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Direct Reaction of Nitroarenes and Thiols via Photodriven Oxygen Atom Transfer for Access to Sulfonamides

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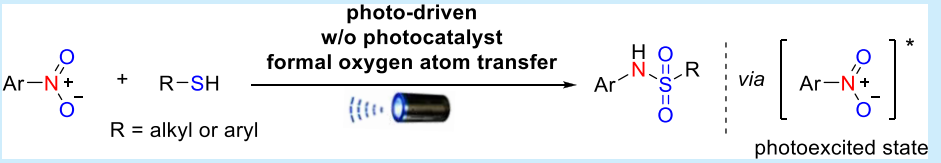

ABSTRACT: Sulfonamide is a common motif in medicines and agrochemicals. Typically, this class of functional groups is prepared by reacting amines with sulfonyl chlorides that are presynthesized from nitro compounds and thiols, respectively. Here, we report a novel strategy that directly couples nitro compounds and thiols to form sulfonamides atom- and redox-economically. Mechanistic studies suggest our reaction proceeds via direct photoexcitation of nitroarenes that eventually transfers the oxygen atoms from the nitro group to the thiol unit.

Sulfonamides are widely found in medicines, agrochemicals, and other functional molecules due to their rich biological activities and chemical and metabolic stabilities.[1] Since the discovery of the first synthetic sulfonamide antibacterial drug (Prontosil) in 1932, many sulfonamide-containing medicines have been developed for a broad range of diseases such as tumors, cancers, inflammation, and hypoglycemia.[2] The sulfonamide moiety has also appeared in multiple classes of important pesticides, such as flumetsulam, flusulfamide, and quinabactin.[3] Given the broad utilities, significant efforts have been devoted to prepare sulfonamides both in academic laboratories and industrial factories.[4] The most common approach involves reaction of amines and sulfonyl chlorides (Figure 1a).[4a] Generally, the amine nucleophiles (especially aryl amines) come from reduction of nitro compounds via catalytic hydrogenation or reduction by a stoichiometric amount of metal reductant (Figure 1a).[5] The sulfonyl chlorides are prepared from the corresponding thiols via a net oxidative process, such as oxidative chlorination (Figure 1a).[6] These separate reduction and oxidation processes (to prepare amines and sulfonyl chlorides, respectively) obviously bring undesired steps, wastes, and costs in reaching the target sulfonamide products. Strategies that can eliminate part or both of these separate redox steps are therefore of significant value. In this regard, Noël disclosed an elegant electrochemical method that directly react amines and thiols to form sulfonamides.[7] In Noël's work, oxidation of the thiol is achieved by removal of electrons by the electrode, without the addition of any chemical oxidant. Other important methods that save one of the two redox steps include transition-metal-catalyzed sulfonamidation of aryl halides (Buchwald–Hartwig coupling or Ullmann type coupling), aryl boronic acids (Chan–Lam coupling), and arene C–H activations.[4,8] Recently, the related sulfinamide was reported to be formed from nitro molecules and thiols mediated by a metal photocatalyst.[9] Despite the impressive progress, it remains challenging to completely

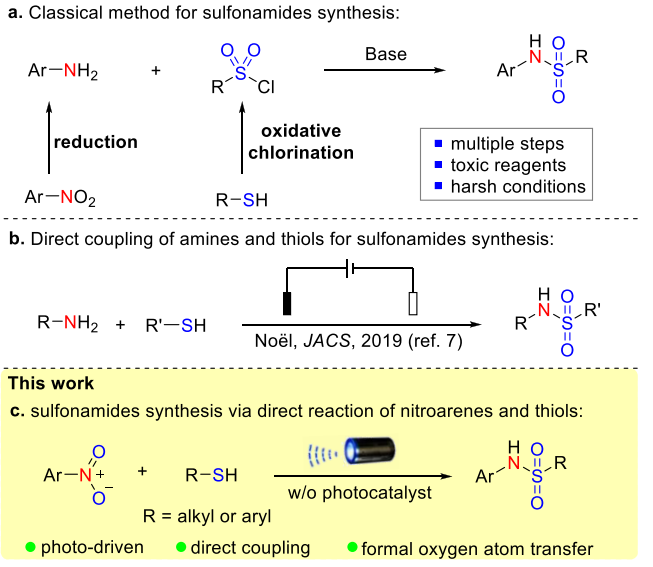

Figure 1. Classical and our new methods for sulfonamide synthesis.

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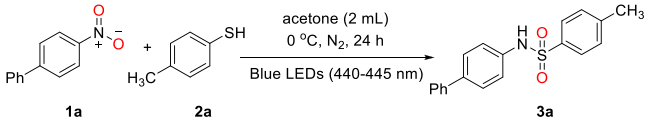
remove these two separate redox steps and direct couple nitro compounds and thiols to form sulfonamides.

We are interested in harnessing the power of photoexcitation to initiate redox reactions.[10,11] Our entry to this sulfonamide synthesis problem was encouraged by our earlier exercise on photodriven alkylation of carboxylic esters in which direct photoexcitation of acyl azolium intermediate with weak oxidizing potentials is realized.[11b] It is well-known that nitro-aromatic compounds have a broad absorption spectrum of light and thus bear rich photochemical reactivities,[12] including C−N bond scission,[13] addition to the π-bond,[14] rearrangement to nitrites,[15] hydrogen abstraction,[16] and nucleophilic substitutions at the aromatic rings.[17] Therefore, we anticipate that under photoexcitation the nitro compound can likely behave as an effective oxidant to react with molecules such as thiols. Here we report that through a photodriven process nitroarenes and thiols can directly couple together to form sulfonamides. In our approach, the nitroarene is directly photoexcited without the need of any metal or organic photocatalyst. Through a number of key radical processes, a new S−N bond is formed and the oxygen atoms on the nitroarene molecule are eventually transferred to the sulfur atom of thiols. The two substrates (nitroarene and thiol) serve as the oxidant and reductant, respectively, for its reaction partner. Although further improvements are still needed, our strategy can potentially lead to a clean method for sulfonamide synthesis from nitro compounds and thiols in an atom- and redox-economic manner.

We started to search for suitable conditions using 4-phenylnitrobenzene (**1a**) and *p*-toluenethiol (**2a**) as the model substrates (Table 1). The operation and reaction system are

Table 1. Optimization of the Reaction Conditions.[a]



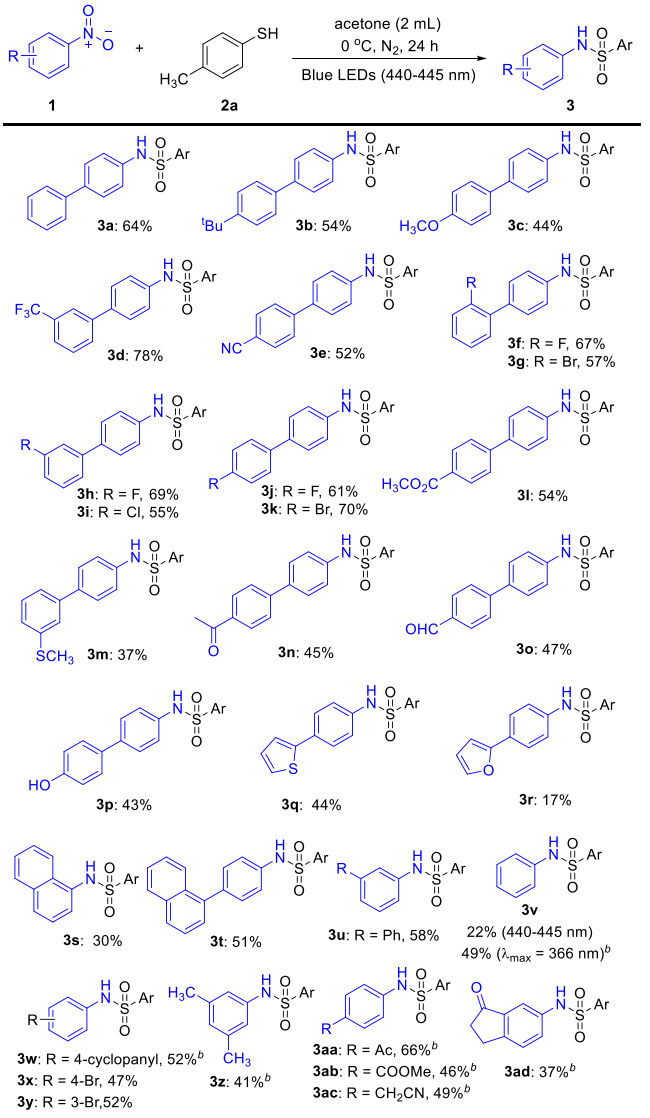
Entry	Variation from standard conditions	Yield (%)[b]
1	none	64 (45[c])
2	Lower the temperature to −10 °C	51
3	Conducted at room temperature	57
4	12 or 18 h instead of 24 h	56−58
5	CH_3CO_2Et, MeCN, THF, or toluene as solvent	40−51
6	**1a**/**2a** = 2:1	55
7	**1a**/**2a** = 1:1	47
8	**1a**/**2a** = 1:2	39
9	2, 4, 6, and 8 W instead of 10 W	35−50
10	without light irradiation (in dark)	0 (99[c], 98[d])
11	without light irradiation (in dark), 80 °C	0 (99[c], 81[d])

[a]Standard conditions: **1a** (0.3 mmol), **2a** (0.1 mmol) in acetone (2.0 mL), blue LED, N_2 atmosphere, 0 °C, 24 h. [b]Isolated yields. [c]The recovery of **1a**. [d]The recover of **2a**.

quite simple. Irradiation (blue LED, λ = 440−450 nm)of a mixture of **1a** (3.0 equiv) and **2a** (1.0 equiv) in acetone under 0 °C for 24 h led to the desired sulfonamide **3a** in an acceptable yield (64%, entry 1). Lowering the reaction temperature to −10 °C resulted in obvious loss of the reaction outcome (51%, entry 2). Similarly, a higher temperature failed to give better results (57%, entry 3). The reaction time proved to have a slight influence on the reaction outcomes, as decreasing the reaction time to 12 or 18 h led to slightly decreased reaction yields (entry 4). Other solvents such as ethyl acetate, acetonitrile, tetrahydrofuran, and toluene were also competent, albeit with lower yields (40−51%, entry 5). An excess amount of **1a** was necessary to get a higher reaction yield (entries 6−8). The power of the blue LED has a clear influence on the reaction outcomes, as decreasing the power led to dramatic losses in the yields (35−50%, entry 9). Control experiments suggested that the light irradiation was crucial for this oxygen atom transfer reaction. No coupling product (**3a**) was observed in the absence of light even at 80 °C with almost all the starting materials recovered (entries 10 and 11).

With the optimized conditions described above (Table 1, entry 1) in hand, we set out to investigate the generality of the coupling of thiols and nitro compounds (Scheme 1, 2). We first evaluated the scope of nitroaromatic compounds (Scheme 1). Various functional groups on the C(4)-benzene ring of nitrobenzene were all tolerated, regardless of their electronic nature and substituted position. For example, electron-donating groups such as *tert*-butyl (**3b**) and methoxyl (**3c**)

Scheme 1. Scope of Nitro-aromatic Compounds[a]



[a]Reaction conditions: **1** (3.0 equiv) and **2** (0.1 mmol) in acetone (2.0 mL), blue LED, N_2 atmosphere, 0 °C, 24 h. [b]The reactions were carried out by using UV light (λ_{max} = 366 nm) at 5 °C.

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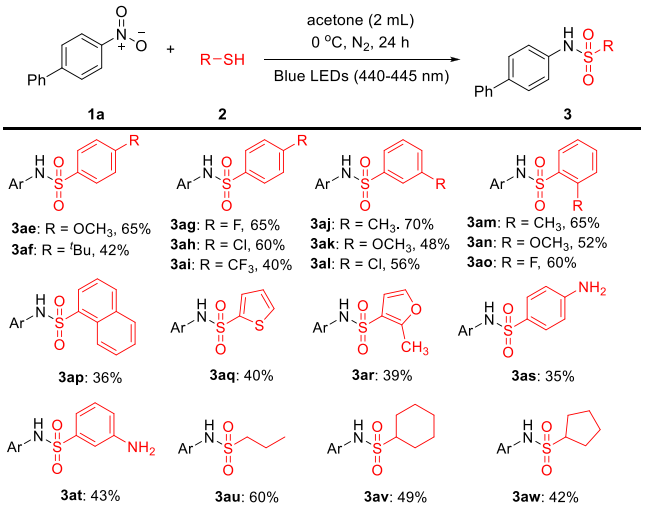
Scheme 2. Scope of Thiols[a]

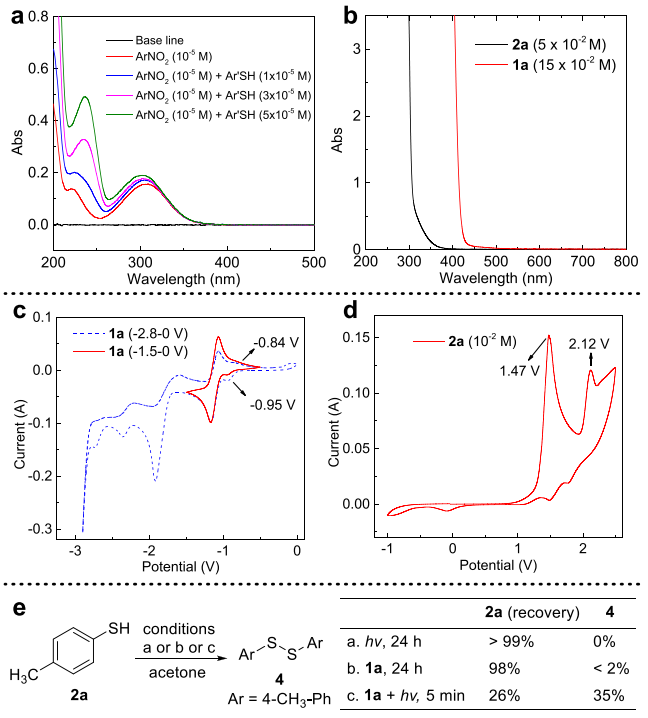


[a]Reaction conditions: **1** (3.0 equiv) and **2** (0.1 mmol) in acetone (2.0 mL), blue LED, N_2 atmosphere, 0 °C, 24 h.

and electron-withdrawing groups such as trifluoromethyl (**3d**) and cyano (**3e**) containing substrates were all converted to the corresponding sulfonamides smoothly in moderate to good yields. All of the *ortho*-, *meta*-, and *para*-halogens such as fluorine, chlorine, and bromine were tolerated, giving sulfonamides (**3f**–**3k**) with the opportunity for further modification. Substrates bearing active functional groups such as ester, thioether, aldehyde, and ketone moieties underwent this reaction successfully, affording the desired products (**3l**–**3o**) with high levels of complexity. A free hydroxyl group was also tolerated, albeit with slightly lower yield (**3p**). Nitro compounds bearing a heteroaryl ring such as thiophene and furan were also compatible, affording the corresponding sulfonamides (**3q**–**3r**) in 44% and 17% yield, respectively. While simple nitrobenzenes generally gave poor yield (e.g., **3v**) under the current conditions, it was found that UV light can dramatically improve the generality of our method for simple nitrobenzenes (see Table S3 in Supporting Information for details). For example, nitrobenzenes bearing various functional groups such as alkyl (**3w, 3z**), carbonyl (**3aa, 3ad**), ester (**3ab**), and cyano (**3ac**) were all transformed into the corresponding sulfonamides with moderate yields under UV light irradiation (λ_{max} = 366 nm). This may be attributable to the more efficient excitation of the nitro compound by UV light.

We then examined the scope of the thiols by using **1a** as a model nitrogen source (Scheme 2). The electronic nature and steric effect of the thiophenol were investigated first. The electronic nature has little effect on the reaction outcomes, as both electron-rich (**3ae**, **3af**) and electron-deficient (**3ag**–**3ai**) 4-substituted thiophenols proceeded smoothly to afford the corresponding sulfonamides in moderate to good yields. Steric effects did not hamper the reaction since sterically hindered thiophenols bearing *ortho*-substituents underwent the reaction effectively without decreasing the reaction yields (**3am**–**3ao**). Heteroaryl rings such as thiophene and furan were tolerated, affording **3aq** and **3ar** in 40% and 39% yields. Of particular note is that the substrate-bearing free amine groups, which would cause chemoselectivity in the classical methods for sulfonamide synthesis, were also competent in this reaction, albeit with slightly lower yields (**3as** and **3at**). The application of this method to synthesize aliphatic sulfonamides would be particularly useful because of the limited availability of aliphatic sulfonyl chlorides used in classical sulfonamide synthesis. In contrast, many thiols are commercially available or can be synthesized routinely from alkyl halides. Therefore, several representative thiols were chosen to test the feasibility of our method for the synthesis of aliphatic sulfonamides. To our delight, after 24 h irradiation of the mixture of **1a** and commercially available thiols in acetone, all of the thiols investigated such as propanethiol, cyclohexanethiol, and cyclopentanethiol proceeded well to produce the corresponding aliphatic sulfonamides in moderate to good yields (**3au**–**3aw**), demonstrating the utility of this method.

Multiple experiments were conducted to gain insight into the reaction mechanism. Control experiments demonstrated in Table 1 (entries 10 and 11) revealed that light irradiation is crucial for the coupling reaction between **1a** and **2a**. Considering the ability of thiols and thiophenols in the formation of an electron donor–acceptor (EDA) complex with electron-deficient aromatic rings,[18,19] we first wondered if an EDA complex between thiophenol **2a** and electron-deficient **1a** would be involved in the reaction. However, the UV–vis absorption spectra of **1a**, **2a**, and their mixture ruled out this possibility since the addition of **2a** neither induced a red shift nor remarkably increased the absorbance of **1a** (Figure 2a). Actually, the UV–vis absorption experiments of **1a** and **2a** under reaction concentration showed that the nitroarene (**1a**) can strongly absorb visible light (Figure 2b),[14b] and the absorption tail wavelength of **1a** reached over 450 nm, pointing



	2a (recovery)	4
a. *hv*, 24 h	> 99%	0%
b. **1a**, 24 h	98%	< 2%
c. **1a** + *hv*, 5 min	26%	35%

Figure 2. (A) UV–vis absorption spectra of **1a**, **2a**, and their mixture (low concentration). (b) UV–vis absorption spectra of **1a** and **2a** under reaction concentration. (c) Cyclic voltammogram of **1a** (0.01 M) in [0.1 M] $TBAPF_6$ in CH_3CN. Sweep rate: 100 mV/s. Pt electrode was used as a working electrode, a calomel electrode as a reference electrode, and a Pt wire as an auxiliary electrode. (d) Cyclic voltammogram of **2a** (0.01 M) under the same conditions as **1a**. (e) Photo-oxidation of **2a**.

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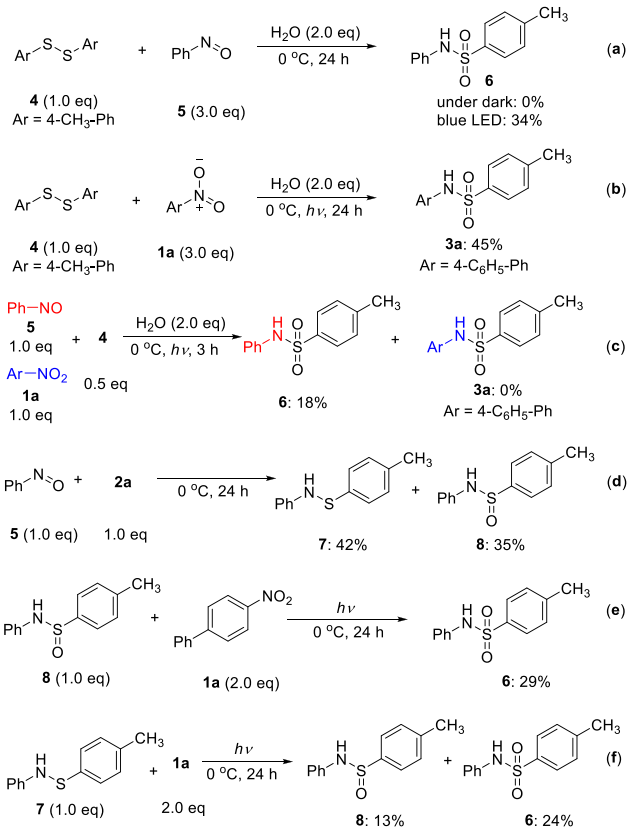
toward a reaction pathway with direct photoexcitation of **1a**.[10,12] To evaluate the feasibility of this pathway, cyclic voltammetry experiments were performed. The cyclic voltammogram revealed that **1a** can undergo multiple steps of sequential single-electron reduction processes (Figure 2c), and the first reductive potential of **1a** was measured as −0.95 V (vs SCE). Combined with the aforementioned UV−vis absorption data, the excited-state potential of **1a** was estimated to be +1.80 V vs SCE (see the SI for details).[20] This redox potential is higher than the first oxidative potential of **2a** (E_{ox} = +1.47 V vs SCE, Figure 2d), supporting the single-electron oxidation of **2a** by excited **1a**. Such an estimation was further supported by the following control experiments (Figure 2e). Sole light irradiation or ground state **1a** cannot promote the oxidation of **2a**. In contrast, **2a** was quickly converted to disulfide (**4**, 35% yield in 5 min, GC yield) in the presence of light irradiation and **1a**. Meanwhile, these results pointed out that the disulfide (**4**) could be one of the intermediates.

We then explored the reactivity of disulfide (**4**) with nitroso compound, one of the reduction products of the nitro compound, which was detected by HRMS in the model reaction mixture. It was found that disulfide (**4**) reacts effectively with nitrosobenzene (**5**) to form the target sulfonamide (**6**, 34%) in the presence of water and light irradiation (Scheme 3a). Control experiments suggested that light irradiation is also crucial for this transformation since no **6** was obtained without light irradiation (Scheme 3a). Indeed, nitroarene (**1a**) was also found to react with disulfide (**4**) smoothly to deliver the model product (**3a**, 45%) under the same conditions (Scheme 3b). To identify these two pathways, a competing reaction between nitrosobenzene (**5**) and nitroarene (**1a**) with disulfide (**4**) was conducted. The reaction was quenched and purified after 3 h. As a result, sulfonamide **6** that derived from nitrosobenzene **5** was formed exclusively (Scheme 3c), suggesting that the disulfide preferentially reacts with nitroso compounds.

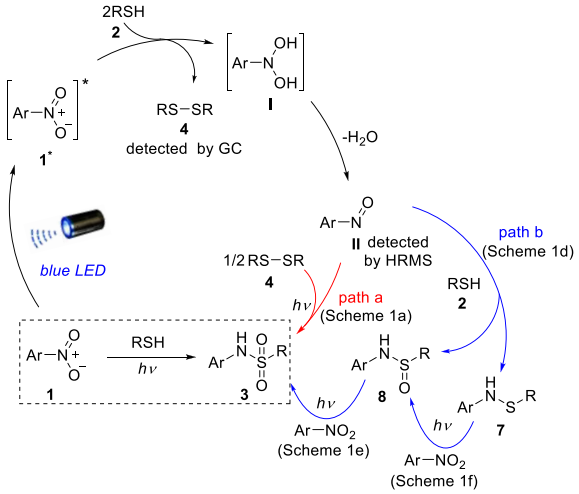
To determine if other pathways were involved in this transformation, the reactivity between nitrosobenzene (**5**) and **2a** was investigated. It was found that nitrosobenzene (**5**) reacts with **2a** effectively to afford sulfenamide (**7**) and sulfinamide (**8**) in 35% and 42% yields, respectively (Scheme 3d). Further investigation revealed that sulfinamide (**8**) can be oxidized to the corresponding sulfonamide (**6**, 29%) by nitroarene (**1a**) under light irradiation (Scheme 3e). Similarly, the sulfenamide (**7**) was also proven to be converted to sulfinamide (**8**, 13%) (via one oxidation step by excited **1a**) and sulfonamide (**6**, 24%) (via two consecutive oxidation steps by excited **1a**) in the presence of nitroarene (**1a**) and light irradiation (Scheme 3f).

The above-mentioned mechanistic studies demonstrate the complexity of this transformation since multiple reaction intermediates were proven to be able to give the target sulfonamide via different pathways. Although it is still unclear which one is dominant, postulated reaction pathways were proposed (Scheme 4) based on the results of the mechanistic

Scheme 3. Mechanistic Studies



Scheme 4. Postulated Reaction Pathway



studies. The reaction starts with the direct photoexcitation of the nitroarene (**1**) to its electronically excited state (**1***) that can act as an oxidant. The excited nitroarene (**1***) reacts with two molecules of thiols (**2**) to afford nitrosoarene (**II**) and disulfide (**4**) via sequential single-electron-transfer, protonation, and dehydration.[21] The resulting nitrosoarene (**II**) can be converted to the target sulfonamide (**3**) via two different pathways. One is to react with the disulfide under light irradiation to afford **3** (path a). Alternatively, nitrosoarene (**II**) can also be trapped by thiol (**2**) to deliver sulfenamide (**7**) and sulfinamide (**8**), which then be oxidized by photoexcited nitroarene (**1**) to eventually afford sulfonamide (**3**).

In summary, we have developed a new approach for direct coupling of nitroarenes and thiols to form sulfonamides. Photons are used to initiate the reaction without the need of a photocatalyst. The oxygen atoms from the nitro compound are transferred to the sulfur atom on the thiol molecule via a net redox-neutral process. Further explorations encouraged by our

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present study can likely lead to atom- and redox-economic reactions with clear benefits in green synthesis and manufacturing.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03770.

Experimental procedures, spectral data, and X-ray data (for **3ag**) for all new compounds (PDF)

Accession Codes

CCDC 2168659 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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