General Electron-Donor-Acceptor Complex Mediated Thioesterification Reaction *via* site-selective C-H Functionalization using Aryl Sulfonium Salts

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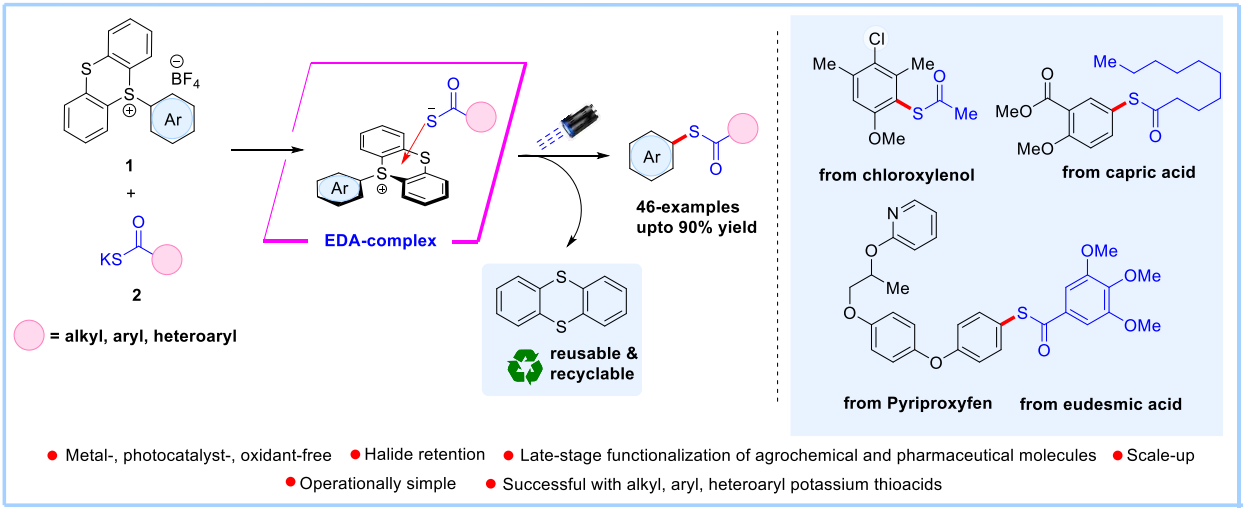
Abstract: Comtemporary methods for synthesizing thioesters often necessitate expensive catalysts, and harsh conditions, making their synthesis from chemical feedstocks challenging. Herein, we report a concise metal-, photocatalyst-, and oxidant-free electron donar-acceptor (EDA) mediated synthesis of thioesters *via* site-selective C-H functionalization using aryl sulfonium salts (acceptor) with potassium thioacid salts (donor) under visible light irradiation. Our approach enables rapid access to thioesters from a wide variety of arenes including pharmaceutical and agrochemical compounds, as well as a diverse range of alkyl, aryl and heteroaryl potassium thioacid salts with excellent efficiency and regioselectivity. Mechanistic studies supported the formation of an EDA-complex and radical trapping experiments corroborated the involvement of a radical-based mechanism for the product formation.

Keywords: Thioesterification, site-selective C-H functionalization, electron donor-acceptor (EDA) complex, aryl sulfonium salt.



Introduction: Thioesters are an essential functional group found in a wide range of complex natural products, polymers, and therapeutics.[1] They serve as high-energy intermediates in numerous biochemical processes, playing a critical role in cellular regulation and biosynthetic pathways such as metabolism, fatty acid synthesis, and the production of esters and polyketides in living organisms.[2] Due to their significant biological and pharmaceutical properties, exemplified in Fig.1a,[3] thioesters are essential intermediates in organic synthesis. Consequently, the synthesis of thioesters has attracted considerable interest, prompting the development of various strategies for their preparation.

Comtemporary methods for the synthesis of thioesters have expanded to a wide range of starting materials, including alkenes, alkynes, amines, halides, alcohols, aldehydes, and phenol derivatives. These methods often employ toxic carbon monoxide (CO) gas as a carbonyl group source, along with toxic and malodorous thiols, sulfonyl hydrazides, disulfides, or sulfonyl chlorides as S-group sources.[4] In addition, these approaches have other notable drawbacks, such as the use of expensive transition metal catalysts, harsh oxidants and high reaction temperatures. In recent years, the synthesis of thioesters have focused on developing more efficient techniques that utilize carbonyl compounds such as aldehydes, acyl chlorides, ketoacids and carboxylic acids or their activated forms with thiols, disulfides, sodium sulfinates, or elemental sulfur (S_8) to construct C-S bonds.[5] Unfortunely, these methods also invariably require expensive transition metal catalysts under harsh reaction conditions, which result in reduced yields and necessitate extensive purification of the final products.

In the past one decade, visible light photoredox catalysis has gone on to become one of the most exciting field in research among chemists, harnessing light energy for chemical transformations.[6] Given its extensive applications in organic synthesis, several light-induced thioesterication approaches have been developed.[7] For instance, Laio and co-workers (2019), demonstrated a visible light induced base-mediated deaminative thioesterification of amino-acid derived Katritzky salts (acceptor) using a single example of non-substituted thiobenzoic acid (donor), thus seriously limiting substrate scope of the method (fig.1b).[8] Additionally, the reaction produced 2,4,6-triphenylpyridine as a non-reusable by-product. Subsequently, the same group published a dual Ru/Cu-catalyzed decarboxylative thioesterification of carboxylic acid derived *N*-(acetoxy)phthalimides with again a single thiobenzoic acid as a sulfur source under visible light irradiation. [9] In addition to the limited substrate scope, the method suffered in terms of expensive transition metal catalyst. In 2022, independent research groups revealed a visible light dual 4-CzIPN/Ni-catalyzed or photo-induced dehalogenative thioesterification of aryl halides (X= -Br, -I) with potassium thioacid salts.[10] However, these methods are limited to simple aryl halides (X= -Br, -I) with a low tolerance of functional groups and has not been tested on more complex molecules, thereby restricting its substrate scope. Additionally, these methods require long reaction times and expensive photocatalyst under light, making them less favorable. Later, Zhang, Wu and co-workers in 2023, made a significant advancement in the synthesis of thioesters by developing a *tetra-n*-butylammonium decatungstate (TBADT)-catalyzed thioesterification of aldehydes with elemental sulfur (S_8) and alkenes or alkynes *via* hydrogen atom-transfer (HAT).[11] The method, however suffer from the use of toxic elemental sulfur (S_8) and expensive transition metal catalyst. In general, a metal-, photocatalyst-, oxidant-, and base-free methods can be a significant addition to thioesterification reactions. Moreover, the synthesis of thioesters *via* C-H functionalization is challenging and highly desirable, and achieving this would represent a substantial advancement in thioesterification reactions.

In this context, site-selective C-H functionalization *via* thianthrenium salt synthesis has emerged as a powerful tool in organic synthesis, enabling the introduction of various functional groups into the aromatic compound and providing streamlined and efficient pathway towards complex molecules.[12]

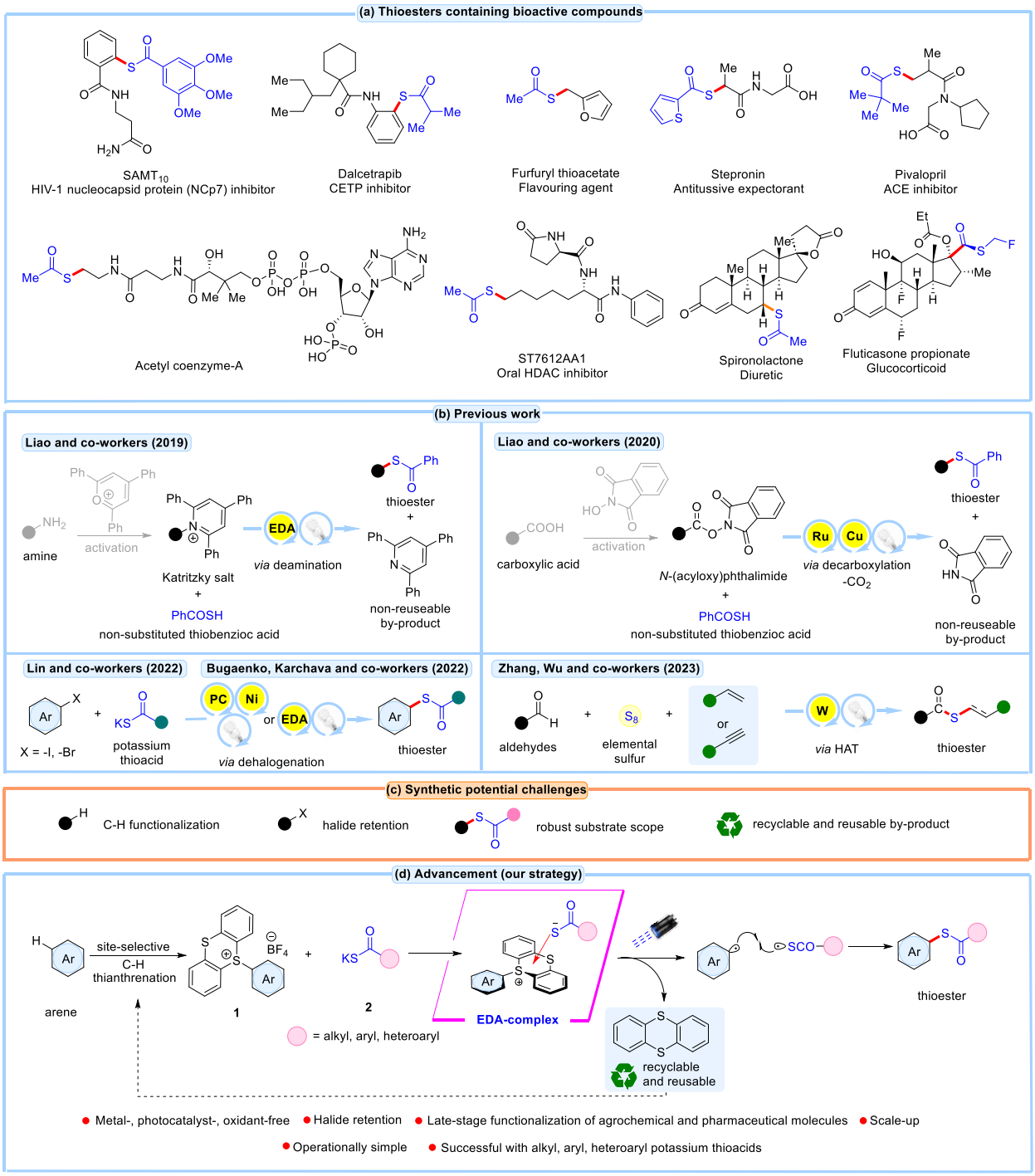
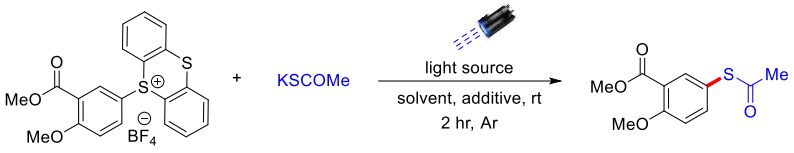


Figure 1. (a) Thioesters containing bioactive compounds; (b) previous work; (c) synthetic potential challenges; (d) advancement (our strategy).

Concurrently, EDA-complex photochemistry has garnered significant interest due to its unique capability to harness visible light to activate colorless substances, generate radical intermediates and drive subsequent reactions without the need of external catalysts.[13] In line with our ongoing research into photoinduced EDA-complex reactions,[14] herein, we present a practical method for synthesizing

thioesters. We hypothesize formation of an EDA-complex between aryl thianthrenium salts (acceptor) and potassium thioacid salts (donor) to synthesize valuable thioester products (Fig. 1d). Under visible light irradiation, potassium thioacid salt (donor) engage in a single electron transfer (SET) process with aryl thianthrenium salts (acceptor), generating an aryl radical intermediate and recyclable thianthrene. This aryl intermediate subsequently interacts with the resulting sulfur-centered radical to give the desired thioester product. By leveraging the EDA-complexes in our reaction, this method enables regioselective C–H thioesterification of arenes, a challenging feat to achieve without transition metal catalysts, aryl halides as radical precursors, and toxic, foul-smelling thiosulfur reagents. Additionally, the thianthrene by-product generated during the reaction is reusable and recyclable, offering further benefits in terms of sustainability and efficiency. Moreover, our method facilitates the coupling of complex agrochemical and pharmaceutical compounds with thioacids, offering substantial benefits to both academia research and industrial applications.

Results and Discussion



1a **2a** (2.0 equiv.) **3a**

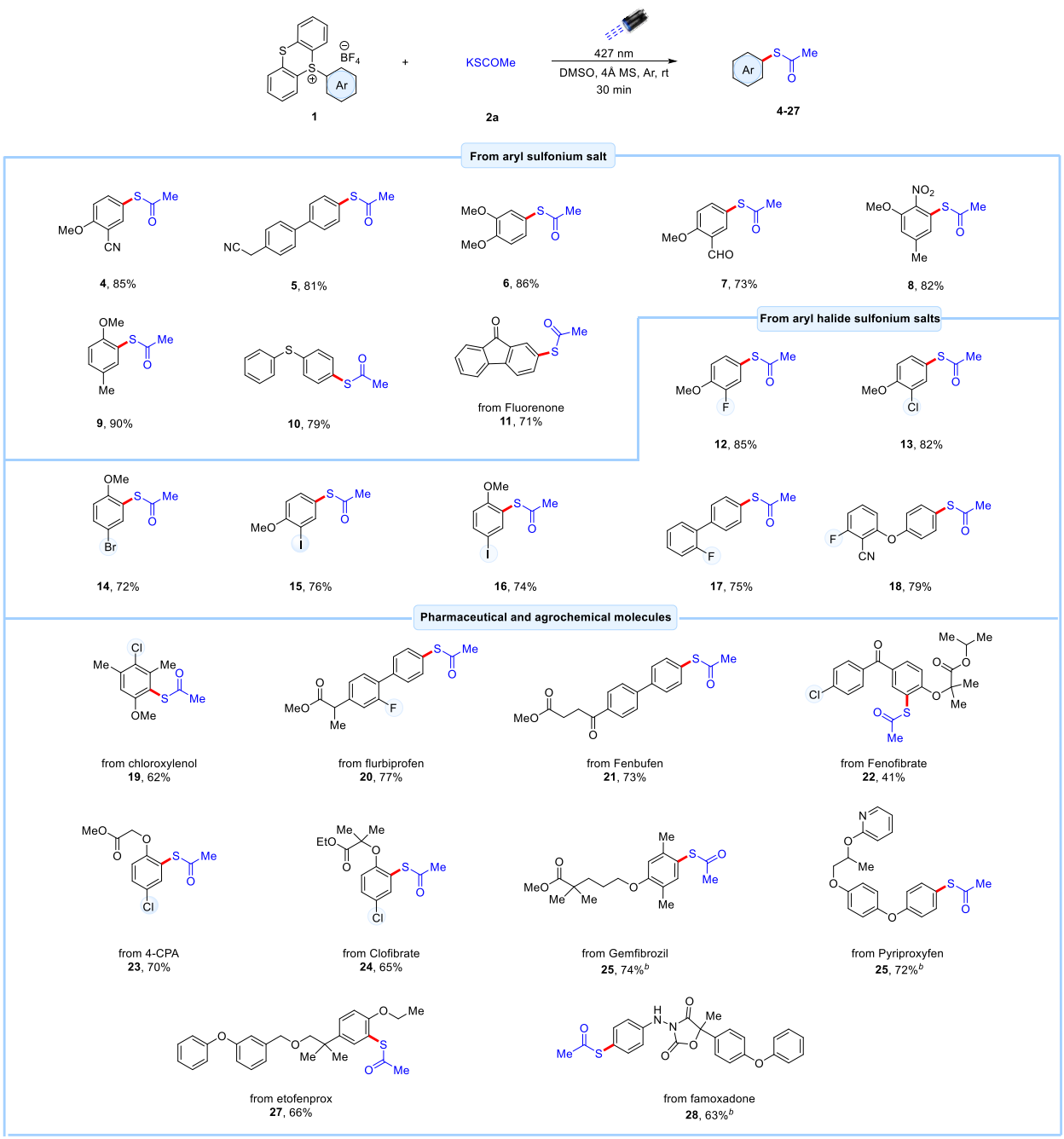
Entry	Solvent	Additive	Light (nm)	Yield (%)
1	DMSO	-	390 nm	69%
2	MeCN	-	390 nm	58%
3	DCM	-	390 nm	37%
4	THF	-	390 nm	25%
5	DMA	-	390 nm	48%
6	DMF	-	390 nm	43%
7	EtOAc	-	390 nm	54%
8	DMSO	SiO_2 (20 mg)	390 nm	72%
9	DMSO	4Å MS (20 mg)	390 nm	77%
10	DMSO	3Å MS (20 mg)	390 nm	70%
11	DMSO	Basic alumia (20 mg)	390 nm	73%
12	DMSO	K_2CO_3	390 nm	12%
13	DMSO	Na_2CO_3	390 nm	17%
14	DMSO	K_2HPO_4	390 nm	15%
15	DMSO	Cs_2CO_3	390 nm	21%
16	**DMSO**	**4Å MS**	**427 nm**	**85% (83%)[b]**
17	DMSO	4Å MS	440 nm	62%
18	DMSO	4Å MS	456 nm	50%
19	DMSO	4Å MS	dark	nr
20	DMSO	4Å MS	427 nm	72%[c]
21	DMSO	4Å MS	427 nm	83%[d]

Scheme 1. Reaction conditions: A mixture of **1a** (0.1 mmol), and **2a** (0.2 mmol, 2.0 equiv.), additive (2 equiv.), solvent (0.8 mL) under visible light irradiation (light source) for 2 h under Ar atmosphere at rt; (b) **1a** (0.3 mmol), and **2a** (0.6 mmol, 2.0 equiv.), 4Å MS (60 mg), solvent (1.5 mL); (c) open-to-air; (d) 30 min; nr = no reaction.

Our study commenced with the use of methyl-2-methoxybenzoate-derived thianthrenium tetrafluoroborate **1a** and potassium thioacetate **2a** as representative substrates in DMSO solvent under 390 nm Kessil lamp irradiation. We were delighted to observe the desired product obtained in 69% yield (entry-1). The use of DMSO efficiently solubilized the reaction components (**1a** and **2a**) resulting in a intense yellow color change in the reaction mixture, that may speculate an EDA-complex. Screening various other solvents resulted in lower yields (entry 2-7). We then investigated the effect of different additives (entry 8-15). To our delight, using 4Å MS as an additive slightly increased the yield to 77% yield (entry-9). We speculate that 4Å MS functions as an ion-trap reagent, which captures the potassium ion of thioacetate **2a**, that may result in the formation of a stable thiolate anion.[15] This can then give rise to a more efficient interaction between the electron accepter **1a** and the electron donor **2a**. Notably, the use of inorganic base such as K_2CO_3 resulted in reduced yield of the product (entry 12). Screening of other inorganic bases as additive such as Na_2CO_3, K_2HPO_4 and Cs_2CO_3 did not improve the reaction yield either (entry 13-15). We next explored the use of different light sources (entry 16-18). Remarkably, under 427 nm visible light irradiation led to an 85% yield of the required product (entry 16). No product formation was observed when the reaction was conducted in the dark, underscoring the necessity of light irradiation for the reaction (entry 19). Moreover, performing the reaction in an open-to-air condition resulted in a lower yield of 72%, indicating the importance of an inert atmosphere for optimal product formation (entry 20). Furthermore, the optimized time to 30 min resulted in no additional change in yield (entry 21).

Substrate scope

With the optimized reaction conditions established, various aromatic feedstock substrates were subjected to the C–H thioesterification using potassium thioacetate **2a** as the coupling partner in the photochemical reaction. Aryl thianthrenium salts bearing electron-donating as well as electron withdrawing substituent such as cyano-, trifluoromethyl-, nitro-, methoxy-, and methyl groups, reacted well under the optimized conditions, yielding the desired thioester products **4**–**9** in 73-90% yields (Scheme **2**). Additionally, diphenyl sulfide derived thianthrenium salt reacted efficiently under this protocol, producing the thioacetate product **10** in 79% yield. The bioactive fluorenone-derived thioacetate **11** was also obtained in 71% yield. The retention of halides is problematic under reported transition metal and light-induced reactions. To evaluate the compatibility of this method, a series of aryl halide derived thianthrenium salts were subjected to the EDA-protocol. Pleasingly, the protocol effectively retained the halide groups to give the corresponding thioester products **12**-**18**. Notably, aryl thianthrenium salts with fluoro-, and chloro-group reacted exceptionally well (**12**-**13**), which slightly gave higher yields than their bromo- and iodo-substituted counter-parts (**14**-**16**). Additionally, *meta*-substituted aryl iodo-substituted thianthrenium salts reacted smoothly under this method, achieving a yield of 74% (**16**). This protocol was also extended to diaryl-fluoro-substituted thianthrenium salts, resulting in the isolation of their corresponding thioester products **17** and **18** in good yields (75 and 79% yield respectively).

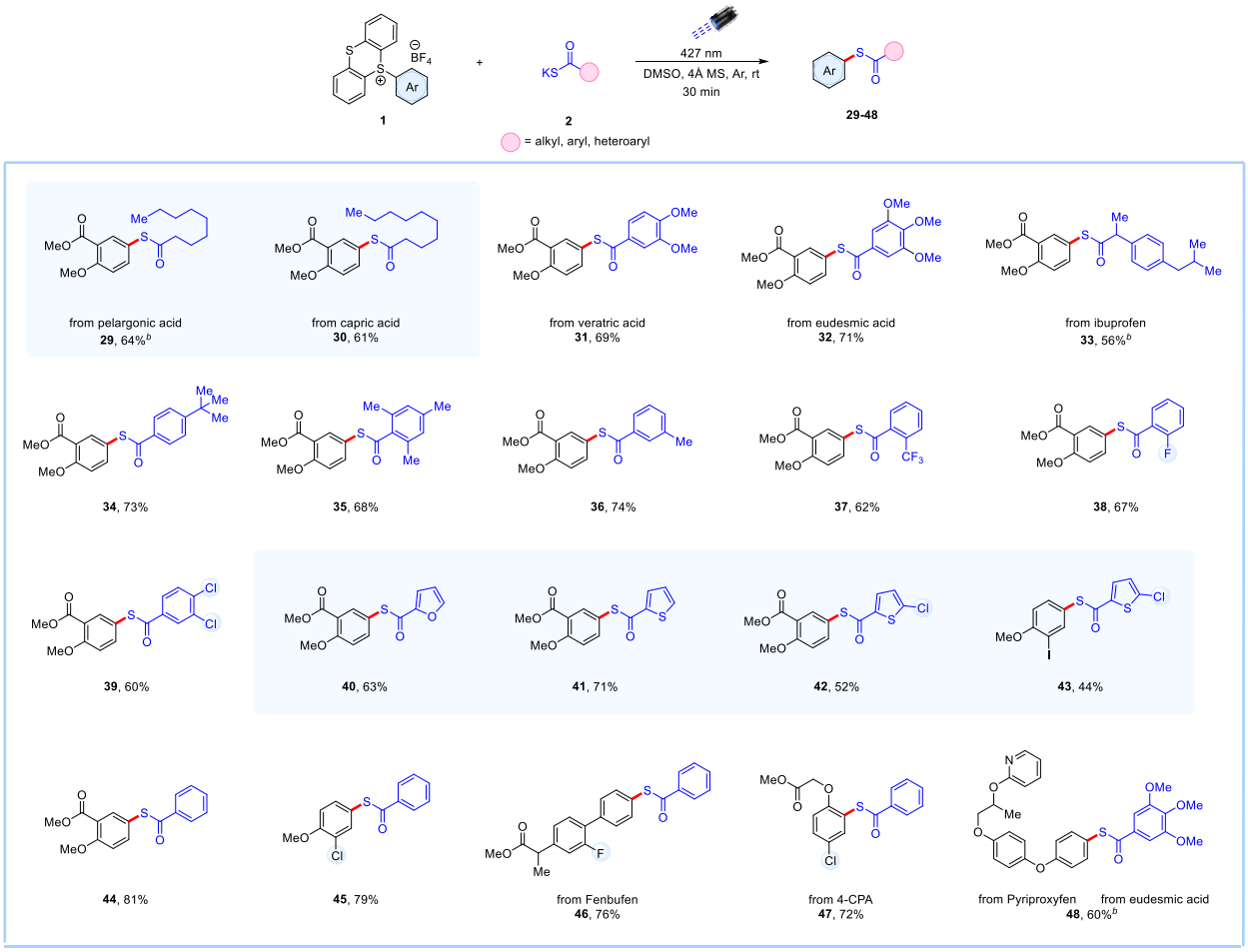


Scheme 2. [a]Reaction conditions: aryl sulfonium salt **1** (0.3 mmol), potassium thioacetate **2a** (2 equiv., 0.6 mmol), 4Å MS (60 mg), in 1.5 mL DMSO, were irradiated with 427 nm Kessil Lamp (40W) at room temperature under argon for 30 min. [b] 2 h.

Thioesterification of pharmaceutical and agrochemical molecules

With the excellent site-selectivity achieved though the synthesis of thianthrenium salts,[12a] combined with the effectiveness of our EDA-complex protocol, makes this method a powerful tool for executing precise late-stage thioesterification of complexed agrochemical and pharmaceutical compounds, as illustrated in the Scheme **2**. The thioesterification of thianthrenium salt derived from the polysubstituted antiseptic and disinfectant agent chloroxylenol proceeded smoothly, yielding the desired thioacetate

product **19** in 62% yield. Moreover, aryl ester bearing thianthrenium salts derived from the anti-inflammatory drugs flurbiprofen and fenbufen underwent successful thioesterification using this protocol, yielding the desired products **20** and **21** in 77% and 73% yield, respectively. Next, a series of aryl ether-substituted agrochemical and pharmaceutical-derived thianthrenium salts were subjected to the optimized conditions. These included thianthrenium salts derived from the hypertriglyceridemia drugs fenofibrate and gemfibrozil, the plant growth regulator *p*-chlorophenoxyacetic acid (4-CPA), antilipidemic drug clofibrate, the insecticidal agents pyriproxyfen, and etofenprox, as well as the amide, ester and ether-bearing fungicidal agent famoxadone. These reactions were well tolerated, affording the corresponding thioester products as single regioisomers in satisfactory to good yields (**22**-**28**). Notably, the hypertriglyceridemia drug fenofibrate **28**, which contains a highly bulky ether group on the corresponding carbon, resulted in a lower yield of 41%, likely due to steric hindrance. In general, the protocol exhibited excellent compatibility with numerous functional groups, including halides (F, and Cl), esters, ethers, amides and heteroarenes.



Scheme 3. [a]Reaction conditions: aryl sulfonium salt **1** (0.3 mmol), potassium thioacid salt **2** (2 equiv., 0.6 mmol), 4Å MS (60 mg), in 1.5 mL DMSO, were irradiated with 427 nm Kessil Lamp (40W) at room temperature under argon for 30 min. [b] 2 h.

Application with different potassium thioacid salts.

To further diversify our EDA-complex strategy, we employed various potassium thioacid salts with alkyl, aryl and heteroaryl functionalities with the aryl thianthrenium salt. We were delighted to find that various potassium thioacid salts reacted smoothly with the aryl thianthrenium salts to yield the corresponding thioester products in moderate to good yields, as illustrated in the Scheme **3**.

Potassium thioacid salts derived from naturally occurring long chain saturated fatty acids such as pelargonic and capric acid, performed well under the established conditions, yielding the corresponding thioester products **29** and **30** with 64% and 61% yield, respectively. Additionally, potassium thioacid salts derived from the antiproliferative agent veratric acid and antioxidant agent eudesmic acid proved to be efficient electron donors in this photochemical strategy, producing the desired thioester products **31** and **32** in 69% and 71% yield, respectively. The potassium thioacid derived from anti-inflammatory drug ibuprofen was also found compatible under this protocol, yielding the thioester product **33** in 56% yield. Aryl potassium thioacid salts bearing alkyl groups were found to be suitable coupling partners with aryl thianthrenium salts, yielding the corresponding thioester products **34**-**36** in yields ranging from 68-74% yield. Furthermore, aryl potassium thioacids bearing trifluoromethyl- and fluoro-, and dichloro-groups were also well tolerated, yielding the required thioester product **37**, **38**, and **39** with yields of 62%, 67%, and 60% yield, respectively. Additionally, potassium thioacids derived from various O-, and S-heterocycles were also effective in this photochemical process, yielding the desired thioester products **40**-**43** in satisfactory to good yields. Moreover, non-substituted potassium benzothioate proved to be a suitable coupling partner under this protocol, efficiently reacting with different aryl thianthrenium salts to produce the required thioester products **44**-**47** in good yields. Lastly, the compatibility of this method was demonstrated in the thioesterification of the insecticidal agent pyriproxyfen with eudesmic acid derived potassium thioacid salt, affording the required thioester product **48** in 60% yield.

Mechanistic insights

Next, a series of mechanistic studies were conducted to elucidate the reaction mechanism as illustrated in Fig. **2**. The UV/Vis-absorption analysis of individual components and the reaction mixture (**1a + 2a**) in DMSO is shown in Fig. **2a**. The DMSO solutions of methyl-2-methoxybenzoate-derived thianthrenium salt **1a** (red line), and potassium thioacetate **2a** (green line) displayed a small absorption band in the visible light region (> 400 nm). Moreover, a clear bathochromic shift was observed (blue band) of the reaction mixture (**1a + 2a**) in DMSO, which was clearly visible by the intense yellow color of the reaction mixture as shown in Fig **2a**. This clearly indicates the formation of an electron donor-acceptor (EDA) aggregate (blue band). Additionally, a Job's plot using UV-visible absorption experiments was performed to determine the stoichiometry of the EDA-complex between **1a** and **2a**. The maximum absorption of the reaction mixture [**1a** + **2a**] at a 50% molar fraction indicated a 1:1 ratio of **1a** and **2a** (Fig. **2b**). Moreover, ^{1}H-NMR titrations were conducted to provide further evidence of an EDA-complex formation in DMSO-d_6 (Fig. **2c**). The ^{1}H-NMR signal of C1-H proton in methyl-2-methoxybenzoate-derived thianthrenium salt **1a**, shifted downfield along with increasing amount of potassium thioacetate **2a**,

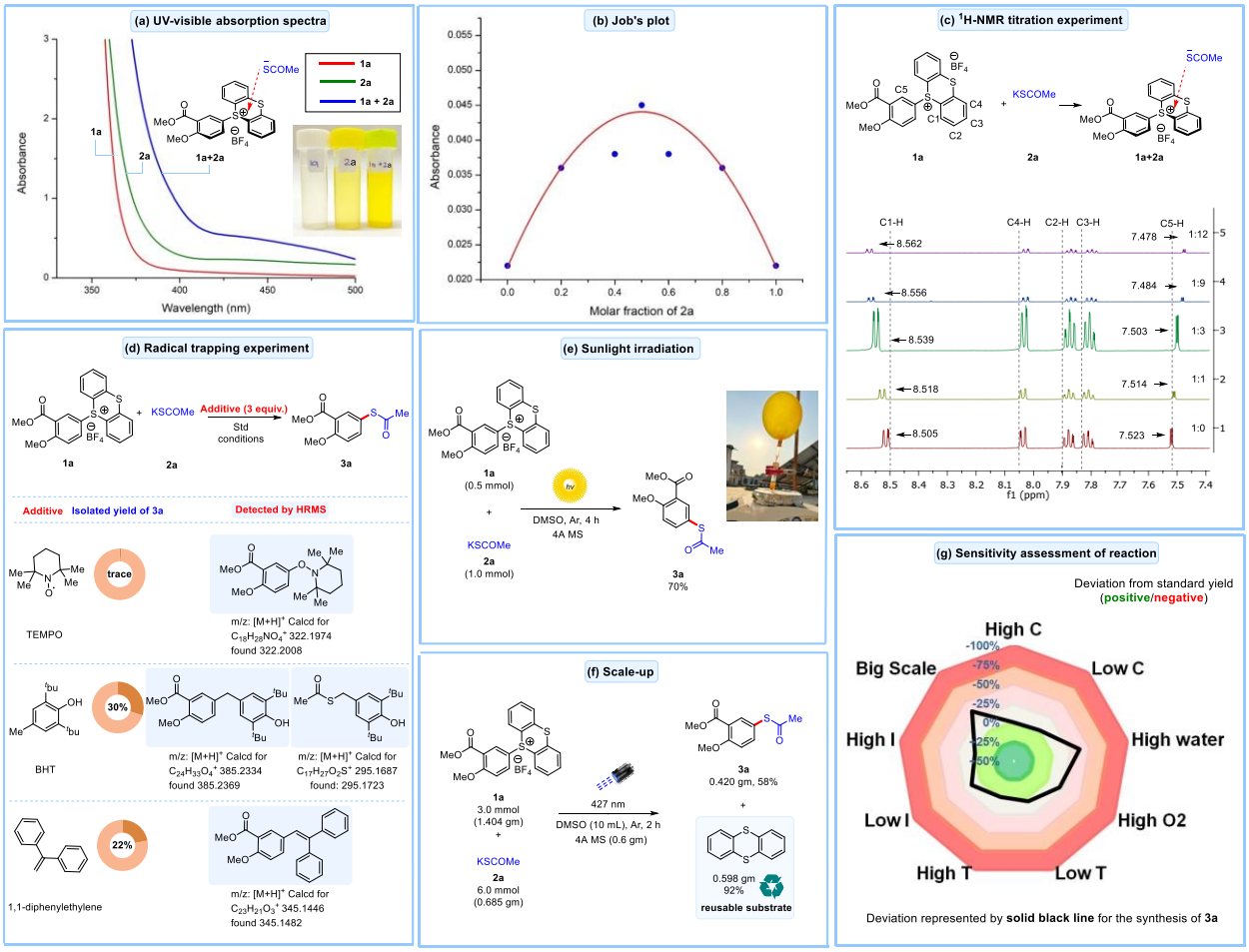
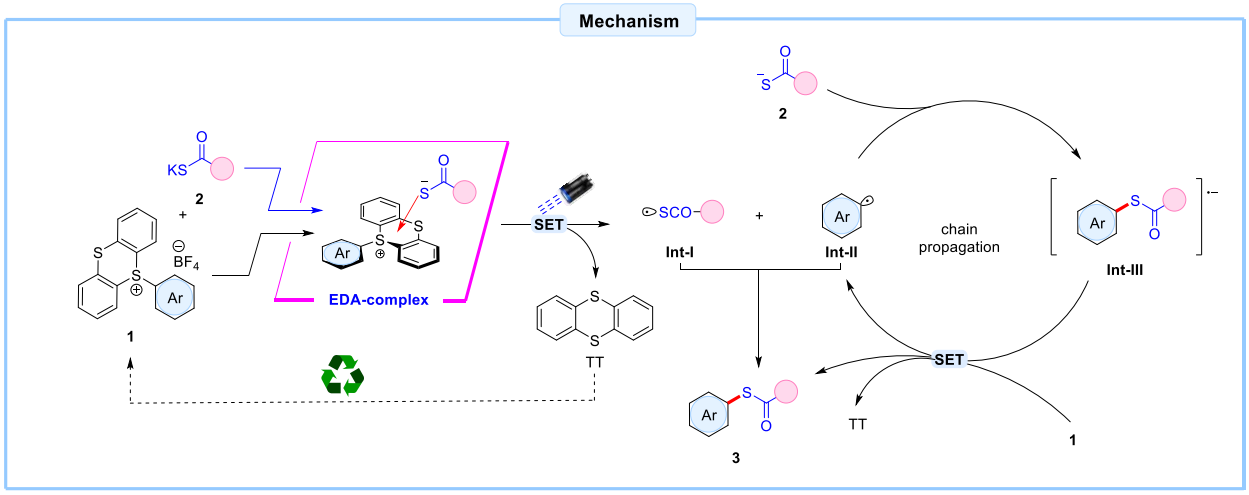


Figure 2. (a) UV-visible absorption spectra; (b) Job's plot; (c) ^{1}H-NMR titration experiment; (d) radical trap experiment; (e) sunlight irradiation; (f) scale-up; (g) sensitivity assessment of reaction.

while C4-H, C3-H, C2-H and C5-H proton shifted upfield, thus indicating the formation of EDA-complex of between **1a** with **2a**.[16] Under standard conditions, the photochemical reaction was subjected to a radical trap experiment with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), butylated hydroxytoluene (BHT) and 1,1-diphenylethylene (Fig. **2d**). The reactions were quenched, and the radical trapped adducts was analyzed and detected by high-resolution mass spectrometry (HRMS). These results support the generation of an aryl radical as well as thiyl radical intermediated in the photochemical transformation, likely initiated by the photoactive EDA-complex between methyl-2-methoxybenzoate-derived thianthrenium salt **1a** and potassium thioacetate **2a**. Additionally, quantum yield experiment was performed to determine a possible reaction pathway for this transformation. The quantum yield was measured to be Φ = 44, which indicates a radical chain pathway (See ESI†). Furthermore, the reaction also proceeded successfully under natural sun light irradiation, yielding the targeted product **3a** in 70% yield (Fig. **2e**). A gram-scale synthesis was conducted using methyl-2-methoxybenzoate-derived thianthrenium salt **1a** (1.404 g, 3 mmol) and potassium thioacetate **2a** (0.685 g, 6.0 mmol, 2 equiv.) (Fig. **2f**). The reaction was carried out under visible light irradiation for 2 h, yielding the desired product **3** in 58% yield (0.420 g). Moreover, 0.598 gm (92% yield) of thianthrene was also recovered *via* chromatographic separation. Next, the efficiency for our reaction protocol for the synthesis of **3a** was

investigated under various sensitivity assessment parameters.[17] This EDA-complex transformation was found to be sensitive to water, oxygen concentration and low light intensity (Fig. **2g**). However, the protocol showed good tolerance towards variations in substrate concentration, temperature, and high light intensity. Moreover, the Ecoscale of our method was evaluated[18] and was determined to be 70.5, which is acceptable synthesis in terms of sustainability.



Scheme 3. Plausible reaction mechanism

Based on the experimental observations, a plausible mechanism for this EDA-complex mediated thioesterification reaction is depicted in Scheme **3**. Initially, an EDA-complex aggregate is formed between **1** and potassium thioester salt **2**. Under visible light irradiation, this EDA complex undergoes a single-electron transfer (SET) event from thiolate anion to the aryl thianthrenium salt **1**, generating thiyl radical intermediate **Int-I**, aryl radical intermediate **Int-II**, and recyclable thianthrene by-product. The generated thiyl radical intermediate **Int-I** and aryl radical intermediate **Int-II**, can undergo subsequent radical-radical coupling, leading to the formation of the desired product **3**. Moreover, the aryl radical intermediate **Int-II** interacts with thiolate anion **2** to gives **Int-III**. This intermediate **Int-III** undergoes SET with **1** to give the desired product **3**, thianthrene by-product and **Int-II**, which propagates the chain again.

Conclusion: In summary, we have developed an EDA-complex mediated thioesterification reaction *via* site-selective C-H functionalization using thianthrenium salts. This protocol is compatible with a wide range of aromatic feedstock, as well as a diverse range of alkyl, aryl and heteroaryl potassium thioacid acid yielding the desired thioester products in good yields. Additionally, we demonstrated versatility of the method through late-stage thioesterification of agrochemical and pharmaceutical compounds. Our method offers several key advantages over previously known methods, including (i) C-H functionalization; (II) halide retention; (III) compatibity with alkyl, aryl and heteroaryl potassium thioacid salts; and (IV) reusuable and recyclable by-products. Furthermore, our method is favorable in terms of safety, economical, and ecological consideration, making it a practical solution for both academic research and industrial applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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