Organophotoredox Catalyzed Formation of Alkyl-Aryl and -Alkyl C-S/Se Bond from Coupling of Redox Active Esters with Thio/Selenosulfonates

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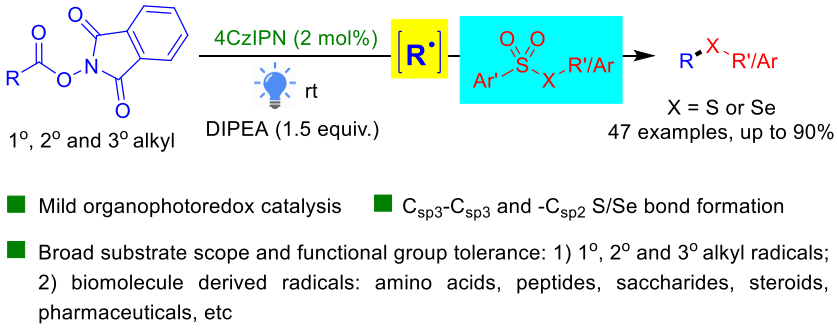
Supporting Information Placeholder



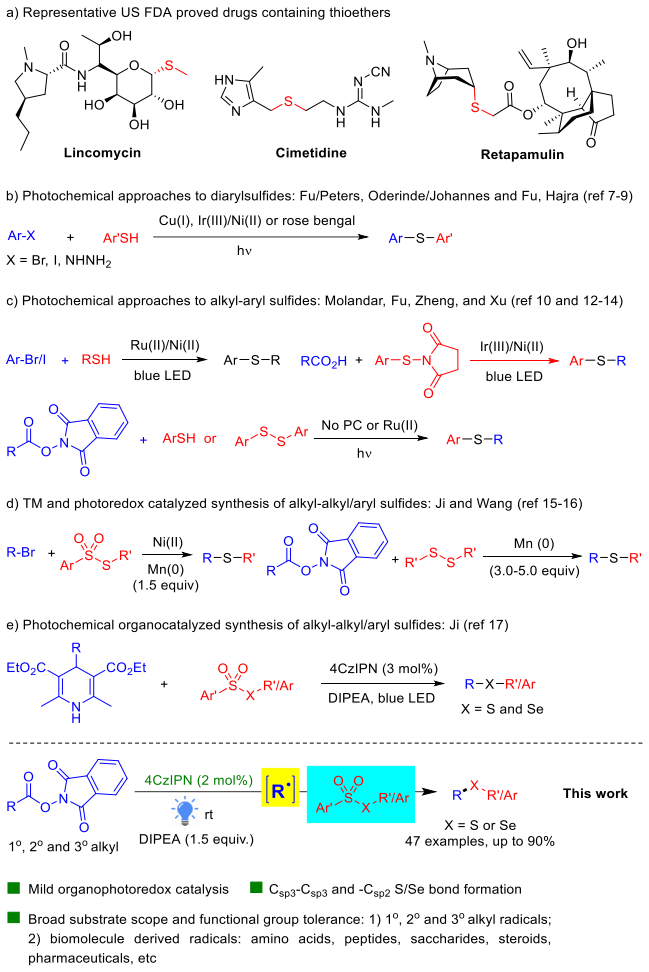
ABSTRACT: A mild, organophotoredox synthetic protocol for forming C_{sp3} -S/Se bond by reacting widespread redox-active esters with thio/selenosulfonates has been developed. The power of the synthetic manifold is fueled by an unprecedented broad substrate scope and wide functional group tolerance.

Despite the fact that C-O ether bond is dominated in organic and biologically active molecules, the C–S thioether linkage is also an important functionality, broadly distributed in numerous biologically active synthetic substances, natural products, and functional materials.[1] Of particular note is that more than 30 drugs such as lincomycin, cimetidine and retapamulin contain the thioether functionality (Scheme 1a).[2] Therefore, the thioether has constituted a long-standing interest in organic synthesis.

The classic substitution reaction between alkyl halides and mercaptans offers the stalwart approach to thioether synthesis. However, harsh alkaline reaction conditions limit the functional group tolerance and in many cases give low reaction yields. Transition-metal-catalyzed C-S bond forming reactions have been the mainstay of the contemporary thioether synthesis.[3] The field has advanced from the precious[4] to base metal catalysis.[5] Furthermore, transition metal (TM) promoted C-S bond processes have been transformed from a $2e^-$ into single electron transfer (SET) strategy.[6] In this context, radical engaged diarylsulfide synthesis was achieved (Scheme 1b). Fu and Peters pioneered the field by uncovering a copper-catalyzed coupling of aryl thiols with aryl halides with Hg lamp (Scheme 1b).[7] Mild visible light photoredox Ir and Ir/Ni catalyzed the formation of C–S bond from thiols with aryl/heteroaryl iodides was independently developed by Oderinde and Johannes and Fu.[8] A rose bengal promoted diaryl sulfide formation with arylhydrazines was unveiled by Hajra *et al*.[9] In addition to diarylsulfide synthesis, significant advances have been made in the preparation of alkyl-aryl sulfides with photochemical approaches (Scheme 1c). Ru/Ni dual-catalytic thioarylation of native peptides and other biomolecules with visible light has been nicely realized by Molander and co-workers.[10] In addition to the use of aryl halides, abundant carboxylic acids and their derivatives[11] have been demonstrated as versatile radical coupling partners in the thioetherification. These processes have been achieved efficiently by Fu, Zheng, and Xu (Scheme 1c). Fu and colleagues developed an impressive photocatalyst free visible-light photoredox decarboxylative coupling of redox-active ester (RAE) *N*-(acetoxy)phthalimides (NHPIs) with aryl thiols.[12] A similar approach using disulfides and a Ru complex as a PC was attained by Zheng.[13] Xu *et al* reported an efficient nickel/photoredox cooperative decarboxylative thioetherification of amino acids with arylthiosuccinimide.[14]

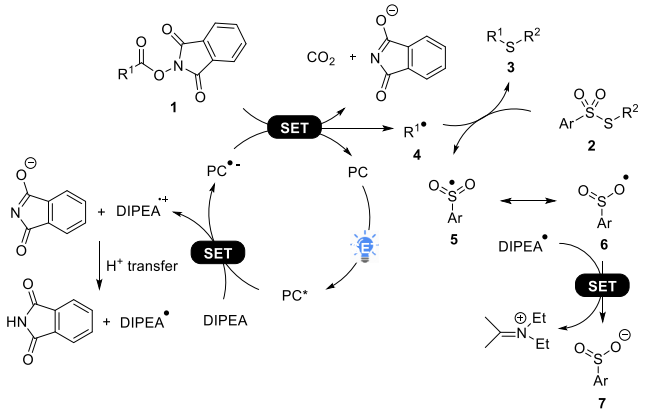
These methods have offered new efficient approaches for the synthesis of sulfides. However, they are limited to the synthesis of aryl-aryl or –alkyl thioethers. Strategies capable of accessing alkyl-alkyl sulfides remains elusive. Recently, Ji reported a Ni(II)-catalyzed thiolation of alkyl bromides with thiosulfonates using Mn(0) as reducing reagent by affording both alkyl-aryl or –alkyl thioethers (Scheme 1d).[15] A strategy using Mn(0) mediated reductive decarboxylation and deamination of respective RAEs and Katritzky's *N*-alkylpyridinium salts with

Scheme 1. Thioether Containing Drugs and Radical Engaged Thiother Synthesis



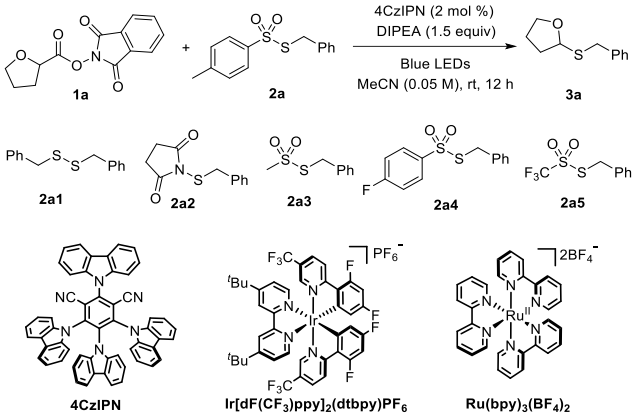
disulfides was revealed by Wang and colleagues.[16] It is noted that a stoichiometric amount (1.5-5 equiv.) of Mn(0) is used for the reductive generation of radicals in both studies. During our investigation, Ji and coworkers have reported a more efficient organophotocatalytic cross coupling of 4-alkyl-1,4-dihydropyridines with thio-/selenium sulfonates (Scheme 1e).[17] While the technique provides a viable approach for the synthesis of alkyl-aryl or –alkyl thioethers,[18] it employs 4-alkyl-1,4-dihydropyridines as radical precursors, and with that, carries an inherent substrate scope limitation.

Scheme 2. Proposed Mechanism



Herein we wish to report an alternative mild organophotoredox thiolation reaction using NHPI derived RAEs as radical precursors with thio/seleno sulfonates (Scheme 1e). The easy accessibility and high radical producing liability of the RAEs[19] enable the generation of structurally diverse radicals for efficient coupling with electrophilic thio/seleno-sulfonates. As demonstrated, 1°, 2° and 3° radicals can effectively participate in the process. Furthermore, biologically relevant molecules such as amino acids, peptides, saccharides and steroids are versatile substrates for the reaction. Therefore, broad substrate scope and various functional group tolerance of the mild process is achieved.

Table 1. Exploration and Optimization[a]



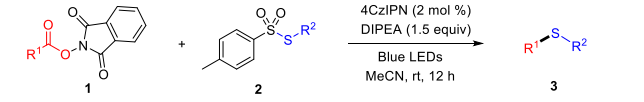
Entry	derivation from standard conditions	yield[b] (%)
1	none	85
2	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ as PC	81
3	$(Ru(bpy)_3(BF_4)_2$ as PC	82
4	Eosin Y as PC	65
5	DCM as solvent	19
6	DMF as solvent	0
7	DMSO as solvent	0
8	**2a1** as reagent	5[c]
9	**2a2** as reagent	5[c]
10	**2a3** as reagent	30
11	**2a4** as reagent	60
12	**2a5** as reagent	45
13	No DIPEA	0
14	No light	0
15	No PC	0

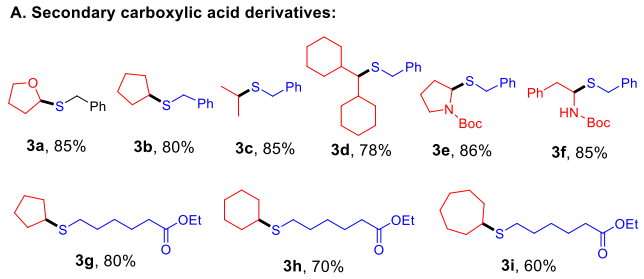
[a] Reaction conditions: Unless specified, a mixture of **1a** (0.15 mmol), **2a** (0.1 mmol), 4CzIPN (0.002 mmol), and DIPEA (0.15 mmol) in MeCN was irradiated by 40 W Kessil blue LEDs in a N_2 atmosphere at rt for 12 h. [b] Isolated Yield. [c] Yield based on ^1H NMR.

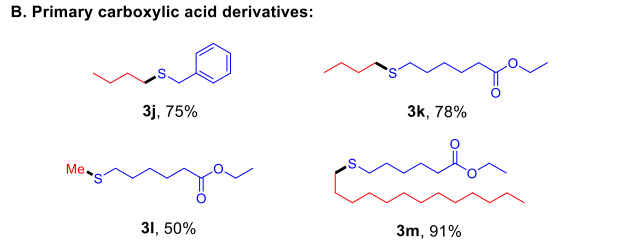
The exploration for developing organophotoredox visible light mediated thiolation of RAEs[19] with thiosulfonates[20] was inspired by our recent studies of thiosulfonates as radical acceptors in the synthesis of thioesters[21] and RAEs as versatile radical progenitors in *C*-glucosylation.[22] We hypothesized that coupling of the radicals R$^{\bullet}$ **4** produced from the corresponding RAEs **1** with thiosulfonates **2** could deliver a new method for the synthesis of thioethers (Scheme 2).

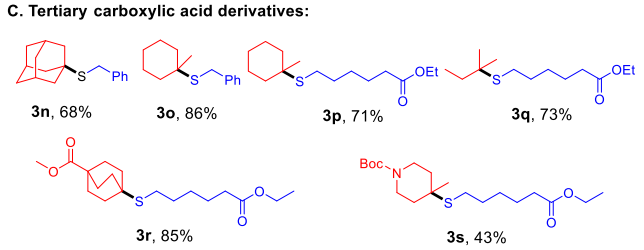
The validation of the feasibility of this proposal commenced with a model reaction of THF derived NHPI derived RAE **1a** with *S*-benzyl 4-methylbenzenesulfonothioate (**2a**) (Table 1 and S1). To our delight, irradiation of a solution of **1a** (0.15 mmol), **2a** (0.1 mmol), and DIPEA (0.15 mmol) in the presence of photocatalyst (PC) 4CzIPN (0.002 mmol) in MeCN using 40 W Kessil blue LEDs led to the formation of the desired thioether **3a** in 83% yield (entry 1). Among the PCs probed, $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ and $(Ru(bpy)_3(BF_4)_2$ are also effective promoters by delivering similar reaction efficiency (entries 2 and 3). Inferior results were observed with eosin Y presumably because it's a weaker reductant compared to 4CzIPN (entry 4).[6j] Survey of reaction media (DCM, DMF and DMSO, entries 5-7) and S precursors **2a-2a5** (entries 1 and 8-12) revealed that they had pronounced effects on the process. The control experiments confirmed that base, light, and PC were prerequisites for this transformation (entries 13-15).

Scheme 3. Scope of Carboxylic Acid Derived RAEs



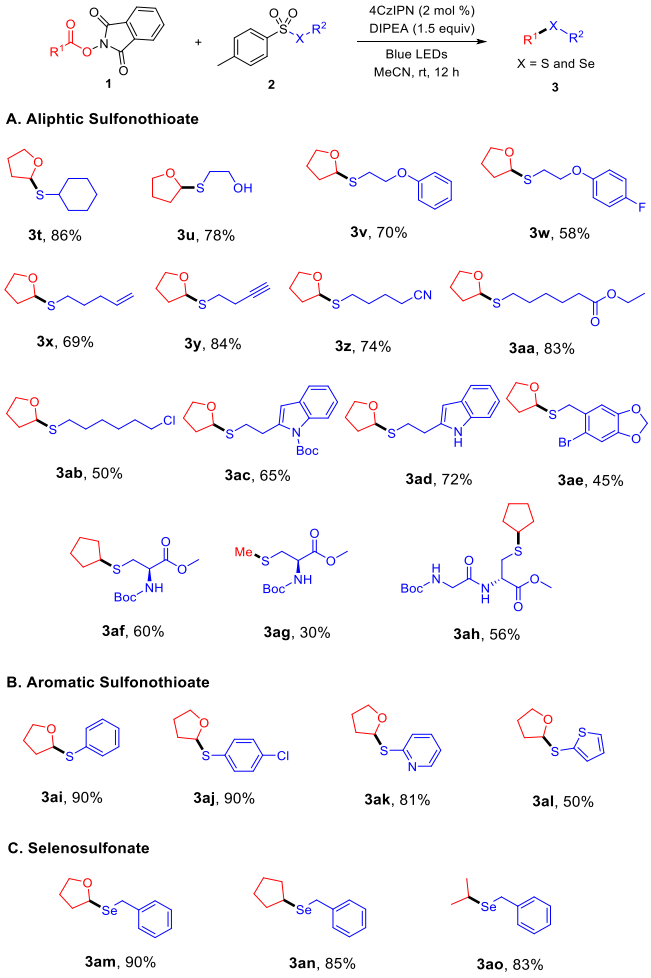






Reaction conditions: unless specified, see Table 1 and the Experimental Section. Yields are calculated based on isolated products.

Scheme 4. Scope of Thiosulfonates



Reaction conditions: uncles specified, see Table 1 and the Experimental Section the Experimental Section. Yields are calculated based on isolated products.

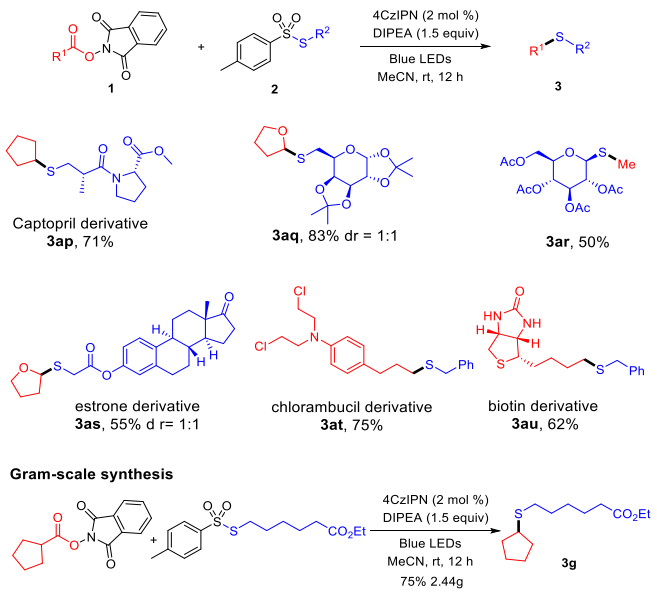
With the optimized reaction conditions in hand, we explored the strategy for the synthesis of structurally diverse thioethers (Scheme 3). We first probed the structural variation of RAEs **1**. We found other secondary alkyl carboxylic acid derived RAEs such as cyclic (**3a, b, 3g-i**), acyclic (**3c, 3d**) and amino acids (**3e, 3f**) could participate in the process with good yields (60-86%). Morevoer, this study was further expanded to primary (**3j-3m**) and tertiary carboxylate RAEs (**3m-3s**) as alkyl radical precursors. It is noted that there is limited success in the method with 4-alkyl-1,4-dihydropyridines as radical progenitors.[17] As shown, the protocol worked smoothly for the cases of **3j-3m** with different length of primary chain. Furthermore, the radical engaged process offers an unrivaled power for accessing sterically hindered tertiary thioethers **3n-3s**, which have been an unmet challenge in their synthesis.

Next, we probed the structural alternation of thiosulfonate S-esters under the optimized reaction conditions (Scheme 4). Again, this strategy servers as a general approach for the synthesis of structurally diverse thioethers. Notably, satisfying results for the synthesis of aliphatic thioethers (**3t-3ah**), which are limited accessed previously, are obtained. Especially the successful modification of cysteine and dipeptide (**3af, 3ag, 3ah**) offers a useful chemical tool for biochemistry study. It is noteworthy that under the mild reaction conditions, this radical-based method exhibits broad functional group tolerance, as

demonstrated for protected amines (**3s**), free hydroxyl (**3u**), alkene (**3x**), alkyne (**3y**), ester (**3g-3i, 3k-3m, 3p-3s and 3aa**), ether (**3v, 3w, 3ae**) and cyano (**3z**). Aromatic iodide is not affected by the reaction conditions (**3ad**), whereas it is generally not compatible with transition-metal catalysis. Furthermore, the protocol also works smoothly in the formation of alky-aryl thioethers (**3ai-3al**) and selenides (**3am-3ao**).

The success in the application of this mild synthetic protocol for a wide array of NHPI esters and thiosulfonate *S*-esters encouraged us to explore the synthetic methodology for more challenging targets of complex biologically active molecules including clinically used therapeutics (Scheme 5). Marketed drug captopril derived thiosulfonate *S*-esters can be efficiently modified to give the desired product in good yield of 71% (**3ap**). In addition to peptides, saccharides derived thioethers **3aq** and **3ar** are efficiently assembled. Of particular note is the methylsulfide is a common functionality in many pharmaceuticals (Scheme 1a).[2] Estrone, chlorambucil and biotin derived RAE esters were selectively thioesterificated to give the products **3as**, **3at** and **3au** in 55, 75 and 62%, respectively. These examples demonstrate the potential of this approach for selective decorating complex molecules under benign reaction conditions. A gram-scale reaction was conducted using NHPI ester **2a** under the same reaction conditions as used in the small-scale process to give **3g** in a similar yield.

Scheme 5. Thiolation of Bioactive Structures and Gram Scale Reaction



Reaction conditions: see Table 1 and the Experimental Section. Yields are calculated based on isolated products.

In conclusion, we have developed a new, efficient method for the construction of C-S/Se bond via visible-light-organophotoredox catalysis of redox-active esters with thio-/seleno sulfonates. The mild process serves as a viable strategy for the synthesis of both alkyl-alkyl and alkyl-aryl sulfides with outstanding functional group tolerance. Furthermore, an unrivaled feature of the process is to employ the feedstock carboxylic acid derived RAEs as radical progenitors and an unprecedented broad substrate scope is achieved. These merits make this protocol a promising strategy for the construction of C–S bonds in widespread applications within organic synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experiment details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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