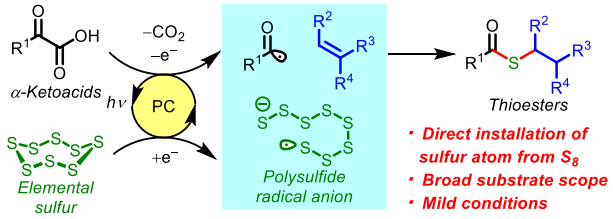
Photocatalytic Activation of Elemental Sulfur Enables a Chemoselective Three-Component Thioesterification

Sho Murakami, Takeshi Nanjo, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information Placeholder

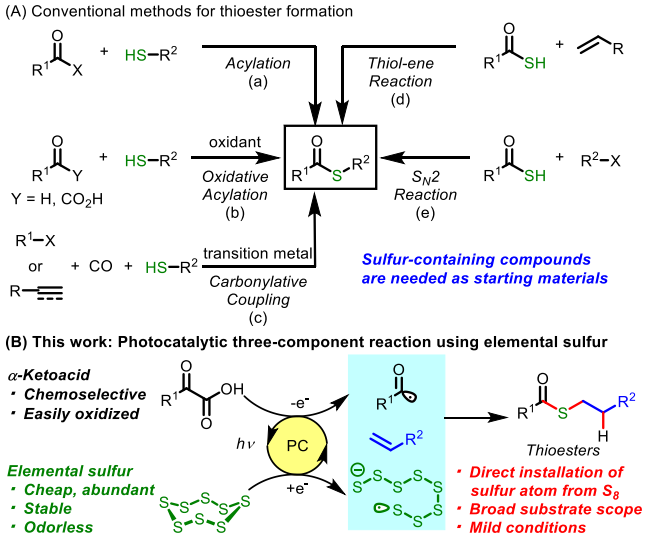


ABSTRACT: A mild and chemoselective three-component thioesterification using olefins, α-ketoacids, and elemental sulfur has been developed. The photocatalytic activation of elemental sulfur, a cheap and abundant sulfur source, enables the rapid installation of a sulfur atom into molecules, reactions that ordinarily would require the use of reactive and malodorous sulfur-containing compounds such as thiols and thioacids. This novel reaction is characterized by high yields and a broad substrate scope, which enables the introduction of thioester moieties into complex molecules including a steroid, a peptide, and a non-protected glycoside. Mechanistic studies indicated that the success of this transformation depends on the multiple roles played by the elemental sulfur, including those of a sulfurizing agent, a terminal oxidant, and a HAT mediator.

Sulfur-containing functional groups are versatile motifs that can be used to impart organic compounds with novel physical properties and/or bioactivity.[1] Thioesters are active esters found in biosynthetic intermediates such as acetyl-CoA and are used synthetically as acyl-transfer agents for the preparation of various carbonyl compounds and during native chemical ligation (NCL).[2,3] Therefore, synthetic chemists have devoted substantial effort to the development of methods for the rapid construction of thioesters. To date, approaches to this end have mainly focused on using thiols or thioacids (Scheme 1A).[4-10] Most conventional methods for the preparation of thioesters are based on the acylation of thiols with activated carboxylic-acid derivatives (reaction (a), Scheme 1A).[4a] During the search for more efficient and chemoselective acylation methods, variants of this approach have arisen that use combinations of aldehydes[5] or α-ketoacids[6] and stoichiometric amounts of oxidants (reaction (b), Scheme 1A). Additionally, transition-metal-catalyzed carbonylative couplings of thiols (reaction (c), Scheme 1A) have been intensively investigated.[7] Thioacids are alternative sulfur sources for the formation of thioesters and thiol-ene reactions with olefins (reaction (d), Scheme 1A)[8] and S_N2 reactions with alkyl halides (reaction (e), Scheme 1A) have been accomplished using this sulfur source.[9] Although some of these transformations give reliable results, both thiols and thioacids are highly reactive species that require special care during preparation and storage as they are oxidized easily and have unpleasant odors. Thus, a new synthetic approach for the formation of thioesters using a readily available, easily handled sulfur source is highly desirable.

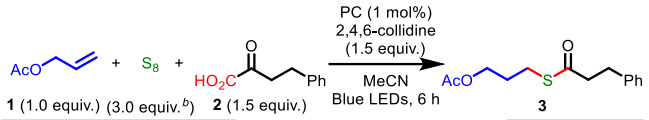
Herein, we propose a strategy for a three-component reaction

Scheme 1. Strategies for the synthesis of thioesters.

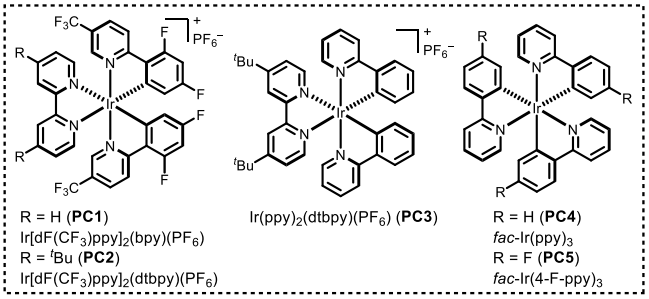


for the formation of thioesters using elemental sulfur (S_8),[11,12] i.e., a sulfur source that is cheap, odorless, and stable under ambient conditions; however, S_8 has not yet been used for the synthesis of thioesters. The highly stable nature of S_8 usually requires the use of harsh activation conditions such as strong acids or bases, or high temperatures,[11] all of which are incompatible with the formation of thioesters. Therefore, we envisioned that the photocatalytic single-electron reduction of S_8 could efficiently initiate a radical-mediated thioesterification. Although

Table 1. Optimization of the reaction conditions.[a]



entry	PC	redox potential (V)		yield (%)
		$[Ir^{III*}/Ir^{IV}]$	$[Ir^{III}/Ir^{IV}]$	
1	**PC1**	−1.00	+1.69	71
2	**PC2**	−0.89	+1.69	83
3	**PC3**	−0.96	+1.21	0
4	**PC4**	−1.73	+0.77	0
5	**PC5**	−1.91	+0.97	0

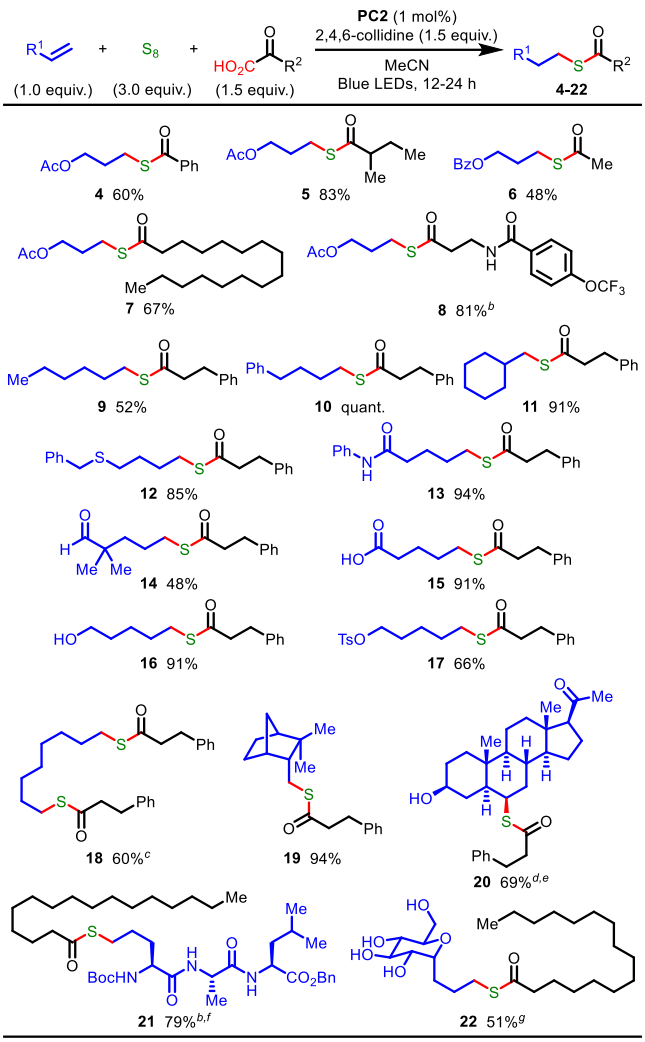


[a]Isolated yields are shown. [b]The number of equivalents was calculated relative to the number of S atoms.

a photocatalytic reaction using S_8 has been reported by Savateev in 2018,[13] it was limited to a heterogeneous system for the synthesis of disulfides and thioamides. S_8 is easily reduced ($E_{1/2}$ = −0.34 V vs NHE[13a]) and therefore we were able to design a photocatalyzed three-component coupling reaction of an α-ketoacid and an olefin (Scheme 1B). We envisaged that S_8 could potentially be reduced by an appropriate photoredox catalyst concomitant with the oxidation of an α-ketoacid to produce a polysulfide radical anion and an acyl radical species. These intermediate radicals could then couple to form a carbonyl thiyl radical and, following a radical addition to an olefin and a hydrogen-atom transfer (HAT) step, provide a thioester. In the catalytic cycle, S_8 would act not only as a sulfur source, but also as a terminal oxidant and as the HAT mediator. We hoped that the multiple roles that S_8 plays would simplify the reaction system whilst the use of α-ketoacids as an acyl equivalent would provide unique chemoselectivity and increase the functional-group tolerance.[14,15]

Initially, we investigated the reaction conditions for our proposed thioesterification using model substrates, i.e., olefin **1** and α-ketoacid **2** (Table 1). A screening of photocatalysts (PC) revealed that in the presence of S_8 and 2,4,6-collidine in MeCN[16] under blue LEDs irradiation, **PC1** ($E_{1/2}[Ir^{III*}/Ir^{IV}]$ = −1.00 V vs SCE and $E_{1/2}[Ir^{III}/Ir^{IV}]$ = +1.69 V vs SCE[17]) and **PC2** ($E_{1/2}[Ir^{III*}/Ir^{IV}]$ = −0.89 V vs SCE and $E_{1/2}[Ir^{III}/Ir^{IV}]$ = +1.69 V vs SCE[18]) could efficiently provide the desired thioester **3** in 71% and 83% yield, respectively (entries 1 and 2).[19,20] In contrast, **PC3**,[17] **PC4**,[21] and **PC5**[22] did not promote the reaction, despite their excited complexes having sufficient reducing power for the reduction of S_8 ($E_{1/2}$ = −0.57 V vs SCE[23]) (entries 3-5). These results and the redox potential of α-ketocarboxylate (E_{pa} = +1.12 V vs SCE[23]) suggest that a highly oxidizing photocatalyst is essential for a successful transformation.

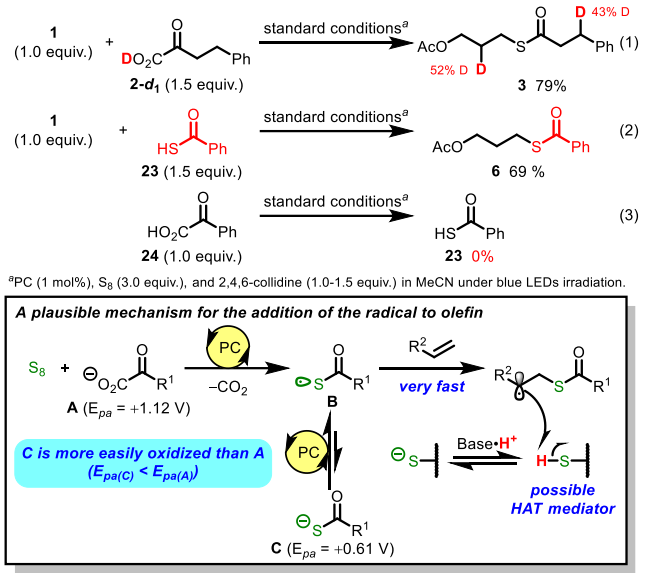
Scheme 2. Substrate scope of the thioesterification reaction.[a]



[a]Isolated yields are shown. [b]α-Ketoacid (2.0 equiv.), S_8 (4.0 equiv.), and 2,4,6-collidine (2.0 equiv.). [c]α-Ketoacid (3.0 equiv.), S_8 (6.0 equiv.), and 2,4,6-collidine (3.0 equiv.). [d]α-Ketoacid (2.5 equiv.), S_8 (5.0 equiv.), and 2,4,6-collidine (2.5 equiv.). [e]THF was used as solvent. [f]CH_2Cl_2 was used as solvent. [g]Thioester **22** was obtained in an α:β ratio of 5.3:1, as 3-(D-glucopyranosyl-1-propene (α:β = 5.3:1) was used as the olefinic substrate.

With the optimum reaction conditions (Table 1, entry 2) in hand, we investigated the substrate scope in order to verify the chemoselectivity and functional-group tolerance of the thioesterification reaction (Scheme 2). α-Ketoacids with aryl or branched alkyl substituents provided thioesters **4** and **5** in 60% and 83% yield, respectively. The reaction of pyruvic acid, a cheap and abundant α-ketoacid that is metabolically converted into Acetyl-CoA, afforded thioacetylated product **6** in good yield. Additionally, a long-chain fatty acid and a functionalized 3-aminopropanoic moiety were successfully incorporated into thioesters **7** and **8**. Next, we explored the scope of the reaction with respect to the olefin moiety. Simple hydrocarbons such as *n*-hexene, 4-phenyl-1-butene, or methylenecyclohexane provided thioesters **9**-**11** in excellent yield, albeit the aryl alkenes did not result in good yields (<20% yield). We then applied our standard conditions to olefins bearing thioethers, anilides, aldehydes, and unprotected carboxy groups; we found that these

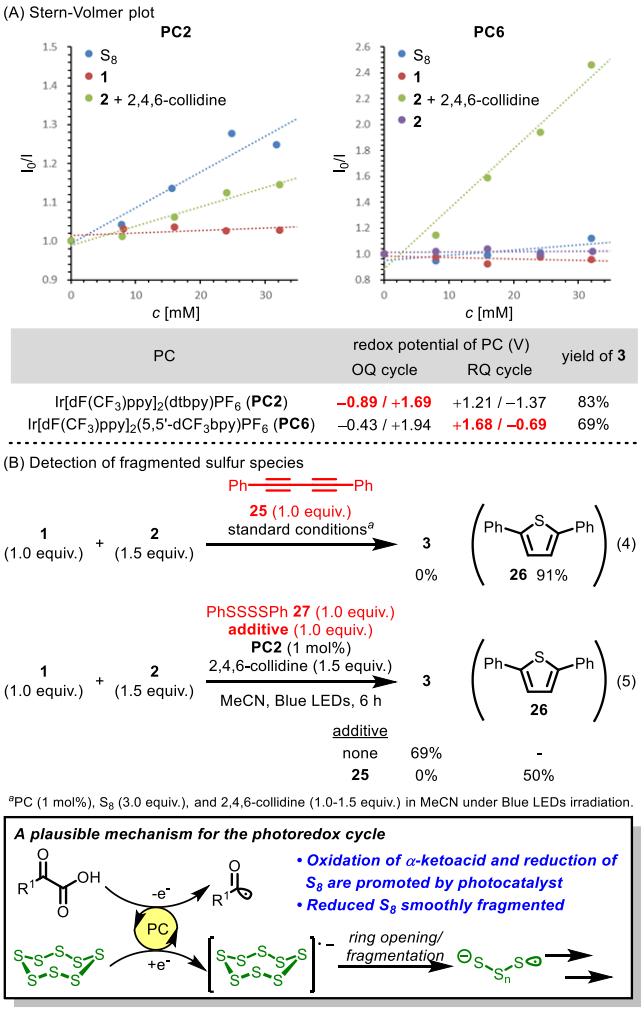
Scheme 3. Mechanistic analysis of the reaction intermediates.



functional groups do not affect the yield of the resulting thioesters (**12-15**). It should be noted here that although **16** and **17** contain an unprotected hydroxy group and a *p*-toluenesulfonyl ester, both of which could potentially be functionalized during conventional thioesterification reactions, they still gave the desired products in 91% and 66% yield, respectively. In addition, a diene was successfully converted into bisthioester **18** by doubling the amount of reagent used. We also applied this method to the synthesis of thioesters derived from various biologically active compounds. The thioesterification of camphene, a bicyclic monoterpene, proceeded successfully to afford **19**. Pregnenolone, a prohormone that has been used as a medication, provided the corresponding thioester **20** in 69% yield as a single diastereomer. Remarkably, a peptide and a glycoside could also be thioesterified effectively under the optimized reaction conditions to provide **21** and **22**.

Next, we conducted a mechanistic analysis of the three-component thioesterification. We initially confirmed that the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical scavenger to the standard reaction shut off the formation of the thioester and this result indicates that the reaction proceeds via a radical pathway (for details, see the Supporting Information).[24] In addition, the use of a deuterated α-ketoacid provided thioester **3** with 52% incorporation of deuterium at the β-position relative to the sulfur functionality (eq. 1).[25] These results suggest that the reaction proceeds via the addition of a thiyl radical to the alkene followed by a HAT step between the β-alkylradical and a protonated species such as a hydropolysulfide. In order to gain insight into the reaction intermediates we conducted a reaction using benzoic thioacid **23** and found that under the optimal conditions, the thiol-ene reaction[9] proceeds smoothly (eq. 2). However, in the absence of an olefin (eq. 3) under otherwise optimal conditions, the reaction of α-ketoacid **24** did not afford a significant amount of thioacid **23**, probably due to the imbalance of the redox potentials of the α-ketocarboxylate **A** (E_{pa} = +1.12 V vs SCE) and the thiocarboxylate **C** (E_{pa} = +0.61 V vs SCE[23]). These results indicate that a thioacid does not form during the thioesterification and that a carbonyl thiyl radical **B** derived from a α-ketoacid and S_8 are directly

Scheme 4. Mechanistic analysis of the reactive species.



consumed in the following radical addition.

Next, we performed luminescence-quenching experiments on the iridium photocatalysts to gain insight into the reaction intermediates. Stern-Volmer plots revealed that an excited state of **PC2** is most efficiently quenched by S_8 and can therefore be expected to initiate the thioesterification via the reduction of S_8 as originally expected (Scheme 4A, left). However, the screening of photocatalyst **PC6** (Scheme 4A, right), which has little reducing power in the oxidative quenching (OQ) cycle ($E_{1/2}[Ir^{III*}/Ir^{IV}]$ = −0.43 V vs SCE[26]), showed that it could also provide the desired thioester **3** and was quenched only by the combination of the α-ketoacid and 2,4,6-collidine. These results indicate that both the single-electron reduction of S_8 and the single-electron oxidation of α-ketocarboxylate could initiate the photocatalytic cycle, and that the resulting S_8 radical anion and α-ketocarboxy radical, which would be immediately converted into an acyl radical, could act as key intermediates in the reaction. Subsequently, we conducted experiments where a 1,3-diyne was added to the thioesterification in order to obtain evidence of the fragmentation of S_8 during photocatalysis. Previous reports have shown that anionic sulfur species such as hydrosulfides, S_3 radical anions, and trithiocarbonate anions can couple with 1,4-diphenyl-1,3-butadiyne **25** to provide a 1,4-diphenylthiophene **26**.[12b,27] We obtained thiophene **28** in 91% yield following the reaction of 1,3-diyne **25** under the optimal

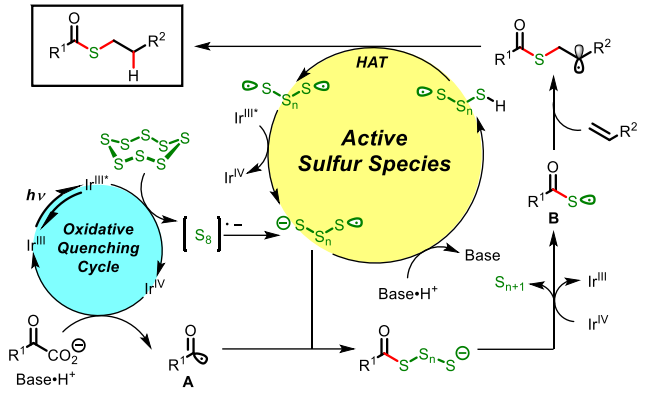


Figure 1. A plausible mechanism for the thioesterification reaction.

conditions in conjunction with the complete cessation of the thioesterification reaction and full recovery of α-ketoacid **2** (Scheme 4B, eq. 4). Moreover, we found that the use of diphenyltetrasulfide **27**[28] ($E_{1/2}$ = −0.53 V vs SCE[23]) instead of S_8 also afforded thioester **3** and a similar inhibition of the thioesterification as seen in eq. 4 was observed (eq. 5). These results indicate that the ring opening and subsequent fragmentation of the reduced S_8 occurs easily and that the fragmented sulfur species might be involved in the sulfurizing step. In addition, we confirmed the requirement for continuous irradiation with visible light by performing light on-off experiments and monitoring using React IR, and the consumption of substrate and the formation of product were observed just under photo irradiation (for details, see the Supporting Information). This result exclude the possibility that the reaction proceeds via a radical-chain pathway.

Based on the experiments described above, a plausible rection mechanism is shown in Figure 1. Under irradiation from blue LEDs, Ir^{III} catalyst **PC2** ($E_{1/2}[Ir^{III*}/Ir^{IV}]$ = −0.89 V vs SCE) is excited and, following oxidative quenching by S_8 ($E_{1/2}$ = −0.57 V vs SCE), furnishes an Ir^{IV} complex and a polysulfide radical anion. Then, the single-electron oxidation of an α-ketocarboxylate (E_{pa} = +1.12 V vs SCE) with Ir^{IV} ($E_{1/2}[Ir^{III}/Ir^{IV}]$ = +1.69 V vs SCE) affords an acyl radical via a decarboxylation with concomitant regeneration of the Ir^{III} catalyst. Acyl radical **A** couples with the polysulfide radical anion or S_8 and the resulting intermediate is converted into carbonyl thiyl radical **B**. The addition of radical **B** to the olefin and a subsequent HAT step with the hydropolysulfide species provides the desired thioester. The exact identities of the sulfur species in the reaction system are still not clear because the cleavage of an S−S bond in the polysulfide species is likely to be a facile process;[12b] this complicates the reaction system and renders the actual reactive species undetectable at present. However, the mechanistic analysis showed that the multiple roles played by S_8 are definitely crucial to the success and the utility of this transformation.

In summary, we have developed a three-component thioesterification of olefins, α-ketoacids, and S_8. Employing S_8 as a cheap and easily employed sulfur source avoids the use of unstable sulfur-containing compounds such as thiols and thioacids. Furthermore, the mild activation of S_8 via photocatalysis ensures that the reaction can tolerate a wide variety of functional groups that include unprotected alcohols and carboxylic acids. These reaction characteristics allow introducing a thioester moiety into complex molecules such as peptides and non-protected glycosides. A mechanistic analysis implied that S_8 may not only serve as a sulfur source but also act as an oxidant and a HAT mediator. The multiple roles played by sulfur in this reaction and the mechanistic details of the transformation are currently under investigation together with further applications of this strategy.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website.
Experimental procedures and analytical data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: takemoto@pharm.kyoto-u.ac.jp

ORCID

Takeshi Nanjo: 0000-0002-5679-6701
Yoshiji Takemoto: 0000-0003-1375-3821

Notes

The authors declare no competing financial interests.

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