Decarboxylative thiolation of redox-active esters to free thiols and further diversification

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Thiols are important precursors for the synthesis of a variety of pharmaceutically important sulfur-containing compounds. In view of the versatile reactivity of free thiols, here we report the development of a visible light-mediated direct decarboxylative thiolation reaction of alkyl redox-active esters to free thiols based on the abundant carboxylic acid feedstock. This transformation is applicable to various carboxylic acids, including primary, secondary, and tertiary acids as well as natural products and drugs, forging a general and facile access to free thiols with diverse structures. Moreover, the direct access to free thiols affords an advantage of rapid in situ diversification with high efficiency to other important thiol derivatives such as sulfide, disulfide, thiocyanide, thioselenide, etc.
The construction of molecule libraries with structural and functional diversity is crucial for the study in the context of chemical biology and drug discovery1-3. Thiols are important precursors for the synthesis of a variety of pharmaceutically important sulfur-containing compounds, including sulfonamides, sulfonyl fluorides, sulfoxides, sulfides, disulfides, and so on, by virtue of their high reactivity and valence labile nature, and widely employed in organic synthesis, polymer preparation, materials science, and biomedicine4-17. In fact, besides their well-known roles in protein structure stabilizations18,19 and many enzymatic processes20, thiols are also one of the most targeted sites in post-translational protein modification (Fig. 1a)21-23. Inspired by the versatile reactivity of thiols, we conceived that, based on the feedstock of abundant carboxylic acid, a decarboxylative thiolation of acid-derived redox-active esters (RAEs)24 to free thiols could forge a novel access to various thiols and related derivatives with considerable structural diversity. In particular, the decarboxylative thiolation of acid-derived carboxylic acid, a decarboxylative thiolation of acid-derived redox-active esters (RAEs)24-39 (RCO2A*) to free thiols could forge a novel access to various thiols and related derivatives with a multiplied diversity by varying the coupling agents (e.g., with various electrophiles E+, Fig. 1b).

A number of radical C-S bond formation reactions43-49 have been reported, including the related decarboxylative transformations pioneered by Barton in 1980s46-49, but a direct radical thiolation to free thiols remains elusive so far. The challenges for the proposed radical decarboxylative thiolation to free thiols probably lie in the labile nature of free thiols, which can lead to dimerization, undesired hydrogen transfer, and other side reactions43. In fact, free thiols are commonly used as hydrogen atom transfer (HAT) catalysts or reagents in radical chemistry46-54, and the HAT from a primary alkyl thiol to alkyl radicals is a fast process (ca. 107 M−1 s−1)49-54. Therefore, in the decarboxylative thiolation process, the desired thiol product (RSH) formed earlier may intercept the newly generated alkyl radicals (R-H), thus leading to the undesired alkane (R-H) formation (Fig. 1c). Nevertheless, in radical polymerization, the chain-transfer agents (CTA) employed in reversible addition-fragmentation chain-transfer polymerization can readily alter the radical addition rate by adjusting the Z group and increase k_{add} to above 10^8 M−1 s−1 (Fig. 1, C, below)55,56, which inspired us to focus on the sulfur donor search in the beginning. Herein, we report our efforts in the successful identification of aryl thioamides as an effective sulfur donor, and the invention of visible light-mediated direct
decarboxylative thiolation of alkyl RAEs to free thiols. Moreover, further diversification to other thiol derivatives, such as sulfide, disulfide, thiocyanide, and thioselenide via in situ trapping, is also demonstrated.

Results

Reaction optimization. We commenced our study with the search for sulfur donors suitable for the radical thiolation reaction, by employing dihydrocinnamic acid-derived RAE (1) as the model substrate and Eosin Y-Na2/diisopropylethylamine (DIPEA) as the photoredox catalytic system (Table 1). Initially, thiourea 2a, which is frequently used as a sulfur donor in the nucleophilic substitution reactions of alkyl halides\textsuperscript{57,58}, was examined first in the reaction, but only the alkane product 3’ was observed (entry 1), indicating the radical reactivity is substantially different from the polar substitution reactions. Other thioureas like 2b and 2c were also examined, but neither of them afforded the desired thiol product (entries 2 and 3). We then turned our attention to other types of sulfur donor (for more details about the reaction development, please see the Supplementary Figs. 1–9 and Table 1). To our delight, benzothioamide (entries 4–6). Electron-withdrawing group (-CF\(_3\), 2e) led to a decreased yield of 35%, while the introduction of an electron-donating group (2f) was found beneficial and further increased the yield to 81% (entry 5 vs. entry 6). The N-H group proved to be crucial for this transformation. Replacement with either one or two methyl groups (2g and 2h), both resulted in a sharp drop in yield (entries 7 and 8). Moreover, sulfur powder was also tested, but no desired thiol product was observed (entry 9). With 2f as the sulfur donor, we conducted a further reaction optimization, including photocatalyst, solvent, light source, and so on (for details, please see the Supplementary Tables 2 and 3). Other photocatalysts, such as Ru(bpy)\(_3\)Cl\(_2\)-6H\(_2\)O and Ir(ppy)\(_3\), gave lower yields (entries 10–13), while Eosin Y was found equally efficient (entry 14). Running the reaction in CH\(_3\)CN could slightly enhanced the selectivity (entry 15). Without light or photocatalyst, no reaction or a low yield was observed (entries 16 and 17). To our delight, the employment of two equivalents of sulfur donor 2f could further suppress the undesired alkane formation and increase the yield of the desired thiol product to a decent level of 88% in the end (entry 18).

Substrate scope. With the optimized reaction conditions in hand, we next examined the reaction scope with a variety of primary, secondary, and tertiary acid-derived RAEs (Fig. 2). Some free thiols are volatile and thus isolated in their disulfide form by in situ trapping with diphenyl disulfide. These results are also included in Fig. 2. In cases of primary acids (3–18), we could see a good functional group tolerance. Br, Cl, ether, ester, and also a triple C–C bond are all compatible in the reaction, and the

| Entry | Sulfur donor | Yield (3/3)\textsuperscript{b} | Entry | Catalyst | Yield (3/3)\textsuperscript{b} |
|-------|-------------|-------------------------------|-------|----------|-------------------------------|
| 1     | 2a          | 0/81                          | 10    | [Ru(bpy)\(_3\)]Cl\(_2\)-6H\(_2\)O | 71/28                          |
| 2     | 2b          | 0/76                          | 11    | Ir(ppy)\(_3\) | 37/32                          |
| 3     | 2c          | 0/79                          | 12    | Rhodamine B | 76/28                          |
| 4     | 2d          | 77/26                         | 13    | Fluorescein | 71/36                          |
| 5     | 2e          | 35/28                         | 14    | Eosin Y  | 81/23                          |
| 6     | 2f          | 81/23                         | 15\textsuperscript{d} | Eosin Y-Na\(_2\) | 83/18                          |
| 7     | 2g          | 2/72                          | 16\textsuperscript{e} | Eosin Y-Na\(_2\) | 0/0                            |
| 8     | 2h          | 3/97                          | 17\textsuperscript{f} | w/o Eosin Y-Na\(_2\) | 38/10                          |
| 9\textsuperscript{c} | Sulfur powder | 0/0                           |       | Eosin Y-Na\(_2\) | 88/6                           |

\textsuperscript{a}Reaction conditions: 0.05 mmol scale, catalyst (2.5 mol%). Left entries: with Eosin Y-Na2 as the photocatalyst. Right entries: with 2f as the sulfur donor.

\textsuperscript{b}Determined by GC-MS analysis with anisole as an internal standard.

\textsuperscript{c}Sulfur powder (5.0 equiv.).

\textsuperscript{d}Reaction was performed in CH\(_3\)CN instead of DCM.

\textsuperscript{e}In dark.

\textsuperscript{f}Without photocatalyst.

\textsuperscript{g}With 2.0 equiv. of 2f.
desired free thiols (4–10) or disulfides (11–18) could be isolated in moderate to good yields. Through this decarboxylative thiolation, simple propionic acid can also be converted to the corresponding disulfide in 40% yield (14). The reaction can be well applied to cyclic carboxylic acids (19–30), and different ring sizes (22–26), including cyclopropane (22), cyclobutane (23), benzocyclopentane (21), and cycloheptane (26), all can be converted to the desired product in reasonable yields. Heterocyclic free thiols

Fig. 2 Substrate scope. Reactions were performed on a 0.2 mmol scale, and trapping reactions were conducted with 2.0 equiv. of PhSSPh in dark for 6 h. In CF3CH2OH.
or disulfides, such as 19, 20, and 30, are also accessible from the corresponding carboxylic acids. Pleasingly, tertiary thiols or disulde (31–36) can be prepared as well with this method. In particular, this visible light-mediated radical decarboxylative thiolation reaction could afford a facile access to tertiary bridgehead thiols (such as bicyclic thiol 31, 1-adamantanethiol 33 and 34) under mild reaction conditions, which are often difficult to prepare via traditional nucleophilic substitution reactions due to the steric shielding of the bridgehead position and bridgehead thiols (such as bicyclic thiolation reaction could afford a facile access to tertiary particular, this visible light-mediated radical decarboxylative disulfide can be adopted for the late-stage modification of drugs, such as gemfibrozil (43), oxaproxin (44), and indometacin (45). In cases of 35, 36, and 43, we could observe less alkane formation when the reactions were performed in CF₃CH₂OH instead of CH₃CN, and thus led to a better yield. As outlined in Fig. 2, under this reaction condition, primary, secondary, and tertiary carbon radicals can all be readily generated from the corresponding alkyl NHPI esters and subsequently trapped by the sulfur donor and converted to the desired thiol or disulfide products.

**Product diversification.** Disulfides are important motifs in life and biological active molecules, due to their unique pharmacological and physiochemical properties. To further explore the scope of this transformation, more diaryl disulfide-trapping agents were examined with dihydrocinnamic acid-derived ester 1 as a model substrate. As shown in Fig. 3a, the reactions worked well with various diaryl disulfides processing different electronic nature, affording the desired unsymmetric alkyl aryl disulfides 47–51 readily in good yields. Importantly, the conversion of carboxylic acids to disulfides via this decarboxylative thiolation/in situ trapping protocol provides a facile approach to synthesize this type of molecules with high structural diversity. Thiols are key precursors to many pharmaceutically important compounds. The direct decarboxylative thiolation to free thiols allows for the establishment of a rapid, in situ diversification to various thiol derivatives without isolating the free thiols, which are often smelly and unstable. As shown in Fig. 3b, the 2-phenylethane-1-thiol can readily undergo alkylation in situ with various electrophiles or Michael acceptors, to provide the corresponding sulfonyl compounds. A possible reaction mechanism is proposed as outlined in Fig. 4. Under the irradiation of light, the photocatalyst Eosin Y (PC) is excited and subsequently reductively quenched by DIPEA or 2f, affording PC− and 2f− in the presence of base. The fluorescence quenching experiments also clearly showed that both DIPEA and sulfur donor 2f can quench the fluorescence of the photocatalyst (Supplementary Figs. 7–9). A single electron transfer (SET) from PC− to the carboxylic acid-derived RAE afford the corresponding radical anion Int-A and concurrently regenerate the photocatalyst (Path A). As product also observed in the absence of PC and 2f showed substantial absorption in the blue light region (Supplementary Fig. 5), Path B might also

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**Fig. 3 Reaction extension and product diversification.** a) Extension to disulfide synthesis. b) In situ diversification.

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**Trapping agents:**

a) CH₃I, b) PhCH₂Br, c) PhCO₂Et, d) CICH₂CN, e) CO₂Bu, f) TseCN, g) PhSeSePh,
involve to some extent. Int-A then undergoes fragmentation to give the alkyl radical R via the N–O bond cleavage followed by the extrusion of CO₂. The alkyl radical can be trapped with TEMPO (Supplementary Fig. 3). The addition of R to the sulfur donor 2f generate the radical intermediate Int-B\(^{57}\), which can be oxidized to imine Int-C by a SET to excited photocatalyst as shown as Path I. The higher yields with alkyl thioamides than alkyl ones may be ascribed to the stabilization of the aryl group to electron oxidation of Int-B to Int-C. Alternatively, a radical coupling of R and 2f' could also afford the intermediate Int-C (Path II). As a competing process, the HAT from thiol (R-SH) to R will lead to the formation of the alkane side product (R-H)\(^{51,52}\), which can be suppressed by a rapid trapping of R with active thiolating agents via Path I or II. In the end, the desired thiol is produced after the elimination of one molecule of ArCN\(^{68,69}\), which could be a relatively slow step, and a slow release of free thiols can decrease the formation of the undesired alkane product. The nitrile byproduct formation was confirmed by gas chromatography-mass spectrometry (GC-MS) analysis, and it can also be isolated by column chromatography. Therefore, the use of N-unsubstituted thioamides is crucial for this transformation. In contrast, N-substituted thioamide 2g and 2h are unable to form the corresponding N-H imine intermediate Int-C.

**Discussion**

In conclusion, a visible light-mediated direct decarboxylative thiolation of carboxylic acid-derived RAEs to free thiols has been developed. Aryl thioamides have been identified as an effective sulfur donor and crucial to this thiolation reaction. The transformation of abundant carboxylic acid feedstock to the corresponding free thiols and their further in situ diversification allows for a rapid and general access to various pharmaceutically important compounds, such as sulfide, disulfide, thiocyanide, and thioseelenide, with diverse structures, which may be utilized for the molecule library construction and benefit the related study in chemical biology and discovery of novel, biologically interesting small molecules.

**Methods**

**General procedure for decarboxylative thiolation.** To an oven-dried 10-ml Schlenk tube equipped with a magnetic stir bar and a Teflon-coated septum screwcap was added the NHPI redox-active ester (0.2 mmol, 1.0 equiv.), 4-methoxythiobenzamide (2f, 0.4 mmol, 2.0 equiv.), Eosin Y-Na\(_2\) (2.5 mol%). The tube was evacuated and backfilled with argon for three cycles. The DIPEA (0.22 mmol, 1.1 equiv.) and dry CH\(_3\)CN (2.0 ml) was added via a gastight syringe under argon atmosphere. Make sure the screwcap was closed, and the solvent was frozen by liquid nitrogen. Then, the screwcap was opened and the tube was evacuated for about 3 min. The screwcap was closed and let the solvent melts in a tepid water bath. Repeat above freeze-pump-thaw procedures for 3–5 times until you no longer see the evolution of gas as the solution thaws. The tube was filled with argon and sealed. Irradiated with 6 W blue light-emitting diode (LED) reactor and stirred at ambient temperature for 24 h. Full experimental details (Supplementary Figs. 1–9 and Supplementary Tables 1–3) and characterization of new compounds (Supplementary Figs. 10–68) can be found in the Supplementary Methods section.

**General procedure for the synthesis of disulfides.** To an oven-dried 10-ml Schlenk tube equipped with a magnetic stir bar and a Teflon-coated septum screwcap was added the NHPI redox-active ester (0.2 mmol, 1.0 equiv.), 4-methoxythiobenzamide (2f, 0.4 mmol, 2.0 equiv.), and Eosin Y-Na\(_2\) (2.5 mol%). The tube was evacuated and backfilled with argon for three cycles. The DIPEA (0.22 mmol, 1.1 equiv.) and dry CH\(_3\)CN (2.0 ml) was added via a gastight syringe under argon atmosphere. Make sure the screwcap was closed, and the solvent was frozen by liquid nitrogen. Then, the screwcap was opened and the tube was evacuated for ~3 min. The screwcap was then closed and the solvents were let to melt in a tepid water bath. Repeat above freeze-pump-thaw procedures for 3–5 times until you no longer see the evolution of gas as the solution thaws. The tube was filled with argon and sealed, irradiated with 6 W blue LED reactor and stirred at ambient temperature for 24 h. Then, the K\(_2\)CO\(_3\) (0.4 mmol, 2.0 equiv.) and diaryl disulfide (0.4 mmol, 2.0 equiv.) was added under argon atmosphere. The tube stirred at ambient temperature for 6 h in the dark. Upon completion, the reaction mixture was carefully concentrated, and the residue was further purified by flash chromatography to give the desired disulfide products. Full experimental details and characterization of new compounds can be found in the Supplementary Methods section.
Data availability

The authors declare that all data supporting the findings of this study are available within the article and Supplementary information files, and are also available from the corresponding author upon reasonable request.

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Author contributions

T.C. and T.X. contributed equally to this work. T.C. developed the reactions, and contributed to the reaction scope investigation, mechanistic study, and product derivatization. T.X. carried out most substrate synthesis, and contributed to the study of reaction scope, product diversification, and reaction mechanism. R.X. and X.S. participated in the synthesis of substrates. S.L. conceived this concept and prepared this manuscript with feedback from T.C. and T.X.

Competing interests

The authors declare no competing interests.

Additional information

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