A Mild, One-Pot Stadler–Ziegler Synthesis of Arylsulfides Facilitated by Photoredox Catalysis in Batch and Continuous-Flow**

Xiao Wang,* Gregory D. Cuny,* and Timothy Noë*l

Many aromatic molecules containing an aryl carbon–sulfur bond display properties that afford them utility in a broad array of fields, including pharmacology.[1–3] Transition metal-catalyzed cross-coupling reactions are now among the most important reaction classes for constructing aromatic C–N[4] and C–O[5] bonds. However, the discovery of efficient aromatic C–S bond forming processes remains a challenge.[6] Several Pd,[7a–c] Cu,[7d,e] and Ni-catalyzed[7f] coupling reactions of aryl halides (or boronic acids) and thiols have been reported for generating arylsulfides (Scheme 1). Nevertheless, high reaction temperatures, the necessity of strong base, as well as limited substrate scope and functional group compatibility remain impediments of these approaches. In addition, many of these methods also suffer from catalyst poisoning by the sulfur-containing substrates and products.

A more traditional process to construct C–S bonds is the Stadler–Ziegler reaction,[8–10] in which arylamines are converted to the corresponding diazonium salts and then allowed to react with thiols to yield arylsulfides. The broad scope and efficiency of this reaction makes it attractive. In addition, arylamines are usually more readily available and less expensive than the corresponding arylhalides. Since the pioneering work by Stadler[8] and later by Ziegler, [9] this process has been applied extensively in industry for manufacturing arylsulfides.[11] Various modifications have also been made to achieve improved yields and milder reaction conditions.[12] However, these methods require multiple steps including both preparation and isolation of the diazonium salts and preparation of the sodium thiolates prior to the coupling step. More importantly, both the diazonium salts and the subsequent intermediate diazosulfides are potentially explosive, especially when heated.[13] Herein we report a single-step, one-pot Stadler–Ziegler process facilitated by photoredox catalysis for preparing a variety of aryl-alkyl and diaryl sulfides at room temperature with minimum formation of diazosulfides.

To avoid the isolation of diazonium salts and to enhance overall reaction efficiency, we envisioned combining the diazotization and coupling steps in a one-pot protocol (Scheme 1). Alkyl nitriles, which require only a catalytic amount of organic acid to generate the reactive [NO]+ intermediate, were considered to replace sodium nitrite for diazonium formation.[12d,14] For the sulfurous coupling fragment, thiols would be used directly instead of thiolates.

We commenced our investigations by exploring the direct Stadler–Ziegler reaction between 4-methoxythiophenol (1) and aniline (2). Preliminary results revealed that in the presence of amyl nitrite and a catalytic amount of p-toluenesulfonic acid monohydrate, 2 could be converted to the phenyldiazonium salt in situ. This compound readily reacted with 1 in MeCN at room temperature either in the presence or absence of light to afford disulfide 4 and diazosulfide 5. Interestingly, only trace amounts of the desired diarylsulfide 3 were detected (Table 1, entries 1 and 2). However, in the presence of the photoredox catalyst [Ru(bpy)3Cl2]·6H2O and visible light,[15,16] 3 was the predominant
product. For example, when the phenyldiazonium salt was generated in situ in the presence of a household 20 W fluorescent light source and 1 mol% \([\text{Ru(bpy)}_3\text{Cl}_2] \cdot 6\text{H}_2\text{O}\), 3 was produced in 59% yield after only 1 h (Table 1, entry 3). Furthermore, when this reaction was conducted in the absence of light irradiation, 3 was only produced in negligible amounts (Table 1, entry 4). Further optimization showed that tert-butylnitrite (tBuONO) was a better nitrite source, leading to an increased yield of 3 to 85% (entry 5). \([\text{Ru(bpy)}_3\text{Cl}_2] \cdot 6\text{H}_2\text{O}\) also proved effective, affording 3 in 77% yield (entry 6). However, copper(I) oxide, a commonly used single electron transfer (SET) catalyst in the Sandmeyer and related reactions, gave a lower yield of 3 (entry 7).

Once the optimal conditions were established, the substrate scope of this transformation was explored (Scheme 2). Reactions of coupling components with meta- and para-substituents provided good to excellent yields of the arylsulfinates. In these cases, the electronic property of the substituents had little impact on the product yields. Ortho-substituted reactants generally led to slightly diminished yields (3d, g, h), depending on the size of the substituent. Alkylthiols exhibited similar reactivities as compared to arylthiols (3m, n). N-heterocyclic reactants resulted in somewhat lower product yields (3j, k, l). Notably, the compatibility of aryl halides in this transformation makes it a suitable complement to the existing Ullmann-type cross-coupling reactions (3e, f, g, h). In the case where both OH and SH groups were presented, the S-thiolation product (3b) predominated.

To further address the safety concerns associated with the diazonium intermediates, a continuous-flow protocol was developed. Due to its small dimensions, microreactor technology provides reduced safety hazards and high surface-to-volume ratios. The latter is particularly advantageous for photochemical syntheses since it allows for a homogeneous irradiation of the reaction medium. An operationally simple microfluidic setup was assembled as shown in Figure 1 and the reagents were introduced through a single syringe pump into a visible light transparent capillary microreactor (464 μL, PFA tubing, 500 μm inner diameter), which was irradiated with blue LED’s. By separating tert-butylnitrite from other reagents, the diazonium intermediates are solely generated in the microreactor and are immediately consumed during the course of the reaction.

The photocatalytic Stadler–Ziegler reaction between 4-methoxythiophenol (1) and aniline (2) was conducted in continuous flow under otherwise similar experimental conditions as described for the batch experiments. The formation of segmented gas–liquid flow served as an indication for the loss of nitrogen from the diazonium intermediates and, therefore, progress of the reaction was qualitatively monitored (Figure 1 c). The short length scale in the microreactor provides increased photon flux. This results in a significant acceleration of the direct Stadler–Ziegler reaction; full conversion could be obtained within 15 s residence time (Scheme 3). In total 13.2 mmol of 3a per hour can be synthesized in continuous flow, which represents a 78-fold improvement when compared to the corresponding batch experiment. As can be seen from Scheme 3, all three reactions could be completed within 15 s.

### Table 1: The effects of light, catalyst and nitrite source on product distribution in the photocatalytic Stadler–Ziegler reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Light</th>
<th>SET</th>
<th>Catalyst</th>
<th>Loading (mol%)</th>
<th>Nitrite</th>
<th>Product 1</th>
<th>Product 2</th>
<th>Product 3</th>
<th>Product 4</th>
<th>Product 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>✓</td>
<td>✓</td>
<td>[Ru(bpy)3Cl2]·6H2O</td>
<td>1.0 amylONO</td>
<td>59</td>
<td>28</td>
<td>62</td>
<td>1</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>✓</td>
<td>✓</td>
<td>[Ru(bpy)3Cl2]·6H2O</td>
<td>1.0 amylONO</td>
<td>59</td>
<td>28</td>
<td>62</td>
<td>1</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>✓</td>
<td>✓</td>
<td>[Ru(bpy)3Cl2]·6H2O</td>
<td>1.0 amylONO</td>
<td>59</td>
<td>28</td>
<td>62</td>
<td>1</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>✓</td>
<td>✓</td>
<td>[Ru(bpy)3Cl2]·6H2O</td>
<td>1.0 amylONO</td>
<td>59</td>
<td>28</td>
<td>62</td>
<td>1</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>✓</td>
<td>✓</td>
<td>[Ru(bpy)3Cl2]·6H2O</td>
<td>1.0 amylONO</td>
<td>59</td>
<td>28</td>
<td>62</td>
<td>1</td>
<td>68</td>
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</tr>
<tr>
<td>6</td>
<td>✓</td>
<td>✓</td>
<td>[Ru(bpy)3Cl2]·6H2O</td>
<td>1.0 amylONO</td>
<td>59</td>
<td>28</td>
<td>62</td>
<td>1</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

*For example, 1.0 amylONO = 1.0 mmol amylONO.*

Scheme 2. Substrate scope of the photocatalytic Stadler–Ziegler process.
The traditional Stadler–Ziegler reaction is well known for its complicated set of possible mechanisms.\textsuperscript{[12]} Normally, it has been proposed to proceed through a S\textsubscript{RN}1 chain mechanism,\textsuperscript{[11a,12b,22]} or in some cases, a S\textsubscript{RN}2 mechanism.\textsuperscript{[12c]} In those mechanisms, with loss of nitrogen, the diazosulfide can generate the sulfide product using the sulfide radical anion as a single electron transfer reagent (S\textsubscript{RN1} and S\textsubscript{RN2}), and/or a disulfide by radical dimerization (S\textsubscript{RN2}). In the absence of photoredox catalyst (Table 1, entries 1 and 2), disulfide 4 was observed along with the unconsumed diazosulfide 5, which might indicate an inefficient S\textsubscript{RN2} mechanism. The significantly decreased amount of 4 and 5 observed under the photoredox conditions (entry 3) may reflect a more efficient SET route over the S\textsubscript{RN}1/S\textsubscript{RN}2 processes. Initially, we surmised that the [Ru(bpy)\textsubscript{3}Cl\textsubscript{2}]\textsubscript{6}H\textsubscript{2}O catalyst facilitates the overall transformation in favor of the desired sulfide product, through the oxidative quenching of *Ru(bpy)\textsubscript{3}\textsuperscript{2+} by either the diazonium salt (Scheme 4, pathway A),\textsuperscript{[16b,23]} the diazosulfide (Scheme 4, pathway B), or the disulfide (Scheme 4, pathway C).\textsuperscript{[24,25]}

![Scheme 4. Possible mechanisms for the photocatalytic Stadler–Ziegler reaction.](image)

To explore the mechanistic details, experiments in Table 1, entries 3 and 4 were performed with quantification of different species at multiple time points (Figure 2). Initially, the reaction was protected from light, during which the amounts of diazosulfide 5 and disulfide 4 accumulated and stabilized at a maximum level after 1 h, with 5 as the predominant species. After 1 h, the reaction was irradiated with light.\textsuperscript{[26]} The sulfide product 3 started to form rapidly, while 5 was consumed at approximately the same rate. Monitoring the reaction revealed that the maximum yield of 3 was approached at
4 h when diazosulfide \( \text{5} \) was undetectable.\(^{[17]} \) These results suggest that diazosulfide \( \text{5} \) is a reactive, photo-labile intermediate in the catalytic cycle (Scheme 4, pathway B). The amount of disulfide \( \text{4} \) remained largely constant, thus it is less likely to be a major reactive intermediate. From these results, we can conclude that the reaction mainly proceeds through pathway B. Other minor and competing mechanisms, including \( \text{S}_2\text{N}_\text{NN}_\text{S} \) and \( \text{S}_2\text{N}_\text{NN}_\text{S}_\text{N} \), are less pronounced under our photo-catalytic conditions. Further mechanistic studies of this reaction are in progress.

In conclusion, a novel one-pot Stadler–Ziegler process to form C–S bonds has been developed that operates under mild reaction conditions. By employing the photoredox catalyst \([\text{Ru(bpy)}_3]^2+\cdot6\text{H}_2\text{O}\) irradiated with visible light, arylsulfides can be prepared from readily available arylamines and arylalkylthiols in good yields. Notably, the process eliminates the need for diazonium salt isolation and minimizes formation of diazosulfides, both of which are potential explosion hazards. To further address the safety concerns associated with diazonium species, a scalable continuous-flow protocol was developed. The use of microreactors led to an improved irradiation of the reaction medium, which resulted in significant accelerations (full conversion within 15 s residence time) when compared to its batch counterpart.

**Experimental Section**

General batch reaction procedure: \(^{[19]} \) In a 40 mL clear glass vial with PTFE septum (from I-Chem) punched with a disposable syringe needle (for venting \( \text{N}_2 \)), photoredox catalyst \([\text{Ru(bpy)}_3]^2+\cdot6\text{H}_2\text{O} \) (0.010 mmol) was added to a mixture of thiol (1.0 mmol), amine (1.3 mmol), and \( \text{TsOH} \cdot \text{H}_2\text{O} \) (0.015 mmol) in MeCN (7.0 mL) at room temperature. The catalyst normally dissolves completely in 5 min upon stirring. Under visible light generated by a 20 W fluorescent bulb, tert-butyl nitrite (2.0 mmol) was slowly added to the mixture. The reaction was monitored by TLC and HPLC, and was stopped after 5 to 16 h. For safety concern, water (0.10–0.20 mL) was added to make the solution volume 10 mL. A second oven-dried volumetric flask (10.0 mL) was fitted with a septum and purged with argon. Next, thiol (3.0 mmol) and amine (3.9 mmol) was added through a syringe pump. The different solutions were added to make the solution volume 10 mL. By employing the photoredox catalyst \([\text{Ru(bpy)}_3]^2+\cdot6\text{H}_2\text{O}\) irradiated with visible light, arylsulfides can be prepared from readily available arylamines and arylalkylthiols in good yields. Notably, the process eliminates the need for diazonium salt isolation and minimizes formation of diazosulfides, both of which are potential explosion hazards. Further mechanistic studies of this reaction are in progress.

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**Keywords:** C–S bond formation · microflow chemistry · one-pot processes · visible-light photoredox catalysis

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No other side products, besides compounds 4 and 5, were observed within detectable range in these experiments.

Although the amount of diazosulfide is minimized in this transformation, appropriate safety measurements are recommended for the batch experiments.


For an experiment of monitoring the reaction under light from the beginning, see the Supporting Information.