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# Photoinduced Rearrangement of Vinyl Tosylates to β-Ketosulfones

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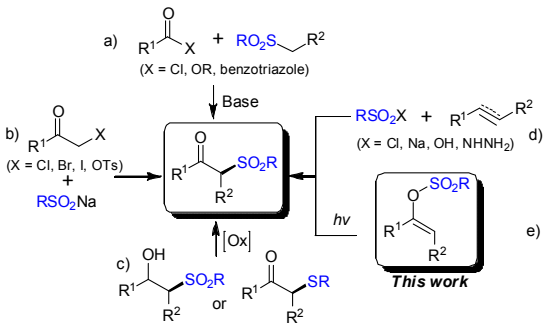
**We developed a photoinduced radical fragmentation and rearrangement of vinyl tosylates that enables efficient formation of β-ketosulfones. The process is based on photoinitiated homolysis of vinyl tosylate to release sulfinyl radical from the tosyl group of and subsequent addition of sulfinyl radical to another vinyl tosylate form the desired β-ketosulfones. This simple protocol features board scope with both aromatic and aliphatic substrates, convenient reagents and operating system.**

Organo sulfones are of considerable importance in synthetic and medicinal chemistry.[1] Particularly, β-ketosulfones have strongly attracted synthetic pursuit of chemists, not only due to their versatile synthetic applications in organic synthesis, but also because of their particular pharmaceutical relevance exhibiting an extensive and broad range of biological activities.[2] Given their value in chemistry and biological systems, intensive efforts have been devoted to the synthesis of β-ketosulfones. The representative protocols to synthesize β-ketosulfones are acylation of alkyl sulfones with acid chlorides, esters or N-acyl benzotriazoles (Scheme 1, a);[3] alkylation of metallic arene sulfinates with α-halo- or α-tosyloxy ketones (Scheme 1, b);[4] and oxidation of β-ketosulfides or β-hydroxysulfones with stoichiometric oxidants (Scheme 1, c).[5]

Recently, radical sulfonylation has drawn intense attention as a useful approach to β-ketosulfones. General strategies to synthesize β-ketosulfones were applying alkenes,[6] alkynes,[7] or activated alkenes[8] to reactions with various radical sulfonylation reagents (Scheme 1, d). For examples, in 2013, Wang group reported a copper-catalyzed oxysulfonylation reaction of alkenes with sulfonylhydrazides for the synthesis of β-ketosulfones.[6a] Lei et al. demonstrated an aerobic oxidative difunctionalization of alkynes with sulfonic acids to generate β-ketosulfones.[7a] In 2016, Lei and co-workers also developed a direct approach to β-ketosulfones via aerobic oxysulfonylation of vinyl phosphates with aromatic thiols.[8b] Recently, Wang et al. disclosed a sustainable synthetic approach to β-ketosulfones with alkenes and sulfonic acids.[6d] While impressive progresses have been made in this area, many of the reported examples generally required the addition of a large excess amount of sulfonylation reagents and external oxidants. Therefore, the development of new and efficient access to synthesize β-ketosulfones still remains highly desirable, especially with less or no use of oxidants, boarder substrate scopes, and milder reaction conditions.




**Scheme 1** Pathways of sulfonylation.

Recently, visible-light promoted photoredox has leveraged remarkable achievements.[9] Among which, organic dyes as photosensitizers showed their superiority to transition metal catalysts, such as ruthenium and iridium complexes, with regard to their lower cost and less toxicity.[10] Considering these advantages of reaction diversities and sustainable conditions, possible application of photoredox in designing and identifying useful paradigms for alternative β-ketosulfone synthesis is particularly appealing. As shown in Scheme 1 e, we anticipated that an oxidative fragmentation might be triggered on vinyl tosylate under visible-light promoted photoredox, thereby converting it into sulfinyl radical specie, which would subsequently undergo a sequence of radical addition and rearrangement to afford β-ketosulfone.

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† Footnotes relating to the title and/or authors should appear here.
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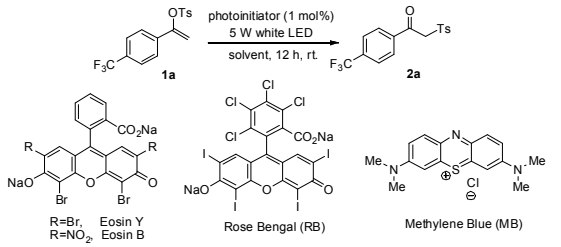
**Table 1** Reaction optimization[a]

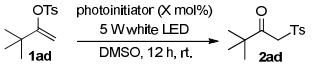



| entry | initiator | solvent | conversion[b] |
|---|---|---|---|
| 1 | eosin Y | *t*BuOH:$H_2O$ 1:1 | 6% |
| 2 | rose bengal | *t*BuOH:$H_2O$ 1:1 | 3% |
| 3 | 9-fluorenone | *t*BuOH:$H_2O$ 1:1 | 33% |
| 4 | methylene blue | *t*BuOH:$H_2O$ 1:1 | 43% |
| 5 | *fac*-Ir(ppy)$_3$ | *t*BuOH:$H_2O$ 1:1 | 41% |
| 6 | eosin B | *t*BuOH:$H_2O$ 1:1 | 46% |
| 7 | eosin B | $CH_3CN$ | 7% |
| 8 | eosin B | DMF | 88% |
| 9 | eosin B | DMSO | 96% (94%)[c] |
| 10 | eosin B | $H_2O$ | 50% |
| 11 | eosin B | DMSO:$H_2O$ 1:1 | 78% |
| 12[d] | eosin B | DMSO | 95% |
| 13 | - | DMSO | N.R. |
| 14[e] | eosin B | DMSO | N.R. |

[a]Vinyl tosylate **1a** (0.2 mmol), 5 W white LED, solvent (1 mL), and initiator (1 mol%) at room temperature for 12 h. [b]Determined by crude $^{19}F$ NMR. [c]Isolated yield was shown in parentheses. [d]Reaction in 1 h. [e]Reaction under daylight lamp.

The feasibility of our exception was tested by exposing vinyl tosylate (**1a**) in a mixed solvent (*t*BuOH:$H_2O$ 1:1) under visible light irradiation from 5 W white light-emitting diodes (LEDs) (Table 1). Performing the transformation in the presence of the commercially available photosensitizer eosin Y (1 mol%) for 12 h at room temperature, we were delight to observe that the corresponding β-ketosulfone **2a** was formed, albeit in 6% conversion (entry 1). Further screening of photoinitiators revealed that eosin B was the best for this transformation with moderate conversion of 46% (entry 6). A number of other photoinitiators, including rose bengal (RB), methylene blue (MB) and *fac*-Ir(ppy)$_3$ were subsequently investigated (entries 2-5), and they were found to be less effective than eosin B. Gratefully, of solvents tested, isolated yield of the desired product **2a** dramatically enhanced to 94% when the reaction was performed in DMSO (entries 7-11). Furthermore, we were delighted to find that one hour turns out to be a sufficient reaction time with an equally matched conversion of 95% (entry 12). In the control experiments, this transformation was found to be completely suppressed in the absence of the photoinitiator or irradiated by a daylight lamp (entries 13, 14).

**Table 2** Reaction optimization for aliphatic vinyl tosylate[a]

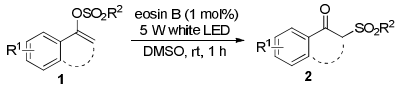


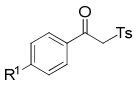

| entry | initiator (X mol%) | conversion[b] |
|---|---|---|
| 1 | eosin B (1 mol%) | 17% |
| 2 | eosin Y (1 mol%) | NR |
| 3 | methylene blue (1 mol%) | NR |
| 4 | rose bengal (1 mol%) | 22% |
| 5 | *fac*-Ir(ppy)$_3$ (1 mol%) | NR |
| 6 | benzophenone (5 mol%) | NR |
| 7 | acetophenone (5 mol%) | NR |
| 8 | 9-fluorenone (5 mol%) | 99% (95%) |

[a]Vinyl tosylate **1ad** (0.2 mmol), 5 W white LED, solvent (1 mL), and initiator (X mol%), under Ar at room temperature for 12 h. [b]Determined by crude $^1H$ NMR. [c]Isolated yield was shown in parentheses.

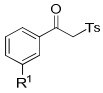
While aromatic vinyl tosylates underwent these transformations in excellent yields under optimized conditions in Table 1, aliphatic derivatives did not, as *tert*-butyl vinyl tosylate **1ad** reacted to afford **2ad** in a disappointing yield of 17% (Table 2, entry 1). Therefore, we set out to further evaluate different photoinitiators for aliphatic substrates. To our delight, reaction with the use of 9-fluorenone[11] as photoinitiator resulted **2ad** in excellent yield (Table 2, entry 8). With the optimized reaction conditions in hand, we then evaluated the synthetic potential of this transformation.

**Table 3** Scope of aromatic vinyl tosylate[a, b]

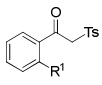


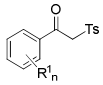
**2a** $R^1$ = $CF_3$: 94%; **2b** $R^1$ = H: 99%; **2c** $R^1$ = F: 98%; **2d** $R^1$ = Cl: 86%; **2e** $R^1$ = Br: 82%; **2f** $R^1$ = I: 92%; **2g** $R^1$ = CN: 95%; **2h** $R^1$ = $CO_2Me$:87%; **2i** $R^1$ = Me: 99%



**2j** $R^1$ = Cl: 93%; **2k** $R^1$ = Br: 94%; **2l** $R^1$ = OMe: 99%

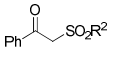


**2m** $R^1$ = Cl: 83%; **2n** $R^1$ = F: 90%; **2o** $R^1$ = Me: 87%

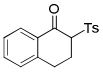


**2p** $R^1_n$ = 3-Br-4-F: 95%; **2q** $R^1_n$ = 3,4-$Me_2$: 94%; **2r** $R^1_n$ = 2,4-$Cl_2$: 99%

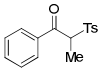
**2s** R = 2-naphthyl: 94%; **2t** R = 4-pyridyl: 92%



**2u** $R^2$ = $C_6H_5$: 84%; **2v** $R^2$ = 4-$ClC_6H_4$: 88%; **2w**$R^2$ = 2,4-$(Me)_2C_6H_3$: 99%; **2x** $R^2$ = Me: 93%; **2y** $R^2$ = Et: 85%; **2z** $R^2$ = 10-camphoryl: 87%



**2aa** 92%



**2ab** 95%

[a]Vinyl tosylate **1** (0.2 mmol), 5 W white LED, DMSO (1 mL), and eosin B (1 mol%), under Ar at room temperature for 12 h. [b]Isolated yield.

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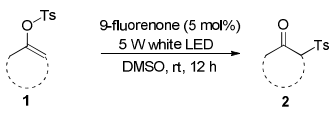
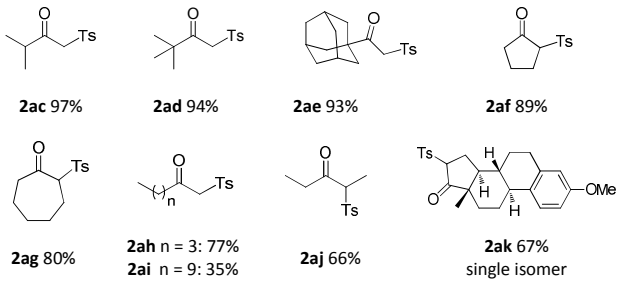
**Table 4** Scope of aliphatic vinyl tosylate[a, b]




[a]Vinyl tosylate **1** (0.2 mmol), 5 W white LED, DMSO (1 mL), and 9-fluoroenone (5 mol%), under Ar at room temperature for 12 h. [b]Isolated yield.

Generally, reactions of aromatic vinyl tosylates containing either electron-withdrawing or electron-donating groups proceeded efficiently to provide the corresponding products in good to excellent yields (Table 3, **2a**-**2o**). The nature of the substituents has almost no effect on the overall course of the reaction. A wide range of functionalities such as halogen (especially I (**2f**)), CN (**2g**), and ester (**2h**) groups were compatible with this reaction, which were suitable for further potential functionalization. Notably, bisubstitutional aromatic vinyl tosylates are tolerated as well as substrates with *meta*-*para*- or *ortho*-*para*-substitutents on the aromatic rings (**2p**-**2r**). Heterocyclic vinyl tosylates could also serve as suitable substrates in this procedure and gave the desired products (**2s** and **2t**) in 94% and 92% yields. Furthermore, aromatic (**2u**-**2w**) or aliphatic substituents (**2x**-**2z**) on the sulfone-motifs were also amendable to this protocol, exhibiting equally reactivity and affording the expected products in mostly good to excellent yields (84%-99%).

This protocol was next extended to the synthesis of aliphatic β-ketosulfones (Table 4). Remarkably, the introduction of sterically hindered substituents, such as *iso*-propyl (**2ac**), *tert*-butyl (**2ad**) or adamantly (**2ae**), had almost no impact on the reactivity; and the desired β-ketosulfones were well generated in good to excellent yields (93%-97%). In addition, substrates **1af** and **1ag**, derived from cyclic ketones, also gave the expected products in 89% and 80% yields. Linear aliphatic vinyl tosylates with long chains reacted smoothly to give the corresponding β-ketosulfones in moderate to good yields (Table 4, **2ah**, **2ai** and **2aj**). We also examined this protocol to the late-stage modification of natural product (**2ak**, 67%).

To gain preliminary inspect into this transformation, we carried out radical-trapping experiments with **1b** under the standard conditions. The addition of the radical scavenger TEMPO completely inhibited the reaction and **1b** was recovered in 99% yield, suggesting the involvement of a radical mechanism (Scheme 2, a). The crossover experiment was performed by applying an equimolar amount of **1n** and **1v** to the standard conditions. As determined by the crude NMR,

**Scheme 2** Mechanistic studies.

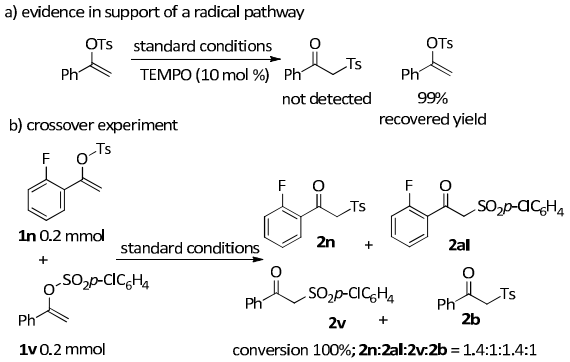
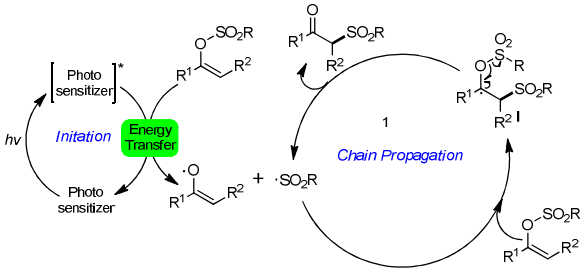



**Figure 1** Proposed mechanism.




four possible crossover products (**2n**, **2al**, **2v** and **2b**) were detected in a ratio of 1.4:1:1.4:1 (Scheme 2, b). Furthermore, the apparent quantum efficiency of the model transformation with **1a** was calculated to be 9.4, which indicates that this protocol probably processed *via* photo-induced chain mechanism. In order to clarify the initiation mechanism, we applied DFT calculations on the triplet energy of photosensitizer and vinyl tosylate. 9-Fluorenone and (*z*)-but-2-en-2-yl methanesulfonate were chosen as the simplified models. The calculated triplet energy of 9-fluorenone is 219 kJ/mol (211 kJ/mol by literature)[12] and the value of substrate is 121 kJ/mol. These results supported the possibility of energy transfer between the initiator and the substrate. (more details found in the SI)

On the basis of the above results and literature surveys, we proposed a putative reaction cycles as shown in Figure 1. Through energy transfer from the excited photosensitizer, vinyl tosylate underwent homolytic decomposition to generate enol radical and sulfinyl radical (initiation cycle). The addition of sulfinyl radical to another vinyl tosylate affords the intermediate **I**. Radical reconstruction of **I** would eventually form the desired product and another sulfinyl radical for next reaction cycle (chain propagation).

## Conclusions

In conclusion, we have described a new strategy to form β-ketosulfones through visible-light initiated radical rearrangement of vinyl tosylates. This protocol features mild sustainable reaction conditions, broad substrate scope for both aromatic and aliphatic compounds, and is compatible

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with various cyclic or sterically bulky skeletons. Further studies to expand the applicability of the present reaction system are currently underway in our laboratory.

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