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A mild and convenient visible-light-induced method has been developed for the construction of 3-sulfonyl and 3-sulfenyl azaspiro[4,5]trienones through metal-free difunctionalization of alkynes with sulfinic acids or thiols at room temperature. The present protocol simply utilizes visible light as the safe and eco-friendly energy source, and inexpensive and non-toxic organic dyes (Eosin Y and Na₂-Eosin Y) as photocatalysts providing various sulfur-containing azaspiro[4,5]trienones in moderate to good yields.

Visible-light-enabled spirocyclization of alkynes leading to 3-sulfonyl and 3-sulfenyl azaspiro[4,5]trienones†

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Spirocycles are a class of key structural motifs frequently found in many natural products, and pharmacologically active compounds and materials.1 Among the various spirocycles, azaspiro[4,5]trienones have spurred considerable interest in organic and medicinal chemistry because of their remarkable biological activities2 and diverse synthetic applications in preparing complex molecular frameworks.3 As a consequence, considerable research efforts have been dedicated to construct azaspiro[4,5]trienones and many useful synthetic methods have been thereby developed.4,5 During the past several years, the difunctionalization of alkynes via electrophilic ipso-cyclization or cascade radical ipso-cyclization has been proved to be a highly attractive and efficient protocol for the synthesis of various functionalized azaspiro[4,5]trienones.6–12 Through this strategy, some functionalities such as halogen,7 carbonyl,8 ether,9 phosphoryl,10 nitro,11 and silyl12 groups could be introduced into the azaspiro[4,5]trienone framework.

Sulfur-containing functionalities including sulfonyl and sulfenyl groups are extremely important in synthetic chemistry, pharmaceutical industry and materials science.13 The importance of sulfur-containing groups has attracted great attention from synthetic chemists in the development of new methods for their incorporation into organic molecules.14 Recently, Li,15 Liang16 and our group17 independently reported the methods for the synthesis of sulfur-containing azaspiro[4,5]trienones via oxidative spirocyclization of alkynes with some thiolation agents. However, toxic metal reagents15,16,17 and hazardous oxidants such as stoichiometric amounts of peroxides16,17a and hypervalent iodine reagents17b are inevitably involved in these reaction systems, which led to the generation of a large volume of waste. Therefore, the development of simple, mild, safe, and especially, environmentally friendly methods to access sulfur-containing azaspiro[4,5]trienones is still highly desirable.

In recent years, photoredox catalysis enabled by green visible-light has emerged as a fascinating and powerful synthetic protocol to promote a wide range of synthetically useful organic transformations under mild conditions.18 In this field, organic dyes are increasingly utilized as an attractive alternative to the transition-metal complexes in photoredox catalysis due to their advantages of being inexpensive, easily available and less toxic.19 As a continuation of our interest in the construction of sulfur-containing molecules,20 we describe herein a mild and convenient visible-light-enabled method for the synthesis of 3-sulfonyl and 3-sulfenyl azaspiro[4,5]trienones via a metal-free organic dye catalyzed difunctionalization of alkynes with sulfinic acids or thiols in air (eqn (1)), in which the C–S, C–C, and C==O bonds were sequentially formed in this visible-light induced process.

![Image](https://example.com/image1.png)

Our initial investigation commenced with the visible-light-induced reaction of N-(p-methoxyaryl)propiolic acid 1a and 4-methylbenzenesulfonic acid 2a in the presence of Na₂-Eosin

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Y (10 mol%). The reaction was conducted by exposure to air in the acetone/H2O (v/v = 1/1) mixed solvent under irradiation with 3 W blue LED lamps. To our delight, the sulfonylation-ipso-cyclization reaction gave the desired 3-sulfonyl azaspiro[4,5]trienone 3a in 34% yield after 6 h at room temperature (Table 1, entry 1). Encouraged by this result, we examined alternative mixed solvents in attempting to improve the yield (Table 1, entries 2–10). Fortunately, the yield was improved to 57% when the reaction was performed in CH3CN/H2O (v/v = 1/1) (Table 1, entry 9), which might be caused by the good solubility of Na2-Eosin Y in the mixed solvent of MeCN and H2O. The reaction efficiency was relatively lower in sole CH3CN or H2O (Table 1, entries 11 and 12). Furthermore, the reaction afforded the desired product 3a in good yield (76%) by decreasing the amount of Na2-Eosin Y to 5 mol% (Table 1, entries 13–15). Next, a series of organic dyes such as Eosin Y, Bengal Rose, Rhodamine B, Acridine Red and Eosin B were examined (Table 1, entries 16–20). Among the above catalysts screened, Na2-Eosin Y still demonstrated the highest catalytic activity (Table 1, entries 13 and 16–20). Notably, this spirocyclization reaction did not occur without a photocatalyst or visible-light irradiation (Table 1, entries 21 and 22).

After determining the optimal reaction conditions, the substrate scope in this visible-light-mediated sulfonylation-ipso-cyclization was investigated (Table 2). The reaction could proceed well by using diverse arylsulfonic acids to afford the desired products (3a–3f) in good yields. As we expected, alkylsulfonic acid such as trifluoromethanesulfonic acid was also compatible with this reaction, but affording the desired

### Table 1 Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photocatalyst (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na2-Eosin Y (10)</td>
<td>Acetone/H2O (1 : 1)</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>Na2-Eosin Y (10)</td>
<td>EtOH/H2O (1 : 1)</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>Na2-Eosin Y (10)</td>
<td>DCE/H2O (1 : 1)</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>Na2-Eosin Y (10)</td>
<td>Toluene/H2O (1 : 1)</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Na2-Eosin Y (10)</td>
<td>THF/H2O (1 : 1)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Na2-Eosin Y (10)</td>
<td>1,4-Dioxane/H2O (1 : 1)</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Na2-Eosin Y (10)</td>
<td>DME/H2O (1 : 1)</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>Na2-Eosin Y (10)</td>
<td>DMEF/H2O (1 : 1)</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>Na2-Eosin Y (10)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>Na2-Eosin Y (10)</td>
<td>CH3CN/H2O (2 : 1)</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>Na2-Eosin Y (10)</td>
<td>CH3CN</td>
<td>46</td>
</tr>
<tr>
<td>12</td>
<td>Na2-Eosin Y (10)</td>
<td>H2O</td>
<td>35</td>
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<td>13</td>
<td>Na2-Eosin Y (5)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>76</td>
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<tr>
<td>14</td>
<td>Na2-Eosin Y (2)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>71</td>
</tr>
<tr>
<td>15</td>
<td>Na2-Eosin Y (1)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>66</td>
</tr>
<tr>
<td>16</td>
<td>Eosin Y (5)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>41</td>
</tr>
<tr>
<td>17</td>
<td>Bengal Rose (5)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>72</td>
</tr>
<tr>
<td>18</td>
<td>Rhodamine B (5)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>68</td>
</tr>
<tr>
<td>19</td>
<td>Acridine Red (5)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>31</td>
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<tr>
<td>20</td>
<td>Eosin B (3)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>61</td>
</tr>
<tr>
<td>21</td>
<td>—</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>Na2-Eosin Y (5)</td>
<td>CH3CN/H2O (1 : 1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1a (0.125 mmol), 2a (0.375 mmol), photocatalyst (1–10 mol%), solvent 2 mL, 3 W blue LED lamps, rt, air, 6 h. DME: 1,2-dimethoxyethane; DCE: 1,2-dichloroethane; THF: tetrahydrofuran. b Isolated yields based on 1a. c Without visible-light irradiation.

### Table 2 Results for visible-light-induced difunctionalization of alkynes with sulfonic acids leading to 3-sulfonyl azaspiro[4,5]trienones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photocatalyst (mol%)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na2-Eosin Y (5)</td>
<td>CH3CN/H2O (2 mL, v/v = 1 : 1), 3 W blue LED lamps, rt, air, 6–24 h.</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>Na2-Eosin Y (5)</td>
<td>CH3CN/H2O (2 mL, v/v = 1 : 1), 3 W blue LED lamps, rt, air, 6–24 h.</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>Na2-Eosin Y (5)</td>
<td>CH3CN/H2O (2 mL, v/v = 1 : 1), 3 W blue LED lamps, rt, air, 6–24 h.</td>
<td>0%</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1 (0.125 mmol), 2 (0.375 mmol), Na2-Eosin Y (5 mol%), CH3CN/H2O (2 mL, v/v = 1 : 1), 3 W blue LED lamps, rt, air, 6–24 h. b Isolated yields based on 1. c N-Methyl-N,3-diphenylpropionamide (0.125 mmol).
product 3g in a relatively lower yield. Then the electronic nature of the substituents on the arylalkynyl (R^2) moiety was examined. The results indicated that the substrates with both electron-donating and electron-withdrawing groups were all tolerated in the process to give the corresponding products in moderate to good yields (3h-3n). The reaction of an alkyl-substituted alkyne such as N-(4-methoxyphenyl)-N-methylbut-2-ynamide with 4-methylbenzenesulfonic acid 2a could proceed smoothly to afford the desired product 3o in 25% yield. Next, the substituent effect of the N-aryl moiety was investigated. N-(p-Methoxyaryl)propiolamides with a Me, OMe, or Cl group at the ortho or meta position of an aniline were all suitable substrates, affording the corresponding 3-sulfonyl azaspiro[4,5]trienones in good yields (3p-3q). A non-substituted N-aryl amide such as N-methyl-N,3-diphenylpropiolamide could also be used in the present reaction system, and the corresponding 3-sulfonyl product 3a was obtained in 40% yield. It is worth mentioning that the amide with a N-H group could also be used in the present reaction system to afford product 3s, albeit in low yield. In addition, changing the N-Me group to the N-Ph group failed to afford the desired product 3t, which might be caused by the electronic effects.

Subsequently, we turned our attention to explore the reaction of sulfonylation-ipso-cyclization of N-(p-methoxyaryl)propiolamides with thiols. After an extensive screening of the reaction parameter for the model reaction between N-(p-methoxyaryl)propiolamide 1a and 4-methylbenzenethiol 4a (see ESI, Table S1†), the highest yield (87%) of the desired 3-sulfonyl azaspiro[4,5]trienone 5a was obtained when the reaction was carried out using Eosin Y (1 mol%) as the photocatalyst in CH3CN under irradiation with 3 W blue LED lamps. Having the optimized reaction conditions in hand, the generality of this sulfonylation-ipso-cyclization was investigated by examining various N-(p-methoxyaryl)propiolamides and thiols. As shown in Table 3, N-(p-methoxyaryl)propiolamides with a series of substituents on the arylalkynyl (R^2) moiety and N-aryl moiety were found to be suitable for this reaction under the standard conditions, providing the corresponding products in moderate to good yields (5a-5j). Gratifyingly, a series of thiols with an electron-donating group or an electron-withdrawing group on the aromatic ring were suitable substrates, thus providing the corresponding products in moderate to good yields (5k-5q). Notably, when 1,2-diphenyl diselenide was employed as the substrate, the reaction could also proceed smoothly to afford the 3-selenyl-substituted azaspiro[4,5]trienone 5r in 63% yield. Unfortunately, none of the desired products were obtained when aliphatic thiols were investigated in the present reaction system. It should be noted that a non-substituted N-aryl amide such as N-methyl-N,3-diphenylpropiolamide would also lead to the formation of the 3-sulfonyl product 5a in 60% yield. In addition, the carbonyl group in the substrate is essential for the present reaction. For example, none of the desired product 5t was detected when propargylamine such as 4-methoxy-N-methyl-N-(3-phenylprop-2-ynyl)aniline was used in the present reaction system.

To understand the possible reaction mechanism, the following control experiments were carried out. When N-(p-methoxyaryl)propiolamide 1a was added independently under the standard conditions, none of the azaspiro[4,5]trienone 1a' was detected (eqn (2)), indicating that azaspiro[4,5]trienone 1a' might not be the key intermediate in the present reaction system. Furthermore, the sulfonylation/sulfonylation-ipso-cyclization reaction was completely inhibited by the addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinoyloxy), and a TEMPO-trapped thyl radical complex (p-MePhS-TEMPO) was detected by LC-MS analysis (see the ESI†), suggesting that a radical reaction pathway should be involved in this transformation (eqn (3) and (4)). The radical reaction pathway was further con-
firmed by electron spin resonance (ESR) spectroscopy (see the ESI†). In addition, when the reaction of N-(p-methoxyaryl)propiolamide 1a with 1,2-diphenyldisulfide was carried out under standard conditions, the desired 3-sulfenyl product was obtained in 55% yield, indicating that the disulfide might be involved in this reaction system (eqn (5)).

\[
1a + 2a \xrightarrow{3 \text{ blue LED}} 3a
\]

On/off visible-light irradiation experiments were performed to certify the effect of photoirradiation. The results demonstrated that the continuous irradiation of visible-light is essential for this reaction (Fig. 1).

Moreover, a number of fluorescence quenching (Stern–Volmer) experiments were also conducted to elucidate an energy transfer process between a photocatalyst and sulfinic acid 2a or thiol 4a. As shown in Fig. 2 and 3, the emission intensity of the excited photocatalyst was dramatically decreased along with the increasing of the concentration of 2a or 4a. In contrast, such an effect was not observed when N-(p-methoxyaryl)propiolamide 1a was added dependently (see the ESI†). The above results strongly indicated that the photocatalyst should participate in single-electron transfer with sulfinic acid 2 or thiol 4 under the standard reaction conditions.

Based on the above results and previous reports,6,10,21,22 a possible reaction mechanism is described in Scheme 1. As shown in path A, initially, Na2-Eosin Y is photoexcited to form Na2-Eosin Y* in the presence of blue LED light. Subsequently, a single electron transfer from sulfinic acid 2 to Na2-Eosin Y* gives the radical cation 6 and Na2-Eosin Y− radical anion. The oxidation of Na2-Eosin Y− by dioxygen (air) affords the ground state Na2-Eosin Y and O2−. Then, the radical cation 6 is deprotonated by O2− leading to the oxygen-centered radical resonating with the sulfonyl radical 7. The resulting sulfonyl radical interacts with 1 to produce the vinyl radical 8. Next, the intramolecular spiro-cyclization of the vinyl radical with an aryl...
ring generates the radical intermediate 9. Finally, 9 is oxidized
to afford the corresponding oxygenium intermediate 10, which
is converted into the final 3-sulfonyl azaspiro[4,5]trienone 3.
A similar reaction pathway has been proposed for the synthesis

In conclusion, a simple and convenient visible-light-
mediated strategy has been established for the synthesis of
various 3-sulfonyl and 3-sulfonyl azaspiro[4,5]trienones from
N-(p-methoxyaryl)propiolamides and sulfinic acids or thiols at
room temperature. This method achieves alkyne difunctional-
ization through a cascade radical addition and ipso-cyclization
process. With advantages such as simple operation, mild con-
ditions, eco-friendly energy source and oxidant, as well as in-
expensive and non-toxic photocatalysts, this new synthetic
method is expected to find wide applications in synthetic and
medicinal chemistry.

Conflicts of interest
There are no conflicts to declare.

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