 – 108.2 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 7.0 Hz, 2H), 7.35 (t, J = 6.9 Hz, 2H), 7.28 (t, J = 6.6 Hz, 1H), 6.09 (t, J = 6.7 Hz, 1H), 4.32 (s, 2H), 3.77 (t, J = 6.2 Hz, 2H), 3.03 – 3.00 (m, 4H), 2.77 (q, J = 5.6 Hz, 2H), 1.44 – 1.39 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 140.9, 132.6, 130.6, 128.3, 127.3, 126.3, 45.9, 44.2, 32.2, 25.1, 23.1; HRMS (ESI-TOF) m/z $[M+Na]^+$ calcd for $C_{16}H_{22}ClNO_2SNa$ 350.0952, found 350.0961.

*1-((2,2-Diphenylvinyl) sulfonyl) piperidine (**9**)*. 64.1 mg, yield: 49%, white solid, mp: 100.4 – 102.8 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.38 (m, 6H), 7.30 – 7.28 (m, 2H), 7.22 – 7.20

(m, 2H), 6.92 (s, 1H), 3.08 – 3.05 (m, 4H), 1.51 – 1.48 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 153.1, 139.3, 136.7, 129.8, 129.2, 128.6, 128.3, 128.1, 127.7, 122.5, 45.8, 25.0, 23.0; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{22}NO_2S$ 328.1366, found 328.1366.

*(E)-1-((4-methoxystyryl) sulfonyl) piperidine (**10**).* 64.1 mg, yield: 41%, white solid, mp: 125.9 – 127.0 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 15.4 Hz, 1H), 7.08 (d, J = 15.4 Hz, 1H), 6.99 (d, J = 8.3 Hz, 2H), 3.80 (s, 3H), 3.04 – 3.02 (m, 4H), 1.56 – 1.44 (m, 6H); ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 161.2, 141.9, 130.4, 125.3, 119.7, 114.3, 55.3, 46.1, 24.8, 23.0; HRMS (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{14}H_{20}NO_3S$ 282.1158, found 282.1157.

Associated Content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX

Reaction optimization, Quantum yield measurement, Luminescence quenching experiment, ^{1}H, ^{13}C and ^{19}F NMR data for all compounds (PDF).

Author Information

Corresponding Author

*E-mail for Y. Wang: yonghuiwang@fudan.edu.cn

Author Contributions

[‡]Luo, Q.-Y. and Mao, R.-Y. contributed equally.

Notes

The authors declare no competing financial interest.

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References

(1) For selected examples, see: (a) Drews, J. Drug Discovery: A Historical Perspective. *Science* **2000**, *287*, 1960-1964. (b) Harrak, Y.; Casula, G.; Basset, J.; Rosell, G.; Plescia, S.; Raffa, D. M.; Cusimano, G.; Pouplana, R.; Pujol, M. D. Synthesis, Anti-Inflammatory Activity, and in Vitro Antitumor Effect of a Novel Class of Cyclooxygenase Inhibitors: 4-(Aryloyl)phenyl Methyl Sulfones. *J. Med. Chem.* **2010**, *53*, 6560-6571. (c) Mojzych, M.; Karczmarzyk, Z.; Wysocki, W.; Ceruso, M.; Supuran, C. T.; Kryštof, V.; Urbańczyk-Lipkowska, Z.; Kalicki, P. New Approaches to the Synthesis of Sildenafil Analogues and Their Enzyme Inhibitory Activity. *Bioorg. Med. Chem.* **2015**, *23*, 1421-1429. (d) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. Data-Mining for Sulfur and Fluorine: An Evaluation of Pharmaceuticals to Reveal Opportunities for Drug Design and Discovery. *J. Med. Chem.* **2014**, *57*, 2832-2842.

(2) Devendar, P.; Yang, G.-F. Sulfur-Containing Agrochemicals. *Top. Curr. Chem.* **2017**, *375*,

82.

(3) Kim, H. T.; Cha, H.; Hwang, K. Y. Structural Insight into the Inhibition of Carbonic Anhydrase by the COX-2-Selective Inhibitor Polmacoxib (CG100649). *Biochem. Bioph. Res. Co.* **2016**, *478*, 1-6.

(4) Reimers, A.; Ljung, H. An Evaluation of Zonisamide, Including Its Long-Term Efficacy, for the Treatment of Focal Epilepsy. *Expert Opin. Pharmaco.* **2019**, *20*, 909-915.

(5) Goldberg, F. W.; Kettle, J. G.; Kogej, T.; Perry, M. W. D.; Tomkinson, N. P. Designing Novel Building Blocks is an Overlooked Strategy to Improve Compound Quality. *Drug Discov. Today* **2015**, *20*, 11-17.

(6) Zhang, F.; Zheng, D.-Q.; Lai, L.-F.; Cheng, J.; Sun, J.-T.; Wu, J. Synthesis of Aromatic Sulfonamides through a Copper-Catalyzed Coupling of Aryldiazonium Tetrafluoroborates, DABCO·$(SO_2)_2$, and N‐Chloroamines. *Org. Lett.* **2018**, *20*, 1167-1170.

(7) Mukherjee, P.; Woroch, C. P.; Cleary, L.; Rusznak, M.; Franzese, R. W.; Reese, M. R.; Tucker, J. W.; Humphrey, J. M.; Etuk, S. M.; Kwan, S. C.; Ende, C. W.; Ball, N. D. Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **2018**, *20*, 3943-3947.

(8) (a) Kong, W.-G.; Yu, C.-J.; An, H.-J.; Song, Q.-L. Photoredox-Catalyzed Decarboxylative Alkylation of Silyl Enol Ethers to Synthesize Functionalized Aryl Alkyl Ketones. *Org. Lett.* **2018**, *20*, 349-352. (b) Yang, H.-B.; Selander, N. Divergent Iron-Catalyzed Coupling of O-Acyloximes with Silyl Enol Ethers. *Chem. Eur. J.* **2017**, *23*, 1779-1783. (c) Zhou, Z.; Cheng, Q.-Q.; Kürti, L. Aza-Rubottom Oxidation: Synthetic Access to Primary α-Aminoketones. *J. Am. Chem. Soc.* **2019**, *141*, 2242-2246. (d) Cai, S.-H.; Xie, J.-H.; Song,

S.-J.; Ye, L.; Feng, C.; Loh, T.-P. Visible-Light-Promoted Carboimination of Unactivated Alkenes for the Synthesis of Densely Functionalized Pyrroline Derivatives. *ACS Catal.* **2016**, *6*, 5571-5574.

(9) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. Photoredox Catalysis: A Mild, Operationally Simple Approach to the Synthesis of a-Trifluoromethyl Carbonyl Compounds. *Angew. Chem. Int. Ed.* **2011**, *50*, 6119-6122.

(10) Zhang, X.-X.; Huang, H.-M. Copper-Catalyzed Oxidative Coupling of AIBN and Ketone-Derived Enoxysilanes to γ□Ketonitriles. *Org. Lett.* **2018**, *20*, 4998-5001.

(11) Fu, M.-C.; Shang, R.; Zhao, B.; Wang, B.; Fu, Y. Photocatalytic Decarboxylative Alkylations Mediated by Triphenylphosphine and Sodium Iodide. *Science* **2019**, *363*, 1429-1434.

(12) (a) Montermini, F.; Lacôte, E.; Malacria, M. Reactivity of β-Lactamido N-Sulfonyl Radicals. *Org. Lett.* **2004**, *6*, 921-923. (b) Kharasch, M. S.; Mosher, R. A. Reactions of Atoms and Free Radicals in Solution. XXVIII. The Addition of N-Chlorosulfonyl-phthalimide to Olefins. *J. Org. Chem*. **1952**, *17*, 453-456. (c) Bougeard, P.; Johnson, M. D. Homolytic Displacement at Carbon: VII. Regiospecific Synthesis of S-Allyl-*N, N*-dimethylsulphonamides from Allylcobaloximes and the Addition of *N, N*-dimethylsulphonyl Chloride to Terminal Olefins. *J. Organomet. Chem.* **1981**, *206*, 221-227. (d) Moutrille, C.; Zard, S. Z. A New, Practical Access to Amidyl Radicals. *Chem. Commun*. **2004**, 1848-1849. (e) Gheorghe, A.; Sire, B. Q.; Vila, X.; Zard, S. Z. Synthesis of 3-Arylpiperidines by a Radical 1,4-Aryl Migration. *Org. Lett.* **2005**, *7*, 1653-1656.

(13) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*,

5322-5363. (b) Yoon, T. P.; Ischay, M. A.; Du, J. Visible Light Photocatalysis as a Greener Approach to Photochemical Synthesis. *Nat. Chem.* **2010**, *2*, 527-532. (c) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102-113.

(14) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.-W.; Ma, D.-W. Selected Copper-Based Reactions for C-N, C-O, C-S, and C-C Bond Formation. *Angew. Chem. Int. Ed.* **2017**, *56*, 16136-16179.

(15) Jiang, H.-J.; Liu, K.; Yu, J.; Zhang, L.; Gong, L.-Z. Switchable Stereoselectivity in Bromoaminocyclization of Olefins: Using Brønsted Acids of Anionic Chiral Cobalt(III) Complexes. *Angew. Chem. Int. Ed.* **2017**, *56*, 11931-11935.

(16) (a) Simon, S.; Emilio, P.; Jerome, E. Zonisamide. *Treatment of Epilepsy (4th Edition)* **2016**, 680-688. (b) Mukarram, J.; Mohammed, S.; Yehanathsa, M. A.; Dat-topant, S. J.; Mushtaqeali, S. A Process for the Manufacture of Zonisamide, Useful as Anti-Convulsant Agent. WO Patent WO2005044808, May 19, 2005.

(17) (a) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. Catalytic Hydrotrifluoromethylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 2505-2508. (b) Svejstrup, T. D.; Ruffoni, A.; Juli, F.; Aubert, V. M.; Leonori, D. Synthesis of Arylamines via Aminium Radicals. *Angew. Chem. Int. Ed.* **2017**, *56*, 14948-14952. (c) Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. Chemo□, Regio□, and Stereoselective Trifluoromethylation of Styrenes via Visible Light-Driven Single-Electron Transfer (SET) and Triplet−Triplet Energy Transfer (TTET) Processes. *J. Org. Chem.* **2014**, *79*, 10434-10446. (d) Dai, C.-H.; Meschini, F.; Narayanam, J.

M. R.; Stephenson, C. R. J. Friedel−Crafts Amidoalkylation via Thermolysis and Oxidative Photocatalysis. *J. Org. Chem.* **2012**, *77*, 4425-4431.

(18) (a) Wang, X.; Cuny, G. D.; Noel, T. A Mild, One-Pot Stadler–Ziegler Synthesis of Arylsulfides Facilitated by Photoredox Catalysis in Batch and Continuous-Flow. *Angew. Chem. Int. Ed.* **2013**, *52*, 7860-7864. (b) Cheng, W.-M.; Shang, R.; Fu, Y. Photoredox/Brønsted Acid Co-Catalysis Enabling Decarboxylative Coupling of Amino Acid and Peptide Redox-Active Esters with N‐Heteroarenes. *ACS Catal.* **2017**, *7*, 907-911. (c) Tlahuext-Aca, A.; Garza-Sanchez, R. A.; Glorius, F. Multicomponent Oxyalkylation of Styrenes Enabled by Hydrogen-Bond-Assisted Photoinduced Electron Transfer. *Angew. Chem. Int. Ed.* **2017**, *56*, 3708-3711. (d) Tlahuext-Aca, A.; Garza-Sanchez, R. A.; Schäfer, M.; Glorius, F. Visible-Light-Mediated Synthesis of Ketones by the Oxidative Alkylation of Styrenes. *Org. Lett.* **2018**, *20*, 1546-1549.

(19) Khan, I.; Reed-Berendt, B. G.; Melen, R. L.; Morrill, L. C. FLP-Catalyzed Transfer Hydrogenation of Silyl Enol Ethers. *Angew. Chem. Int. Ed.* **2018**, *57*, 12356-12359.

(20) Yuan, L.-H.; Luo, W.; Yu, Q.; He, X.-L.; Wang, Q.; Zhang, Y.-J.; Yan, Y.-Y.; Cao, L.-H.; Guo, J.-K.; Liang, X.-Q.; Chen, J.-F. 5-(3-Isopropyl benzisoxazol) pyrazin-2-amine and Preparation Method Thereof. CN Patent CN105936633, September 14, 2016.

(21) Xiong, Z.-X.; Pei, C.-F.; Xue, P.; Lv, H.; Zhang, X.-M. Highly Enantioselective Transfer Hydrogenation of Racemic α-Substituted β-keto Sulfonamides via Dynamic Kinetic Resolution. *Chem. Commun.* **2018**, *54*, 3883-3886.

(22) John, B. P.; Stephen, C. D.; Samuel, D. C.; Elizabeth, P. J. 2-Oxo-ethanesulfonamide Derivates. WO Patent WO2004041264, May 21, 2004.

(23) Bouchez, L. C.; Dubbaka, S. R.; Turks, M.; Vogel, P. Sulfur Dioxide Mediated One-Pot, Three- and Four-Component Syntheses of Polyfunctional Sulfonamides and Sulfonic Esters: Study of the Stereoselectivity of the Ene Reaction of Sulfur Dioxide. *J. Org. Chem.* **2004**, *69*, 6413-6418.

(24) Park, W. K. C.; Kennedy, R. M.; Larsen, S. D.; Miller, S.; Roth, B. D.; Song, Y.-T.; Steinbaugh, B. A.; Sun, K.; Tait, B. D.; Kowala, M. C.; Trivedi, B. K.; Auerbach, B.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.-W.; Lu, G. H.; Robertson, A.; Sekerke, C. Hepatoselectivity of Statins: Design and Synthesis of 4-Sulfamoylpyrroles as HMG-CoA Reductase Inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1151–1156.

(25) Leclercq, M.; Brienne, M. J. A Simple and Versatile Synthesis of Substituted Ethynesulfonamides. *Tetrahedron Lett.* **1990**, *31*, 3875-3878.

(26) Tsui, G. C.; Glenadel, Q.; Lau, C.; Lautens, M. Rhodium (I)-Catalyzed Addition of Arylboronic Acids to (Benzyl-/Arylsulfonyl)acetonitriles: Efficient Synthesis of (Z)-β-Sulfonylvinylamines and β-Keto Sulfones. *Org. Lett.* **2011**, *13*, 208-211.

(27) Olivato, P. R.; Bonfada, É.; Rittner, R. Carbon-13 NMR Spectra of Some 2-Ethylthio-4′-substituted Acetophenones and Their Mono- and Di-oxygenated Derivatives. *MRC*. **1992**, *30*, 81-88.

(28) Bender, A.; Guenther, D.; Willms, L.; Wingen, R. Eine Einfache Synthese von 2-Oxoalkansulfonamiden. *Synthesis* **1985**, *1*, 66-70.

(29) Uno, H.; Kurokawa, M. Studies on 3-Substituted 1, 2-Benzisoxazole Derivatives. VII. Catalytic Reduction of 3-Sulfamoylmethyl-1, 2-benzisoxazole and Reactions of the Resulting Products. *Chem. Pharm. Bull*. **1961**, *30*, 333-335.

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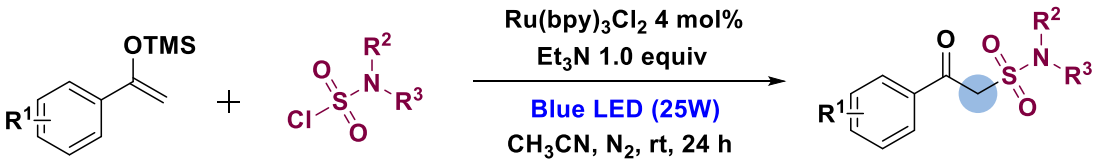

- Photoredox-catalyzed reaction
- Sulfamyl radicals
- Room temperature
- 29 examples, up to 96% yield