Letter

Controllable Sulfoxidation and Sulfenylation with Organic Thiosulfate Salts via Dual Electron- and Energy-Transfer Photocatalysis

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Controllable Sulfoxidation and Sulfenylation with Organic Thiosulfate Salts via Dual Electron- and Energy-Transfer Photocatalysis

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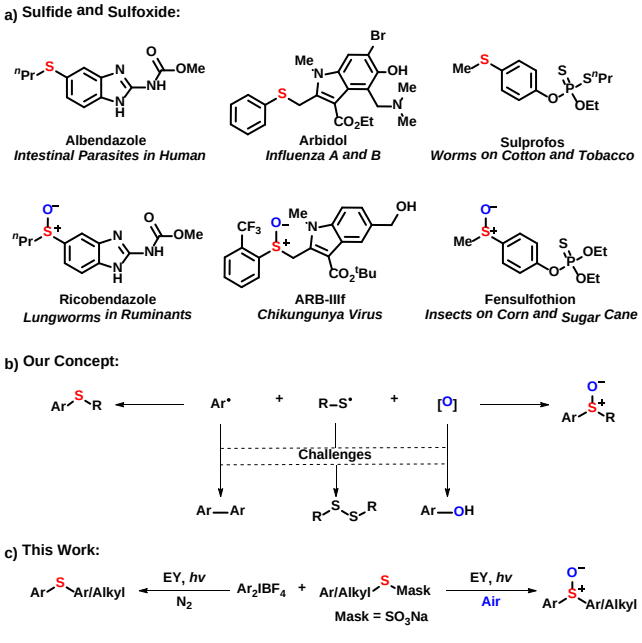
ABSTRACT: Sulfoxides and sulfides are two important functional groups in organic molecules, containing different valence states of sulfur. Both sulfoxidation and sulfenylation with common sulfurating reagents were successfully tuned via a facile variation of the atmosphere under photocatalyzed conditions. The sulfoxidation and sulfenylation transformations involved tandem electron-/energy-transfer and single electron-transfer processes, respectively. Late-stage sulfoxidation for pharmaceuticals and sugar derivatives was established to be highly compatible. Divergent formal syntheses of sulfoxide/sulfide-containing marketed pharmaceuticals were switchably implemented. Gram-scale operations further demonstrated the practicability of the protocol.

KEYWORDS. Sulfoxidation, Sulfenylation, Electron Transfer, Energy Transfer, Photocatalysis

Various organosulfur molecules widely exist in nature.[1] In addition, synthetic sulfur-containing compounds are also abundant with miscellaneous functions especially for pharmaceuticals.[2] Sulfide and sulfoxide are usually studied with each other in drug discovery, due to their mutual transformations assisted by enzymes in vivo.[3] Similar molecular backbones with different oxidation states of sulfur in pharmaceuticals have afforded a diversity of drug activities (Scheme 1a). Sulfide-containing albendazole,[4] an oral medication for the treatment of intestinal parasites in humans, is a vital drug on the list of essential medicines from the World Health Organization (WHO).[5] The corresponding sulfoxide-containing ricobendazole is commonly applied as an antihelminthic agent against lungworms and roundworms in ruminants.[6] Sulfide-containing arbidol (umifenovir) is an antiviral pharmaceutical for prophylaxis and treatment of infections with influenza A and B viruses in Russia and China,[7] while its sulfoxide derivative ARB-IIIf has been found to be an exclusive inhibitor of chikungunya virus (a mosquito-borne arthrogenic *alphavirus*).[8] Sulfide-containing sulprofos is applied to control worms on cotton and tobacco,[9] while the similar sulfoxide-containing fensulfothion[10] is an insecticide for corn and sugar cane. Considering the accompanying and complementary characteristics between sulfides[11] and sulfoxides,[12,13] a divergent construction strategy with a common precursor is in urgent demand. However, contradictions[11,14] between sulfenylation and oxygenation in transition-metal-catalyzed coupling have brought challenges toward this goal. A mild photocatalyzed[15] system with different kinds of catalytic modes (single electron transfer and energy transfer)[16] provides an opportunity for both sulfenylation[17] and oxygenation,[18] despite the poor compatibility among the sulfur species, aryl radical, and active oxygen (Scheme 1b). Our masked strategy,[19] in which stabilization of a sulfur radical was realized through an electronic conjugation and steric hindrance effect, could impede the highly active undesired processes, such as homocoupling and over oxidation. (Scheme 1c).

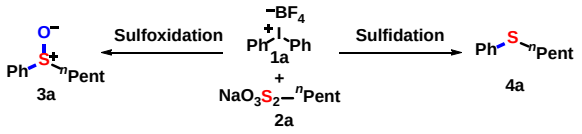
Scheme 1. Selective Sulfoxidation and Sulfenylation.



We commenced this study using *n*-pentyl thiosulfate salt and diphenyl iodonium in air under photocatalyzed conditions. Unfortunately, no sulfoxide was detected when catalyzed by tris(bipyridine)ruthenium(II) chloride with potassium carbonate in a mixture of dimethyl sulfoxide and water.[19f] When subjected to the dye eosin Y (EY) in methanol, pentyl(phenyl)sulfoxide **3a** was delightedly obtained in 20% yield (Table 1, entry 1). Other solvents, such as dimethyl sulfoxide,

N,*N*-dimethylformamide, and water, did not deliver **3a** (Table 1, entries 2-4). Different bases were also checked (Table 1, entries 5-7), in which Hünig's base, diisopropylethylamine, improved the yield to 31%. Zinc acetate, which is known to improve the selectivity during oxidation,[20] elevated the yield to 53% (Table 1, entry 8). Other Lewis acids and Brønsted acids did not elevate the efficiency (Table 1, entries 9 and 10). A higher concentration afforded a better result with 65% yield (Table 1, entry 11). The solvent combination of methanol and acetonitrile, adjusting the solubility of starting materials, yielded 77% sulfoxide (Table 1, entry 12). A green LED (λ = 530 nm), which matches the maximum absorption wavelength of eosin Y (520 nm), afforded **3a** in 82% isolated yield (Table 1, entry 13). Conveniently, by only altering the atmosphere to nitrogen, pentyl(phenyl)sulfane **4a** was efficiently obtained in 84% isolated yield (Table 1, entries 14 and 15).

Table 1. Selectivity Establishment[a]



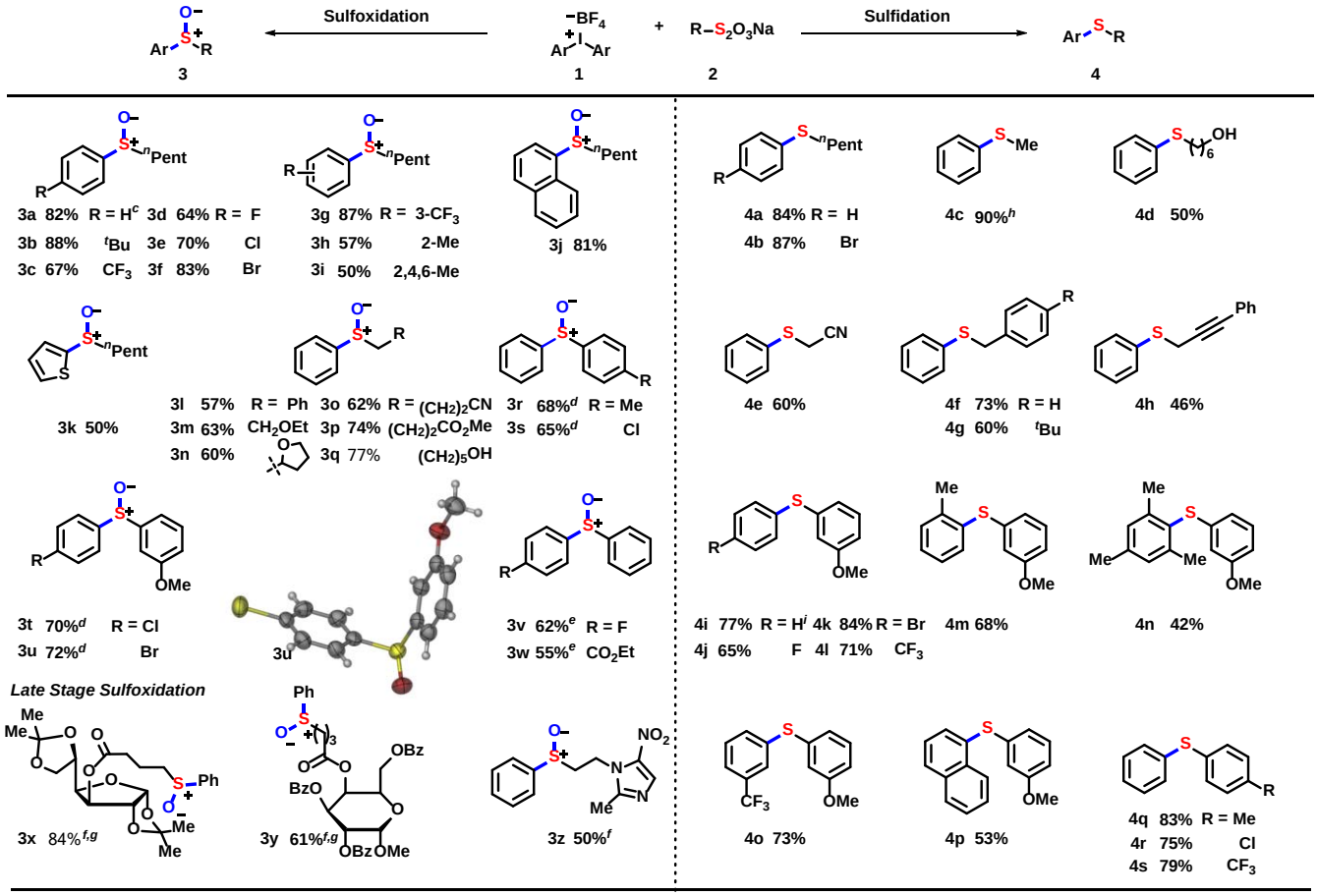
entry	base	additive	solvent	yield/3a[b]	yield/4a[b]
1	K_2CO_3	-	MeOH	20	-
2	K_2CO_3	-	DMSO	trace	-
3	K_2CO_3	-	DMF	trace	-
4	K_2CO_3	-	H_2O	trace	-
5	KOH	-	MeOH	15	-
6	KO^{t}Bu	-	MeOH	12	-
7	DIPEA	-	MeOH	31	-
8	DIPEA	$Zn(OAc)_2$	MeOH	53	-
9	DIPEA	$BF_3{\cdot}OEt_2$	MeOH	30	-
10	DIPEA	HOAc	MeOH	22	-
11	DIPEA	$Zn(OAc)_2$	MeOH[c]	65	-
12	DIPEA	$Zn(OAc)_2$	MeOH/MeCN[d]	77	-
13	*DIPEA*	*$Zn(OAc)_2$*	*MeOH[d]*	*85(82)[e]*	-
14[g]	DIPEA	$Zn(OAc)_2$	MeOH[d]	-	68
15[g]	*DIPEA*	*$Zn(OAc)_2{\cdot}2H_2O$[f]*	*MeOH[c]*	-	*86(84)*

[a]Standard conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (2 mol%), additive (0.4 mmol), base (2 equiv.), and solvent (1.0 mL) were added and stirred for 24 h under the irradiation of a 23 W CFL. [b]^{1}H NMR yields (%). Isolated yields (%) are in parentheses. [c]0.5 mL. [d]0.3/0.1 mL. [e]18 W green LED. [f]10 mol%. [g]Nitrogen atmosphere was applied instead of air.

With this tunable protocol in hand, the sulfoxide library was first established (Table 2). Diaryliodonium salts with electron-donating (**3b**) and electron-withdrawing groups in different positions (**3c** and **3g**) delivered the corresponding sulfoxides smoothly. Fluoro, chloro, and bromo substituents were well tolerated (**3d-f**), which could be further modified with cross coupling reactions. Sterically hindered substrates with 2-methyl and 2,4,6-trimethyl groups still efficiently underwent the reaction (**3h** and **3i**). Fused- and hetero-aromatic sulfoxides (**3j** and **3k**) were also achieved. Various thiosulfate salts substituted with benzyl (**3l**), ether (**3m** and **3n**), cyano (**3o**), and ester (**3p**) groups were successfully converted. It is noteworthy that a functional group with an active hydrogen hydroxyl (**3q**) was well retained. In addition to aryl alkyl sulfoxides, diaryl ones were delightedly afforded, which can be hardly achieved under mild visible-light-promoted oxygenation of sulfides.[12c,18] Electron-neutral **3r** and **3s** were acquired in good yields. Chloro and bromo substituents were compatible (**3s**-**3u**). Sulfoxide **3u** was further confirmed by X-ray diffraction.[21] Impressively, diarylsulfoxides with electron-deficient groups, such as fluoro (**3v**) and ester (**3w**) groups, were also synthesized. Late-stage sulfoxidation of the functional molecules furanose (**3x**) and pyranose (**3y**) were implemented from side-chain-derivatised thiosulfates. Moreover, nitro-containing metronidazole was sulfoxidized in 50% yield (**3z**). On the other hand, aryl alkyl sulfides were obtained in good to excellent yields with a variety of functional substituents, such as bromo (**4b)**, hydroxyl (**4d**), nitrile (**4e**), benzyl (**4f** and **4g**), and propargyl (**4h**) groups. Particularly, this method showed great potential for constructing diaryl sulfides, wherein the electronic effects of substituents on both the diaryl iodonium salts and thiosulfate salts did not affect the efficiency (**4i-4s**). The steric effects were illuminated through the synthesis of 2-methyl- and 2,4,6-trimethyl-substituted sulfides **4m** and **4n**. Gram-scale operation further demonstrated the utility, in which **3a** and **4i** were synthesized on a 10 mmol scale under these mild and easily handled conditions. With these tunable systems in hand, the controllable formal synthesis of albendazole,[22] ricobendazole,[22] ARB-IIIf,[8] and fensulfothion[23] was conducted, as discussed below (Scheme 2).

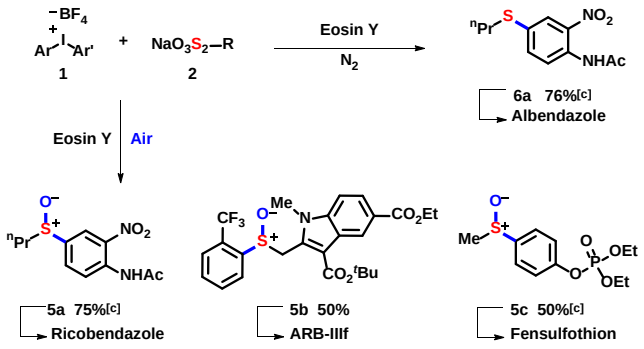
Further control experiments were pursued to gain insight into the mechanism. First, UV-Vis absorption experiments showed that only eosin Y possessed obvious absorption in the visible-light region (SI, Figure S1). Stern–Volmer fluorescent quenching experiments demonstrated that diaryl iodonium, instead of the thiosulfate salt, quenched the excited catalyst EY* efficiently (SI, Figure S2). Moreover, radical quenching experiments with 2,2,6,6-tetramethylpiperidinooxy (TEMPO) completely suppressed both the sulfoxidation and sulfenylation pathways (SI, Tables S1 and S2). The results above indicate that the current reactions started with a single electron transfer between EY* and the aryliodonium salt. Second, a control experiment with sulfide **4a** was carried out under standard conditions for sulfoxidation (Table 3, entry 1), providing an almost quantitative transformation to the related sulfoxide **3a**, which indicated that the sulfoxidation operated by cascade sulfenylation and oxygenation processes. The fluorescence of Eosin Y was not quenched by a sulfide, which demonstrated that there is no direct interaction of the sulfide with EY* (SI, Figure S2). The oxygen radical anion ($O_2^{\cdot-}$) quencher 1,4-benzoquinone (BQ)[18d] had no effect on the oxygenation reaction (Table 3, entry 2). However, the singlet oxygen ($^1O_2$) quencher cobaltic acetylacetonate, [Co(acac)$_3$],[18g] dramatically decreased the yield with a recovery of 85% sulfide (Table 3, entry 3). Additional fluorescent quenching experiments revealed that neither BQ nor Co(acac)$_3$ quenched EY* (Figure 1, for details, see Figure S3), which showed that $^1O_2$ is the key active oxygen species generated through energy transfer between EY* and $^3O_2$. Over

Table 2: Substrate Scopes of Sulfoxides[a] and Sulfides[b]



[a]Standard conditions for sulfoxidation: diaryl iodonium salt (0.2 mmol), thiosulfate salt (0.6 mmol), eosin Y (0.004 mmol), DIPEA (0.4 mmol), $Zn(OAc)_2$ (0.4 mmol), MeOH/MeCN = 0.3/0.1 mL, air, 18 W green LED, 24 h. [b]Standard conditions for sulfenylation: diaryl iodonium salt (0.2 mmol), thiosulfate salt (0.6 mmol), eosin Y (0.004 mmol), DIPEA (0.4 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (0.02 mmol), MeOH = 0.5 mL, N_2, 23 W CFL, 24 h. [c]76%, 10 mmol scale. [d]Air, 12 h, then O_2, 24 h. [e]Air, 12 h, then O_2, 48 h. [f]23 W CFL, [g]CH_3CN (0.4 mL). [h]Methyl thiosulfate salt (5 equiv.). [i]63%, 10 mmol scale.

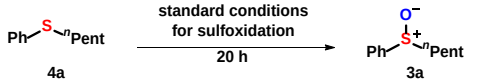
Scheme 2: Formal Synthesis of Albendazole, Ricobendazole, ARB-IIIf, and Fensulfothion[a,b]



[a]Standard conditions for sulfoxidation. [b]Standard conditions for sulfenylation. [c]Ar' = 2,4,6-trisopropylphenyl.

all, a proposed mechanism was depicted, as show in Scheme 3 below: EY^* was generated from EY under visible-light irradiation, which subsequently interacted with diaryliodonium salt **1** through a single electron-transfer process. The newly formed aryl radical **7** coupled with the thiosulfate salt to produce sulfide radical **8**. The following electron-transfer process between **8** and $EY^{+\cdot}$ produced the sulfide and regenerated the low-energy EY. An energy-transfer process was involved between $^3O_2$ and EY^*, generating $^1O_2$. The persulfoxide **9**,[12c,18b,g] which was obtained via the combination of the sulfide and $^1O_2$, stabilized by zinc acetate[18c] and finally delivered the sulfoxide with another sulfide.

Table 3: Control Experiments



entry	alteration of conditions	yield
1	-	99%
2	+ BQ (6 mol%)	97%
3	+ $Co(acac)_3$ (6 mol%)	11% + 85% 4a

In conclusion, a selective construction of organic sulfurs in different valence states from common thiosulfate salts was developed under visible-light-catalyzed conditions via easily tuning the reaction atmosphere. Late-stage sulfoxidation, switchable synthesis of pharmaceuticals, and gram-scale operations were systematically established. Mechanistic studies

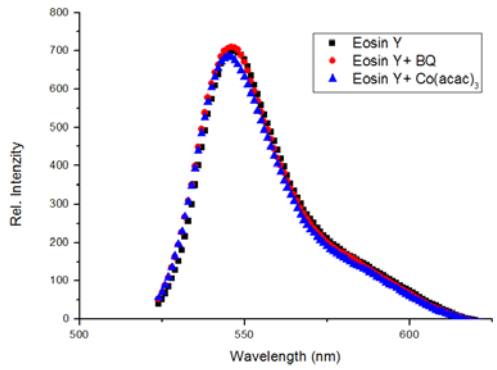
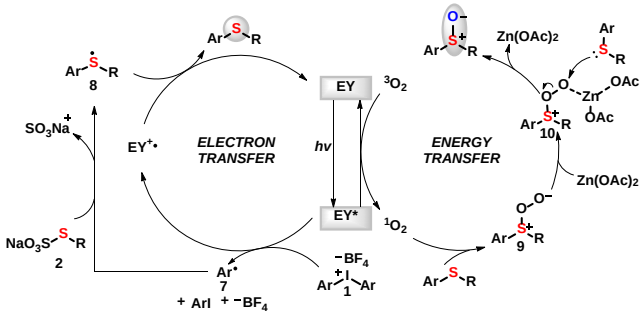


Figure 1: Stern–Volmer Fluorescent Quenching Experiments

Scheme 3: Proposed Mechanism



indicated that the sulfoxidation might involve cascade electron- and energy-transfer processes, whereas a single electron transfer might dominate in the sulfenylation pathway. A sulfoxide-containing pharmaceutical library is being constructed in our group.

ASSOCIATED CONTENT

Supporting Information.

The supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Detailed mechanistic studies, experimental procedures, characterization data, X-ray analyses of compound **3u**, and NMR spectra for the compounds (PDF).

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