ChemPubSoc Europe

DOI: 10.1002/chem.201900932

CHEMISTRY
A European Journal
Communication

Synthetic Methods

Organocatalytic Transformation of Aldehydes to Thioesters with Visible Light

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Abstract: A metal- and oxidant-free catalytic method for accessing structurally diverse thioesters from readily accessible, widespread aldehydes, is described. A strategy of a simple organic 9,10-phenanthrenequinone-promoted hydrogen atom transfer (HAT) with visible light was successfully implemented to selectively generate acyl radicals without inducing crossover reactivity of thioester products. The preparative power of the method was demonstrated by broad substrate scope and wide functional group tolerance, and enabled the late-stage modification of complex structures, which are difficult to achieve with the existing protocols.

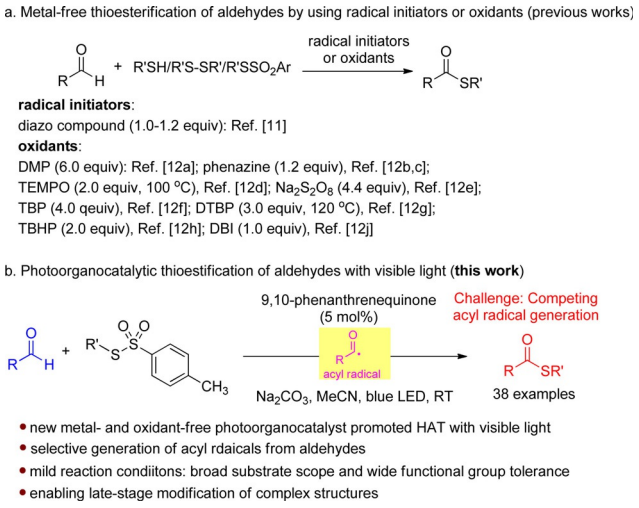
Thioesters are a class of compounds widely used in chemical and biological synthesis. Thioester acetyl-CoA is a ubiquitous acetylation reagent in biosynthesis and metabolism.[1] Their comparable reactivity to acyl chlorides but high stability make them attractive in organic synthesis.[2] Notable examples include native chemical ligation (NCL) for peptide and protein synthesis as well as amide and ester formation.[3]

The acylation of thiols with carboxylic acids, acid anhydride, or acyl chloride is the most widely used protocol for thioester synthesis.[2b] Significant advances on developing atom-economical catalytic methods have been made,[2c] typically carried out with transition metals as catalysts such as carbonylation,[4] cross-coupling[5] and allylic substitution.[6] However, some of these processes can be complicated by metal-sulfur poisoning, and thus, often require high catalyst loading, long reaction time and/or high temperature.[7] Therefore, catalytic methods, which can overcome these issues, will streamline thioester synthesis and significantly broaden their synthetic application.

Organocatalysis using small organic molecules as promoters offers a solution to address these issues.[8] Metal free acyl radical engaged thioester formation process by employing widely available aldehydes as radical coupling progenitors[9] has long been investigated since the seminal work by Takagi.[10] These transformations are generally carried out with a catalyst. However, stoichiometric radical initiators,[11] or oxidants[12] are essential for effective radical generation (Scheme 1 a). Such a large amount of reagents particularly peroxides and the accumulation of in situ produced highly concentrated radicals often induce more side reactions and displays low functional tolerance, which is crucially important in the elaboration of structurally complex, medicinally relevant frameworks.

We questioned whether use of visible light instead of oxidants as radical generation force could afford a milder, and more general and atom economical approach for the synthesis of thioesters.[13] However, it is recognized that the development of photocatalytic thioesterification of aldehydes is particularly difficult because both aldehydes (reactants) and thioesters (products) are often used as acyl radical progenitors in photocatalytic acyl radical formation.[9] The potential cross reactivity could significantly affect the process. The development of a photocatalytic system to selectively control their reactivities is vital.

With this in mind, we propose to design a photocatalytic hydrogen-atom transfer (HAT) process for selective abstraction of H atom of aldehyde (Scheme 1 b). Furthermore, a photocatalyst solely serving as HAT without photoredox or energy-transfer capacity is critical because they can activate thioesters to produce acyl radicals. In our continuing effort on developing organocatalytic processes, we pursued to explore organic dyes as promoters.[14] Benzophenones and quinones have been used for HAT.[15] Nonetheless, they mediated HAT generally carried



Scheme 1. Metal-free thioesterification of aldehydes. DMP: Dess–Martin periodinane; TEMPO: (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; TBP: *tert*-butyl peroxide; DTBP: di-*tert*-butyl peroxide; TBHP: *tert*-butyl hydroperoxide; DBI: dibromoisocyanuric acid.

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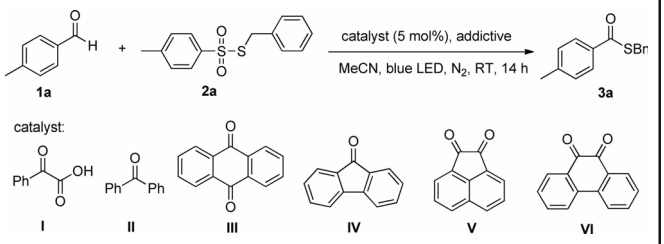
out under UV light. Such strong irradiation can induce homolytic cleavage of the thioester C–S bond.[16] Studies have shown that bond dissociation enthalpy (BDE) considerations are less important than C–H bond polarity in HAT.[16] We therefore conceived that direct hydrogen abstraction of highly polarized C–H bond of aldehyde by using this class of activators with weak visible light might be possible.[17,18]

Herein, we wish to disclose the results of the investigation, which leads to the first photoorganocatalytic, selective process for thioester formation from aldehydes with visible light (Scheme 1 b). A simple, cost-effective 9,10-phenanthrenequinone photocatalyst was discovered to chemoselectively promote the process under mild reaction conditions. Notably, the process displayed broad substrate scope and wide functional group tolerance, and enabled late-stage modification of complex structures, which are difficult to achieve with the existing protocols.[4,11,12]

Our exploratory studies began with a model reaction of aldehyde **1a** (0.2 mmol) with commonly used sulfenyl donors (0.24 mmol) including thiol, disulfide and thiosulfonate S-ester **2a** in the presence of a ketone catalyst (0.01 mmol) in MeCN (2.0 mL) irradiated with blue LEDs under N_2 atmosphere (Table 1). Thiol and disulfide did not produce desired product **3a** with phenylglyoxylic acid (**I**), whereas 10% of **3a** was obtained with thiosulfonate **2a** (entry 1).[19] We believe that highly polarized S–SO_2 bond renders S electrophilic, and thus, enables it to selectively react with the acyl radical. Encouraged by this result, we evaluated several ketone catalysts and found that acenaphthoquinone (**V**) promoted the thioesterification of aldehyde more efficiently with yield of 40% (entries 2–5). To further improve the reaction yield, we reasoned that the by-product 4-methylbenzenesulfinic acid might be detrimental. Therefore, a base was applied. Indeed, the yield was improved dramatically to 75% with 1.0 equiv Na_2CO_3 (entry 6). Furthermore, analysis of the photocatalysts suggests that the ketones containing an adjacent dicarbonyl moiety displayed higher catalytic activity presumably due to stronger electron acceptance capability in HAT process. Thus, we probed diketone compound (**VI**), which delivered much better yield of 95% (entry 7). It is worth noting that catalyst **VI** is highly cost-effective ($0.5 g^{-1}). Decreasing Na_2CO_3 loading to 0.5 equiv and increasing reaction concentration to 0.2 M did not affect the yield (entries 8 and 9). As expected, visible light is indispensable for this process (entry 10) and O_2 hampers the radical-engaged process (entry 11) in control studies. These findings led to establish the optimal protocol, used for probing the scope of the photocatalytic thioesterification process.

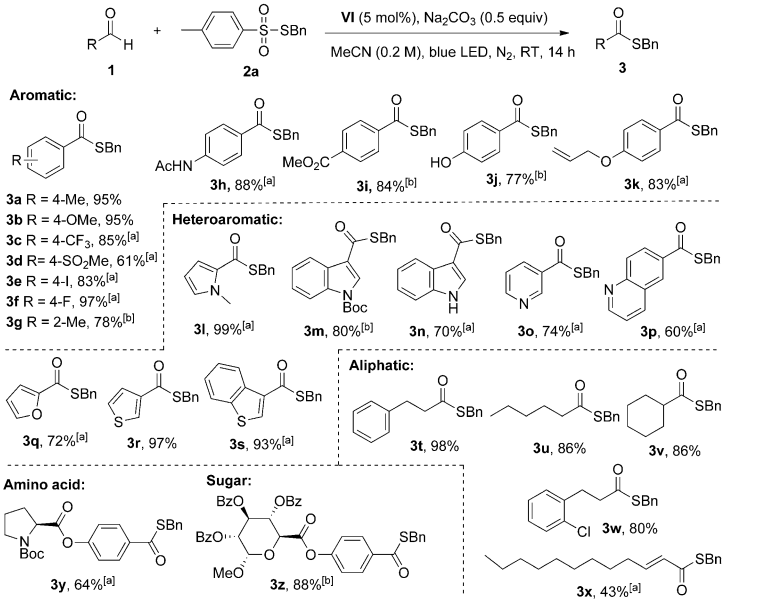
The methodology serves as a mild, general approach for the synthesis of a wide array of thioesters. Significant structurally diverse aldehydes including aromatic (**3a**–**3k**), heteroaromatic (**3l**–**3t**) and aliphatic structures (**3u**–**3x**) and biologically relevant frameworks amino acid (**3y**), and saccharide (**3z**) can be employed as substrates for the process and deliver the thioester products in good to excellent yields (61–95%) (Scheme 2). The mild procedure can tolerate a variety of functional groups. For example, aromatic iodide is not affected by the reaction conditions (**3e**), whereas it is generally not compatible with transition-metal catalysis. Selective acylation of thiols over phenol hydroxy group without requiring protection can be achieved (**3j**). Moreover, radical sensitive C=C double bond (**3k**, **3x**) are not affected by the mild protocol.

Table 1. Exploration and optimization studies.[a]



Entry	Catalyst	Addictive	Yield [%][b]
1	**I**	none	10
2	**I**	none	trace
3	**III**	none	trace
4	**IV**	none	trace
5	**V**	none	40
6	**V**	Na_2CO_3[c]	75
7	**VI**	Na_2CO_3[c]	95
8	**VI**	Na_2CO_3[d]	95
9[e]	**VI**	Na_2CO_3[d]	95
10[f]	**VI**	Na_2CO_3	trace
11[g]	**VI**	Na_2CO_3	0

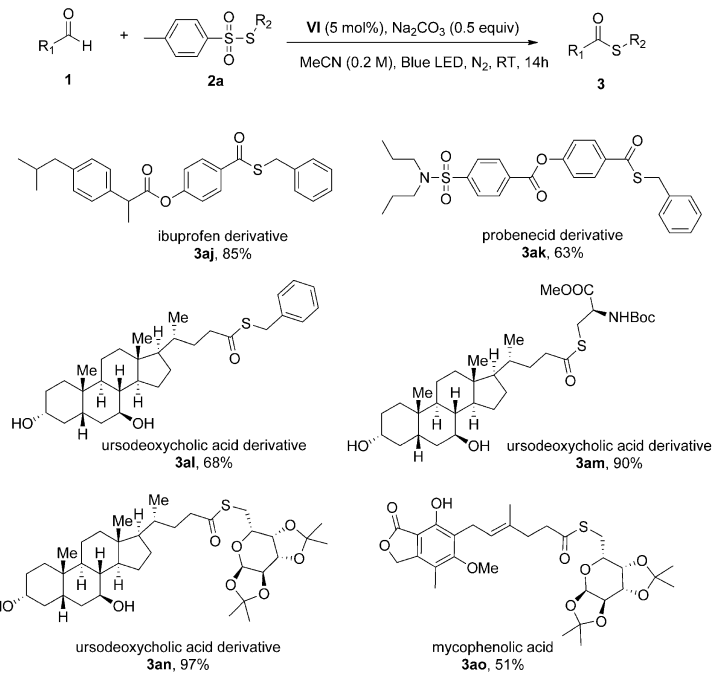
[a] Reaction conditions: unless specified, a mixture of **1a** (0.2 mmol), **2a** (0.24 mmol), and catalyst (0.01 mmol) in MeCN (2.0 mL) was irradiated with blue LEDs in N_2 atmosphere at RT for 14 h. [b] Yield of isolated products. [c] 1.0 equiv used. [d] 0.5 equiv used. [e] 1 mL of MeCN used. [f] In the dark. [g] Exposed to air.



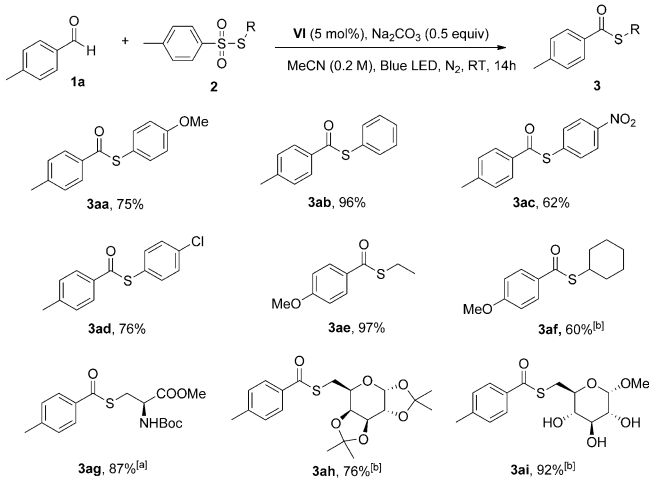
Scheme 2. Scope of aldehydes. Reaction conditions: unless specified, see the Experimental Section. Yields are calculated based on isolated products. [a] Reaction time: 24 h. [b] Reaction time: 36 h.

Next, we probed the structural alternation of thiosulfonate S-esters under the optimized reaction conditions (Scheme 3). Again, this strategy provides a preparative power for the synthesis of various thioesters. In addition to aliphatic thioesters (Scheme 2), aromatic (**3 aa**–**3 ad**) and amino acid (**3 ag**) and saccharide (**3 ah**–**3 ai**) derived compounds can be efficiently constructed (62–92 % yield) from their corresponding thiosulfonate S-esters. Particularly, the example of non-protected monosaccharide provides an opportunity to modify carbohydrates eliminating tedious protection and deprotection procedures.

The success in the application of this mild synthetic protocol for the structurally diverse aldehydes 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 4).[20] Marketed drug ibuprofen and probenecid aldehyde precursors were selectively thioesterificated to give the products **3 aj** and **3 ak** in good yields of 85 and 63 %, respectively. When the native ursodeoxycholic acid derived aldehyde was subjected to the thioesterification reaction with benzyl, amino acid and monosaccharide derived thiosulfonate S-esters, the desired products **3 al**, **3 am** and **3 an** were obtained in high yield (68, 90 and 97 %, respectively). Furthermore, unprotected mycophenolic acid aldehyde derivative was selectively modified to produce thioester **3 ao** with 51 % yield. These examples demonstrate the potential of this approach to selectively decorate complex molecules under benign reaction conditions.



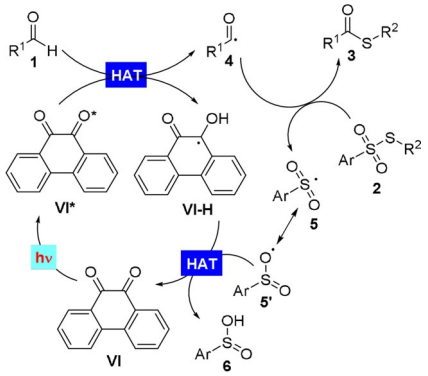
Scheme 4. Scope of complex molecular architecture. Reaction conditions: uncles specified, see the Experimental Section.



Scheme 3. Scope of thiosulfonates. Reaction conditions: uncles specified, see the Experimental Section. [a] Reaction time: 24 h. [b] Reaction time: 36 h.

A plausible mechanism is proposed for the **VI** promoted radical involved thioesterification of aldehyde (Scheme 5). In a typical ketone promoted HAT,[15] irradiation of catalyst **VI** by visible light generates the excited state **VI***, which promotes a HAT to give radical **4**. The resultant nucleophilic radical **4** attacks the electrophilic thiosulfonate S-ester **2** affords thioester product **3**. The second HAT between radical **5′** and **VI-H** radical generates catalyst **VI** and by-product sulfinic acid **6** to complete the catalytic cycle. The by-product **6** (Ar = *p*-MeC_6H_4) was isolated in 61 % yield and verified by ^{1}H NMR spectroscopy.

In conclusion, we have developed a metal- and oxidant-free method for the thioesterification of aldehydes. A new strategy using a simple organic 9,10-phenanthrenequinone promoted HAT with visible light was successfully implemented to selectively generate acyl radicals without inducing crossover reactivity of thioesters. The mild method exhibits excellent substrate scope and outstanding functional group tolerance. Significantly, it is also proved to be useful in a late-stage functionalization of complex molecules at room temperature.



Scheme 5. Proposed mechanism.

Experimental Section

General procedure: See Schemes 2–4. To an oven-dried 10 mL-Schlenk tube equipped with a stir bar, was added Na_2CO_3 (10.6 mg, 0.1 mmol), 9,10-phenanthraquinone (2.1 mg, 0.01 mmol), aldehyde **1** (0.24 mmol), thiosulfonate S-ester **2** (0.2 mmol) and MeCN (1 mL). The mixture was degassed the freeze-pump-thaw method, then sealed with parafilm. The solution was then stirred at RT under the irradiation of a blue LED strip for specified time. After completion of the reaction, the mixture was concentrated and purified by flash chromatography on silica gel.

Acknowledgements

Financial support for this work provided by the NSF (CHE-1903983) and the ACS-PRF (57164-ND1) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · organocatalysis · photochemistry · thioesters

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Manuscript received: February 27, 2019

Accepted manuscript online: April 15, 2019

Version of record online: May 28, 2019