Selective C–S Bond Constructions Using Inorganic Sulfurs via Photoinduced Electron Donor–Acceptor Activation

Fan Yang, Gu-Cheng He, Shao-Han Sun, Ting-Ting Song, Xiang-Ting Min, Ding-Wei Ji, Shi-Yu Guo, and Qing-An Chen

ABSTRACT: By complementing traditional transition metal catalysis, photoinduced catalysis has emerged as a versatile and sustainable way to achieve carbon–heteroatom bond formation. This work discloses a visible-light-induced reaction for the formation of a C–S bond from aryl halides and inorganic sulfuration agents via electron donor–acceptor (EDA) complex photocatalysis. Divergent formations of organic sulfide and disulfide have been demonstrated under mild conditions. Preliminary mechanistic studies suggest that visible-light-induced intracomplex charge transfer within the monosulfide-anion-containing EDA complex permits the C–S bond construction reactivity.

INTRODUCTION

Aryl sulfides and disulfides are prevalent in a wide range of bioactive natural products and pharmaceuticals, including Lissoclibadin, Arbidol, and Vortioxetine (Scheme 1A). Furthermore, aromatic sulfides and disulfides are also valuable architectures in drug development, organic materials, and polymers. Therefore, the development of environmentally friendly methods for constructing a C–S bond is of significant importance with a broad impact across the areas of small-molecule synthesis and materials.

Traditionally, active organosulfur reagents are required to synthesize aryl sulfides using the following two main strategies (Scheme 1B): (a) Transition-metal-catalyzed coupling of aryl halides, aryloboronic acids, or other active metal reagents with thiophenols, disulfides, or functionalized sulfurs. The use of precious metals, strong bases, or high temperature is generally indispensable for these protocols. (b) Photoinduced C–S bond formation has become a powerful strategy for the development of aryl sulfide construction under mild conditions. However, most of these organic sulfuration agents need to be prepared in advance from inorganic sulfuration agents. Moreover, some of them are easily oxidized or deactivate the transition metal catalysts.

As clean and sustainable sulfur sources, inorganic sulfuration agents (Na2S2O3, KSCN, AcSK, etc.) have been developed for aryl sulfide synthesis under transition metal catalysis (Scheme 1C). However, some inherent issues, such as expensive transition metal catalysts or substrates presynthesis still exist. Moreover, visible-light-driven methods using inorganic sulfuration agents still remain underdeveloped. Therefore, the development of more environmentally friendly and more atom-economical methods is still in great need. As our ongoing interest in photocatalysis, we herein developed visible-light-induced C–S bond construction by employing inorganic sulfurs as both a donor of an EDA complex and a sulfur donor. Through simple control of the type of sulfides and the photoredox catalyst, (hetero)aryl halides were selectively transformed into (hetero)aryl sulfides and (hetero)aryl disulfides in high efficiency (Scheme 1D). Notably, these divergent C–S bond formations also feature abundant starting materials, mild conditions, and transition metal free and scalable preparation.

RESULTS AND DISCUSSION

Initially, we commenced our investigations by exploring visible-light-induced direct C–S bond construction between 4-bromobenzonitrile 1a and Li2S. In the absence of a photoredox...
catalyst, the reaction mixture containing 4-bromobenzonitrile 1a and Li₂S under blue LEDs (440 nm) irradiation did not give any desired product 2a at room temperature (Table 1, entry 1). The evaluation of photoredox catalysts (entries 2−6) suggested that simple aryl sulfide PC3 was the best choice for the formation of sulfide 2a with respect to yields (entry 4). A decrease in yields of 2a was observed when using Na₂S or K₂S instead of Li₂S (entries 7−8). Cheaper Na₂CO₃ emerged as the optimal base for this transformation (entries 9−10). The reactivity was maintained with lower catalyst loading (entries 11 vs 10). The irradiation with longer wavelength blue LEDs (460 nm) resulted in an excellent yield (entries 13 vs 11−12).

The optimization of less developed aryl disulfide synthesis was subsequently carried out to divert the chemoselectivity (Table 1, entry 8). Replacement of 4-bromobenzonitrile 1a with 4-bromoacetophenone 1b significantly improved the outcome delivering the aryl disulfide product 3b in a moderate yield (entry 14). The control experiments revealed that desired product 3b was also obtained with a better yield and chemoselectivity (3/2) in the absence of the organic photoredox catalyst and the base when 3.0 equiv of K₂S was used (entries 16 vs 14−15).

Having optimized the reaction conditions, the substrate scope of this visible-light-induced thioetherification was first investigated (Scheme 2a). Reactions of benzonitrile with para-halide substituents provided excellent yields of the aryl sulfide 2a (83−87%). The aryl halides with some sensitive groups, such as CHO, CO₂R, and NO₂ at the para-position of the phenyl ring, all could be performed smoothly and gave the desired products in moderate to good yields (2c−2f, 53−83%). In contrast, the electron-donating methyl group on the phenyl ring was not applicable to this transformation (2m).

Applying this strategy to para-haloacetophenones, including bromo and iodo, could provide 3b in decent yields. The nitryl on different positions of the substrate could be compatible in this reaction as well (3c−3e). It was observed that substituents at the meta- or ortho-position of aryl halides were also well tolerated to deliver the corresponding sulfides (2g−2l) in 32−62% yields. In contrast, the electron-donating methyl group on the phenyl ring was not applicable to this transformation (2m).

To gain insight into the reaction mechanism of the photoinduced sulfuration process, several control experiments...
were performed (Scheme 3). When 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was added to the model reaction, an aryl radical was captured by TEMPO with only a trace amount of target product 2a could be detected (Scheme 3a). The addition radical suppressed experiment with butylated hydroxytoluene (BHT) further supports that a radical process is probably involved in the reaction (Scheme 3b). Ultraviolet-visible (UV–vis) spectroscopic measurements on various combinations of 1f, PC3, and Li2S in MeCN were performed to figure out the active photo-responded species (Scheme 3c). It shows that there was no strong light absorbance for the solution of 4-bromonitrobenzene 1f (I) or PC3 (II). The mixture of aryl halide 1f or PC3 with Li2S in the presence of Na2CO3 showed significant visible-light absorptions (IV and V). It is believed that Li2S could trigger this reaction through the formation of the EDA complex, which induces the single-electron transfer (SET) upon the irradiation of visible light to produce radical ion pairs.10 In addition, the hypothetical benzenethiol intermediate 4-nitrobenzenethiol 1f′ (III) shows a small absorption band, while the mixture of PC3-1f′-Na2CO3 (VI) or 1f-1f′-Na2CO3 (VII) exhibited an obvious increase in visible-light absorption. These

Table 1. Optimization for the Formation of Aryl Sulfides and Disulfides<sup>abc</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>PC (mol%)</th>
<th>[S] (equiv.)</th>
<th>Base (2.0 equiv.)</th>
<th>LED (nm)</th>
<th>Yield of 2 (%)</th>
<th>Yield of 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>--</td>
<td>Li2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>PC1 (10)</td>
<td>Li2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>10</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>PC2 (10)</td>
<td>Li2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>39</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>PC3 (10)</td>
<td>Li2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>46</td>
<td>N.D.</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>PC4 (10)</td>
<td>Li2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>2</td>
<td>N.D.</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>PC5 (2)</td>
<td>Li2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>43</td>
<td>N.D.</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>PC3 (10)</td>
<td>Na2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>40</td>
<td>N.D.</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>PC3 (10)</td>
<td>K2S (1.0)</td>
<td>Cs2CO3</td>
<td>440</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>PC3 (10)</td>
<td>Li2S (1.0)</td>
<td>K2CO3</td>
<td>440</td>
<td>44</td>
<td>N.D.</td>
</tr>
<tr>
<td>10</td>
<td>1a</td>
<td>PC3 (10)</td>
<td>Li2S (1.0)</td>
<td>Na2CO3</td>
<td>440</td>
<td>72</td>
<td>N.D.</td>
</tr>
<tr>
<td>11</td>
<td>1a</td>
<td>PC3 (5)</td>
<td>Li2S (1.0)</td>
<td>Na2CO3</td>
<td>440</td>
<td>72</td>
<td>N.D.</td>
</tr>
<tr>
<td>12</td>
<td>1a</td>
<td>PC3 (5)</td>
<td>Li2S (1.0)</td>
<td>Na2CO3</td>
<td>405</td>
<td>56</td>
<td>N.D.</td>
</tr>
<tr>
<td>13</td>
<td>1a</td>
<td>PC3 (5)</td>
<td>Li2S (1.0)</td>
<td>Na2CO3</td>
<td>460</td>
<td>91(87)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N.D.</td>
</tr>
<tr>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1b</td>
<td>PC3 (10)</td>
<td>K2S (3.0)</td>
<td>K2CO3</td>
<td>430</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1b</td>
<td>--</td>
<td>K2S (3.0)</td>
<td>K2CO3</td>
<td>430</td>
<td>19</td>
<td>60</td>
</tr>
<tr>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1b</td>
<td>--</td>
<td>K2S (3.0)</td>
<td>--</td>
<td>430</td>
<td>18</td>
<td>67(65)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>abc</sup>Conditions: 1a (0.20 mmol), [S] (0.10 mmol), PC (10 mol%), base (0.20 mmol), MeCN (1.0 mL), 440 nm LED, 10 W, N2 atmosphere, rt, and 4 h. Yields were determined by 1H NMR analysis of the crude reaction mixture. <sup>1</sup>Conditions: 1b (0.10 mmol), [S] (0.30 mmol), PC (10 mol%), MeCN (1.0 mL), 430 nm LED, 10 W, N2 atmosphere, rt, and 16 h. Yields were determined by 1H NMR analysis of the crude reaction mixture. <sup>2</sup>Isolated yield.
significant absorptions are probably derived from the charge transfer of newly formed EDA complexes.

The reactivity profile of this protocol was obtained from visible light on/off control experiments (Scheme 3d). It is found that constant light irradiation is essential for the formation of the desired product. Besides sulfide and disulfide products, trace amounts of trisulfide and tetrasulfide products were also observed when 4-bromobenzaldehyde was subjected to the protocol not involving PC3.

Scheme 2. Substrate Scope of Sulfides and Disulfides

| (a) Substrate scope of sulfides
| X = Br, 83% yield | X = Br, 75% yield | X = Br, 87% yield | X = I, 87% yield |
| 2a | 2c | 2d |
| O2N | OHC | MeO2C |
| | | |
| (b) Substrate scope of disulfides | X = Br, 65% yield | X = I, 67% yield | X = Br, 48% yield |
| 3b | 3b | 3c | 3d |
| Ac | Ac | O2N |
| | | |

*Conditions: 1 (0.20 mmol), Li2S (0.10 mmol), PC3 (5.0 mol%), Na2CO3 (0.20 mmol), MeCN (1.0 mL), Blue LEDs 460 nm, 4 h, rt.

*Conditions: 1 (0.10 mmol), K2S (0.30–0.50 mmol), MeCN (3.0 mL), 430 nm LEDs (10 W), N2 atmosphere, rt, and 16 h. An isolated yield was given.

*Accompanied by a small amount of inseparable corresponding sulfide; the yield of the product has been adjusted accordingly.
visible-light-induced process with 5.0 equiv of K₂S. It suggested that a monosulfide anion radical might be transformed to polysulfides subsequently (Scheme 3e).₇₉,₁₁

Based on the aforementioned mechanistic studies, a proposed mechanism for visible-light-induced C–S bond construction is shown in Scheme 3f. In the presence of external photocatalyst PC, an association of electron-rich anion S²⁻ with electron-poor
PC forms aggregate EDA-1. Irradiation of the EDA-1 complex under the blue LED triggers an intracomplex electron transfer from anion S$_2^-$ to PC, generating monosulfide radical anion S$•^-$ and radical anion PC$•^-$. A subsequent single-electron reduction of aryl halide 1 by the resulting reductant PC$•^-$ promotes the generation of aryl radical A and regenerates photocatalyst PC. The transient radical A could couple with monosulfide radical anion S$•^-$ to form thiolate anion B. Based on Miyake’s C$-$S cross-coupling study$^7b$ and the significant absorption of 1f$-$1f$'$-Na$_2$CO$_3$ (VII), it is feasible to propose that the association of thiolate anion B with aryl halide 1 could form EDA-3. Subsequently, photoexcitation of the EDA-3 complex gives rise to thyl radical C and aryl radical A via a SET process. The coupling of the resulting thyl radical C with aryl radical A produces target aryl sulfide 2.

In the absence of external photocatalyst PC, monosulfide anion S$^-$ of K$_2$S associates with aryl halide 1 to generate EDA-2 in the ground state. The visible-light-induced intracomplex SET event of the EDA-2 complex produces aryl radical A and monosulfide radical anion S$•^-$. A subsequent radical coupling of each other produces thiolate anion B. Similarly, aryl halide 1 could interact with thiolate anion B to generate the EDA-3 complex and undergo another SET process to form aryl radical A and thyl radical C. Aryl radical A could be captured by monosulfide radical anion S$•^-$. A final self-quench of two molecules of thyl radical C produces the desired aryl disulfide 3 product. In general, it is supposed that the photocatalyst might interact more easily with Li$_2$S than K$_2$S to achieve selective thioetherification, while the excess K$_2$S is more feasible to interact with substrate aryl halides to generate thyl radical C to produce disulfide products.

Inspired by the catalyst-free synthesis of aryl disulfides, we found that photocatalyst PC3 could be easily accessed from the coupling of 4-bromoacetophenone 1b and Li$_2$S under autocatalysis (Scheme 4a). When the visible-light-induced reaction was carried out under standard conditions, the target

\[
\text{Entry} \quad \text{Deviation from standard conditions} \quad \text{Yield (%)}
\]

<table>
<thead>
<tr>
<th></th>
<th>none</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>without PC3</td>
<td>76</td>
</tr>
</tbody>
</table>

*Standard Conditions: 1b (0.20 mmol), Li$_2$S (0.10 mmol), PC3 (2.5 mol%), Cs$_2$CO$_3$ (0.20 mmol), MeCN (1.0 mL), 460 nm LED, 10 W, N$_2$ atmosphere, 4 h. Isolated yield was given.

**Scheme 4. Autocatalytic Thioetherification and the Photoinduced Scale-Up Reaction in Flow**

(a) Autocatalytic thioetherification

(b) Thioetherification in flow

(c) Disulfide etherification in flow

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product obtained an 85% yield (entry 1). Furthermore, only a slight decrease in the product yield of PC3 was observed under photocatalyst-free conditions (entry 2).

To further test the scalability of these protocols, the photoinduced C−S bond constructions have been demonstrated in flow. The reaction between 1a and Li2S was efficiently promoted in a homogeneous system using PC3 as a photoredox catalyst in an operationally simple microtubating continuous-flow reactor. Desired product 2a was obtained in a 75% yield (1.77 g) with 45 min as the residence time (Scheme 4b). Disulfide 3b could also be produced in the same flow reactor in a 54% yield (1.63 g) with 2 h as the residence time (Scheme 4c).

■ CONCLUSIONS

In summary, a mild and efficient visible-light-induced protocol has been developed for C−S bond constructions without the use of a transition metal catalyst. This strategy uses sustainable and readily available Li2S or K2S as both the sulfuration agents and the trigger for photocatalysis. The UV–vis spectroscopic measurements suggest the formation of a keyEDA complex between the monosulfide anion and aryl halide with an electron-withdrawing group. Photoexcitation of the EDA complex by visible light is the key process to promoting intracomplex electron transfer. Moreover, the scalability of these protocols has been demonstrated in flow. Overall, the current strategy could act as an important complement to traditional approaches to the preparation of useful aryl sulfides and disulfides.

■ EXPERIMENTAL SECTION

General Procedure for the Photoinduced Synthesis of Aryl Sulfides. To an oven-dried 4 mL borosilicate glass vial, aryl halides 1 (0.2 mmol, 2.0 equiv), lithium sulfide (0.1 mmol, 1.0 equiv), PC3 (0.005 mmol, 5.0 mol %), Na2CO3 (0.2 mmol, 2.0 equiv), and MeCN (1.0 mL) were added in a nitrogen glovebox. The vial was capped with a septum and wrapped with parafilm. The reaction mixture was stirred for 4 h and positioned approximately 4 cm from a visible-light source (WATTCAS WP-TEC-1020HSL, λ = 460−465 nm, 10 W, irradiation temperature maintained between 25 and 30 °C). After the reaction was completed, the crude product was neutralized with an acetic acid solution (2% v/v) and extracted with ethyl acetate. After the reaction was completed, the crude product was neutralized with an acetic acid solution (2% v/v) and extracted with ethyl acetate. The organic layer was washed with a brine solution and dried over anhydrous Na2SO4. The removal of the organic solvent in a vacuum rotavapor followed by flash silica gel column chromatographic purification (hexane/ethyl acetate) afforded the desired product.

General Procedure for the Photoinduced Synthesis of Aryl Disulfides. To an oven-dried 4 mL borosilicate glass vial, aryl halides 1 (0.1 mmol, 1.0 equiv), potassium sulfide (0.3−0.5 mmol, 3.0−5.0 equiv), and MeCN (3.0 mL) were added in a nitrogen glovebox. The vial was capped with a septum and wrapped with parafilm. The reaction mixture was stirred for 16 h and positioned approximately 4 cm from a visible-light source (WATTCAS WP-TEC-1020HSL, λ = 430−435 nm, 10 W, irradiation temperature maintained between 25 and 30 °C). After the reaction was completed, the crude product was extracted with ethyl acetate−water. The organic layer was washed with a brine solution and dried over anhydrous Na2SO4. The removal of the organic solvent in a vacuum rotavapor followed by flash silica gel column chromatographic purification (hexane/ethyl acetate) afforded the desired disulfide product.

■ ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01750.

Experimental procedures, characterization data, spectroscopic data, and NMR spectra (PDF)

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Notes
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Thiols.


Science.


