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Fe-catalyzed dithiane radical induced C–S bond activation–addition to α, β-unsaturated ketones

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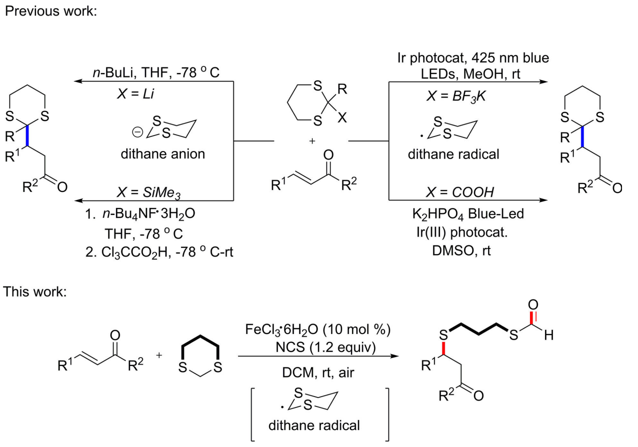
Abstract: An efficient and clean strategy to construct organosulfur compounds has been developed via a Fe-catalyzed dithiane C–S bond activation/addition process with α, β-unsaturated ketones. This C–S activation protocol exhibits excellent reactivities, and up to 92% yield of the corresponding thioether-thioester derivatives could be obtained under the mild conditions, allowing the ready preparation of a number of synthetically valuable S-linked conjugates.

Keywords: Dithiane; Organosulfur Compounds; C–S Addition; Conjugates; Iron

Organosulfur compounds such as thioethers, thioesters, and their derivatives are widely present in a variety of biologically active molecules and play important roles in areas of bioconjugate chemistry, polymer science, and pharmaceutical chemistry.[1] Organosulfur compounds also serve as useful synthetic intermediates with applications in organic and medicinal chemistry.[2] Generally, reliable protocols to access the organosulfur compounds include thiol-Michael additions and thiol-ene reactions of diverse alkenes with free thiols.[3,4] These are mechanistically distinct transformations that have been widely recognized as powerful methods for the generation of a wide variety of organosulfur compounds. However, these available processes use highly volatile and stinky free thiols, leading to serious environmental, safety problems as well as the issues of the side reactions owing to the oxidation of free thiols. In addition, common thiol-addition methodologies require harsh conditions and the use of rare, expensive, and toxic metal-photocatalysis. In order to minimize the encountered problems, the development of an environmental, efficient and concise protocol that enables the conversion of suitable coupling partners to the thioethers or/and thioesters would be worthwhile.[5]

Dithianes, introduced by Corey and Seebach are attractive building blocks for construction of C–C bonds in organic synthesis (Scheme 1).[6] Extensive research in the unique umpolung field have resulted in the development of nucleophilic addition of α, β-unsaturated alkenes through the anionation of dithiane as an acyl anionic synthon.[7] In 2014, Denmark group developed a novel addition of dithiane derivatives to unactivited α, β-unsaturated ketones and esters using a fluorodesilylation strategy via a dithianyl anion process.[8] Next year, Gaggero reported an efficient organocatalytic conjugate addition of 2-carboxythioesters-1,3-dithiane to nitroalkenes.[9] While these transformations are important, radical processes of 1,3-dithianes to alkenes can offer a feasible alternative to anionic reactions that can lead to similar products.[10] Among these, there are several reports on the radical atom transfer additions of alkenes with dithianyl radicals through the use of radical initiator groups such as phenylseleno,[10b] xanthates,[10c] and



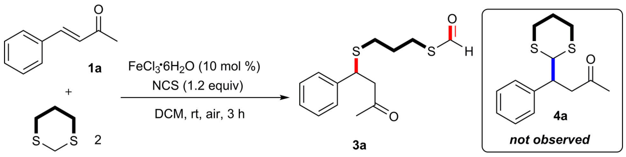
Scheme 1. Development of coupling reactions of dithianes.

TEMPO[10d]. More recently, Leow and co-workers reported a visible-light photocatalytic addition of 1,3-benzodithianes to several Michael acceptors.[10e] Additionally, Koike and Akita reported the reaction of potassium 1,3-dithian-2-yltrifuoroborate with terminal olefins bearing electron withdrawing groups.[10f] In 2017, Cozzi and Sambri have developed an effective photocatalytic addition of dithiane-2-carboxylates to Michael acceptors by Iridium (III) photocatalyst.[10g]

Over the past years, our group has a long-standing interest in the radical oxidative coupling reactions from the use of commercially available dithiane.[11] We recently developed a radical oxidative coupling reaction of aryl alkenes with 2-chloro-dithiane for the construction of complex dithiane derivatives by in situ generation of dithianyl radical. As part of an ongoing project on the development of new transformation of dithiane, we examined the reaction of α, β-unsaturated ketones with 1,3-dithiane via the corresponding radical oxidative process. Interestingly, the iron catalyzed dithiane radical route with α, β-unsaturated ketones was unique in comparison with the results of traditional cross-coupling addition reactions of α, β-unsaturated alkenes via a dithianyl radical process. Herein, we report the first example of the direct synthesis of thioether-thioformates via a C–S bond activation of 1,3-dithiane and an addition to α, β-unsaturated ketones by an inexpensive iron catalyst.

Accordingly, we began our study by evaluating the coupling of enone **1a** with 1,3-dithiane **2** (Table 1). Previously, $FeCl_3$ has been successfully proved to be optimal in these dithianyl radical oxidative coupling reactions; thus, it was utilized in this system.[11a] Surprisingly, there was no dithianyl cross-coupling product observed under this typical conditions (Table 1, entry 2). In particular, we found that by increasing the reaction time and by exposing the reaction mixture to air, a modest yield of thioether-thioformate coupled product **3a** could be isolated. In contrast, the expected cross-coupling product **4a** was not observed. To the best of our knowledge, the process of the direct formation of thioether and thioester simultaneously has not yet been reported. The significance of this result from the viewpoint of conjugate chemistry, as well as sulfur chemistry, prompted us to carry out further study. As expected, the inclusion of water in the reaction mixture improved the yields.[3a,d,4g] An examination of different iron sources was carried out. Gratifyingly, the use of easily available catalyst $FeCl_3 \cdot 6H_2O$ gave the best result. The reaction proceeded to completion in just over 3 h at room temperature in the presence of 10 mol % $FeCl_3 \cdot 6H_2O$, and the product **3a** was obtained in 89% yield. Interestingly, the addition of base or the use of NBS as a promoter did not significantly improve the coupling process. Reactions employing Lewis acid $BF_3 \cdot Et_2O$ that had previously been used provided unsatisfactory yields of the desired product.[11b] The use of a solvent such as DCE[11a–c] was found to be critical in obtaining high yields. As compared with photocatalyzed dithianyl radical coupling chemistry[10e–g], the formation of thioether-thioester molecule in this type of oxidative radical reaction is highly unusual.

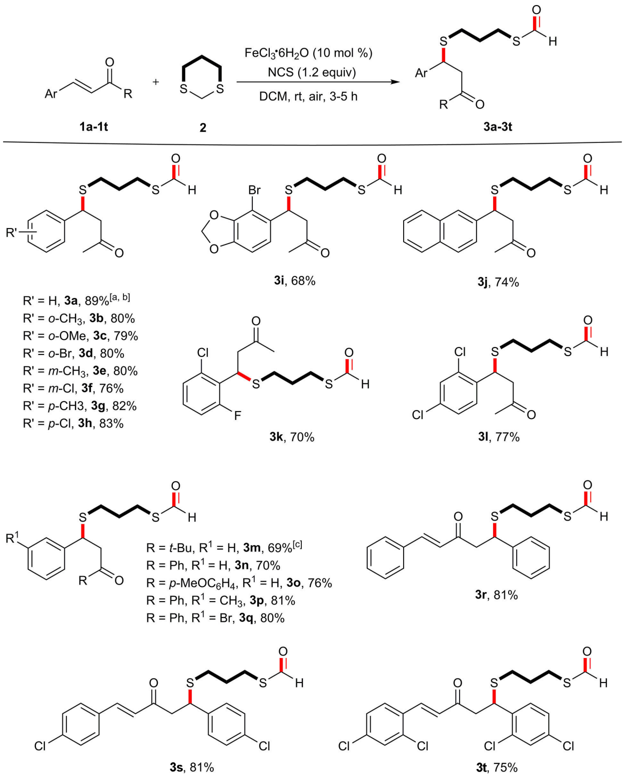
Table 1. Optimization of addition of enone **1a** with dithiane.[a]



Entry	Variation	Yield (%)[b]
1	none	89
2	$FeCl_3$ (10 mol%), under Ar, 12 h	trace
3	$FeCl_3$ (10 mol%), 24 h	78
4	$Fe(acac)_3$ (10 mol%), 12 h	62
5	FeS (10 mol%), 24 h	45
6	$FeSO_4$ (10 mol%), 24 h	33
7	$FeSO_4 \cdot 7H_2O$ (10 mol%), 12 h	52
8	$FeCl_2 \cdot 4H_2O$ (10 mol%)	70
9	$BF_3 \cdot Et_2O$ (10 mol%), 24 h	trace
10	DTBP[c] (200 mol%), 24 h	30
11	NBS instead of NCS, 24 h	-[d]
12	DCE instead of DCM	81
13	THF instead of DCM, 12 h	trace

[a] Reaction condition: **2** (30 mg, 0.25 mmol), NCS (40 mg, 0.30 mmol), **1a** (30 mg, 0.21 mmol), $FeCl_3 \cdot 6H_2O$ (7 mg, 0.025 mmol), DCM (2 mL), room temperature.
[b] Isolated yield.
[c] DTBP = di-*tert*-butyl peroxide.
[d] Not detected.

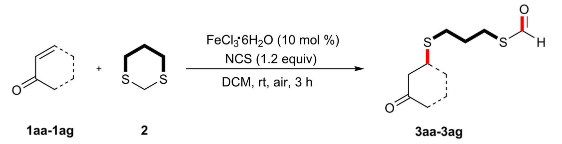
With the optimized protocol in hand, we then explored the substrate scopes with respect to the aryl enone component with 1,3-dithiane **2** to provide a range of thioether-thioester derivatives (Scheme 2). Consequently, this transformation tolerates a variety of substituents on the aryl ring of enones. Aryl enones containing both electron-withdrawing groups (F, Cl and Br) and electron-donating groups (Me and OMe) on the aromatic rings were all found suitable for this reaction. Substrates with ortho (**1b–1d**), meta (**1e** and **1f**), and para (**1g** and **1h**) substituents were tolerated with comparable efficiencies. Chalcone and the corresponding chalcone derivatives were also viable substrates for this reaction (**1n–1q**). Increasing the bulkiness of R of aryl enones resulted in comparable yields. Good yields (68–89%) and the corresponding coupled type products were observed within 3–5 hours in all cases. These thioester-thioether derivatives could be challenging to access via the existing C–S bond methodologies.

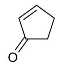
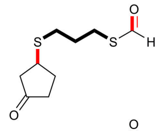
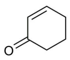
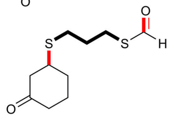
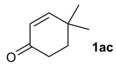
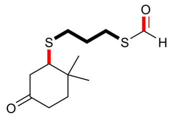
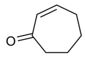
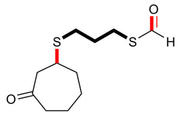
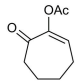
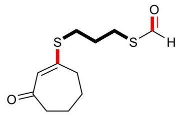
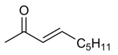
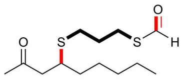
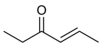
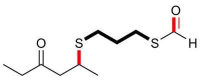


Scheme 2. Scope of aryl enones. [a] Unless otherwise specified **2** (30 mg, 0.25 mmol), NCS (40 mg, 0.30 mmol), **1** (0.21 mmol), $FeCl_3·6H_2O$ (7 mg, 0.025 mmol) in DCM (2 mL) was stirred for 3–5 h at room temperature under air. [b] Isolated yield. [c] 0.3 mmol of alkene was used.

The substrate scope of the alkyl enones was briefly examined under standard reaction conditions as shown in Table 2. Not surprisingly, cyclic enones could be effectively coupled with 1,3-dithiane under the same conditions. Excellent yields (78–92%) were obtained for additions to a variety of cyclic enones, including five- and seven-membered rings (**1aa** and **1ad**, respectively). In fact, these coupling reactions proceeded with lower quantities of catalyst (5 mol%) in shorter reaction times, were still providing the desired products in comparable yields. Sterically encumbered enone (**1ac**) was also viable substrates. Particularly noteworthy is the reaction of the derivative of cycloheptyl enone, which proceed to afford product **3ae** as single product in 83% yield. Interestingly, alkyl substituents of enones (**1af** and **1ag**) had no significant impact on its reactivity. The above procedure proved to be general for the synthesis of organosulfur compounds bearing a 1,3-bithiopropanyl linkage that would provide a useful complement to the common S-linked conjugates.

Table 2. Substrate scope of simple alkyl enones.[a]



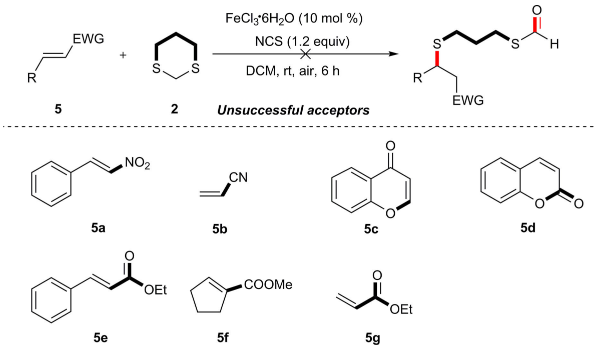
Entry	Substrate		Product		Yield (%)[b]
1		1aa		3aa	81(80)[c]
2		1ab		3ab	92(86)
3		1ac		3ac	78
4		1ad		3ad	81
5		1ae		3ae	83
6		1af		3af	84
7		1ag		3ag	85

[a] Reaction conditions: **2** (30 mg, 0.25 mmol), NCS (40 mg, 0.30 mmol), **1** (0.21 mmol), $FeCl_3·6H_2O$ (7 mg, 0.025 mmol) in DCM (2 mL) at room temperature under air, 3 h.

[b] Isolated yield.

[c] 5 mol % of catalyst was used, 1 h.

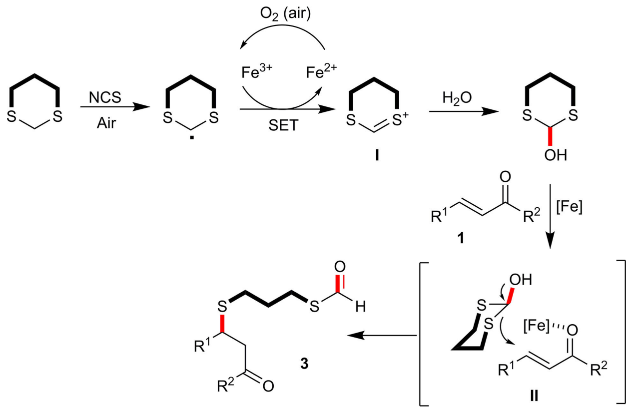
In the interest of expanding the reaction scope, we focused on the other electron-deficient alkenes as substrates. Unexpectedly, a variety of α, β-unsaturated Michael acceptors did not participate successfully under the optimized reaction conditions (Scheme 3). In these cases, α, β-unsaturated esters (**5e**–**5g**) remain challenging substrates for this methodology, which is most likely due to differences in the relative coordination of α, β-unsaturated esters and enones with dithianyl and iron species. It was noted that attempts to extend this method to 2-substituted dithiane substrates met with difficulty under the current reaction conditions.



Scheme 3. Unsuccessful α, β-unsaturated acceptors.

In order to aid interpretation of the mechanism process, radical trapping experiments and oxygen-labeling experiments were performed.[12]The addition of TEMPO as a radical scavenger quenched the addition reaction, demonstrating that a dithiane radical process might take place under the iron catalyzed reaction conditions. Meanwhile, the ^{18}O-labeled product was formed in the presence of $H_2{}^{18}O$, suggesting that water was involved in the thioformates formation.

On the basis of previous studies in radical oxidative couplings[11] and above experimental results, a plausible mechanism for this process is depicted in Scheme 4. Firstly, the dithianyl radical is generated via the activation of 2-H-dithiane with NCS under air atmosphere.[11b] The generated dithiane radical undergoes a single-electron transfer (SET) with Fe (III) catalyst to facilitate ionization for the formation of ionic species **I**, which then reacts with water originated from $FeCl_3{\cdot}6H_2O$ or air, affording the corresponding 2-OH-dithiane. Meanwhile, iron catalyst also acts as a Lewis acid to facilitate the coordination process with the carbonyl group of α, β-unsaturated ketone **1**.[11c] Subsequently, the dithianyl ring opening and conjugate addition would take place to furnish the thioether-thioformate products via a dithianyl C–S bond activation/addition process. At present, our results suggest that a coordination transition state **II** formed predominately under the reaction conditions.[13] This mechanism is not similar to that of the previous photocatalyzed addition reaction processes.



Scheme 4. Plausible mechanism.

In conclusion, we have developed a protocol for the preparation of organosulfur compounds via a tandem process involving an iron-catalyzed C–S bond activation of dithiane followed by an addition to α, β-unsaturated ketones. This operationally simple method uses a readily available iron catalyst in an efficient manner, particularly the absence of thiols, to access an array of valuable thiolether-thioester compounds in excellent yields and with short reaction times. Importantly, the C–S bond activation method provides a general complementary for the efficient and safe generation of a range of novel organosulfur conjugates. Further investigations into the asymmetric version of dithiane induced activation, as well as the application in biological conjugates area are ongoing in our laboratory.

Experimental Section

General procedure for compound 3: To a flame-dried 10 mL flask 1,3-dithiane **2** (30 mg, 0.25 mmol) and NCS (40 mg, 0.30 mmol), DCM (2 mL) after dissolved the mixture was stirred at 0 °C, then **1** (0.21 mmol) and $FeCl_3{\cdot}6H_2O$ (7 mg) were added at room temperature. Reaction mixture was stirred at room temperature for 3–5 h until the reaction was completed (as determined by TLC analysis). Then reaction mixture was diluted with ethyl acetate (10 mL) and H_2O (5 mL). The organic layer was separated, and the aqueous phase was re-extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with H_2O (10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and then the residue was purified by column chromatography on silica gel with petroleum/ethyl acetate (EA/PE = 1: 50 ~ 1:5) to yield the product **3**.

Acknowledgements

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Fe-catalyzed dithiane radical induced C–S bond activation–addition to α, β-unsaturated ketones

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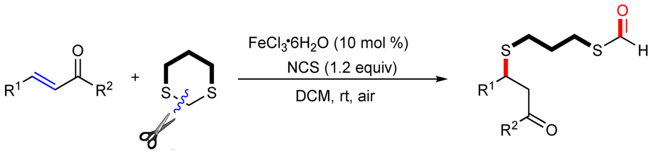

Dithane C-S activation/addition process
27 examples, up to 92% yield
Mild reaction conditions