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Iodine-Catalyzed Intramolecular Oxidative Thiolation of Vinylic Carbon-Hydrogen Bonds *via* Tandem Iodocyclization and Dehydroiodination: Construction of 2-Methylene-3-thiophenones

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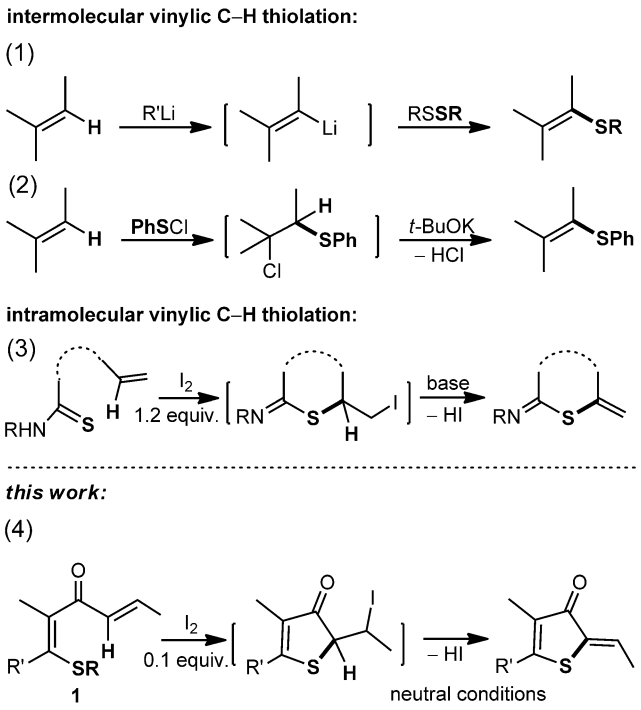
Abstract: A metal-free vinylic carbon-hydrogen bond thiolation has been developed. Under the catalysis of iodine (10 mol%), the cyclization of α-alkenoyl ketene dithioacetals afforded a broad range of polyfunctionalized 2-methylene-3-thiophenones in good selectivity with moderate to excellent yields *via* tandem iodocyclization and dehydroiodination. The synthetic strategy can also be extended to the cyclization of *ortho*-methylthiophenyl vinyl ketones leading to 2-methylene-3-benzothiophenones.

Keywords: carbon-sulfur bond formation; heterocycles; iodine; selectivity; synthetic methods

C–S bond formation[1] presents a key step for the synthesis of numerous structurally interesting and biologically active compounds.[2] The thiol-based transformations, including thiol-aryl/vinyl halides cross-coupling[1,3] and hydrothiolation of alkynes,[1,4] have become two main methods for the construction of sp^2C–S bond. Over the past few decades, transition metal-catalyzed C–H functionalization has fascinated organic chemists.[5] Accordingly, significant progress has been achieved in inter- and intramolecular sp^2C–S cross-coupling based on the C–H bond. In this field, many transition metals, such as Cu,[6] Pd[7] and Fe,[8] have proved to be efficient catalysts for aromatic C–S bond oxidative coupling. Recently, a metal-free thiolation of aromatic heterocycles with diaryl disulfides was also developed[9] with the advantages of safety and no risk of deactivation of the metal catalyst by S-containing substrates. In contrast, the vinylic C–H thiolation has been seldom investigated and often lacks generality although it is anticipated to be a process of synthetic potential for sp^2C–S bond formation.

Among the limited methods for vinylic C–H thiolation, deprotonation of sp^2C–H bonds by a strong base or metalating agent followed by quenching with S-containing electrophiles could directly afford olefinic C–S cross-coupling products [Scheme 1, Eq. (1)].[10] Tandem addition of PhSCl to olefins and elimination of HCl in the presence of *t*-BuOK also provided olefinic C–H thiolated products [Scheme 1, Eq. (2)].[11] The intramolecular version alternatively involved the iodocyclization and sequential dehydroiodination of unsaturated thioamides/thioesters under basic conditions [Scheme 1, Eq. (3)].[12] However, stoichiometric iodine and basic additives were required for efficient conversions of the substrates in these processes.[12] It is true that a catalytic method for vinylic C–H thiolation still challenges this field. Herein, we are pleased



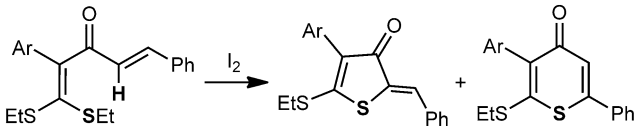
Scheme 1. Inter- and intramolecular vinylic C–H thiolations.

to disclose a new I_2-catalyzed intramolecular sp^2C–H thiolation of olefins tethered with an alkylthio group under neutral conditions leading to 2-methylene-3-thiophenones in good regioselectivity [Scheme 1, Eq. (4)].

The present work arose from our interest in seeking new cyclization strategies based on α-alkenoyl ketene dithioacetals **1** [Scheme 1, Eq. (4), R′ = SR][13] for the construction of various functionalized cyclic compounds.[14] Recently, electrophilic cyclization of heteroatom nucleophiles with alkenes/alkynes has become an extremely active and original field of heterocycle synthesis.[15] On the basis of the structural nature of compounds **1**, a kind of olefinic substrate bearing a suitably placed sulfur-based nucleophilic group, we envisioned an I_2-mediated electrophilic cyclization of **1** providing a straightforward access to useful S-heterocycles. Fortunately and interestingly, the cyclization was successfully achieved along with some attractive new chemistry: (i) the formation of the sp^2C–S bond occurs only in the presence of a catalytic amount of iodine (10 mol%); thus, (ii) a new oxidative thiolation of olefinic C–H bonds is realized; and (iii) the polyfunctionalized 2-methylene-3-thiophenone products provide additional opportunities for structural diversification.

Initial investigations showed that the cyclization of **1a** could take place in DMSO in the presence of I_2 (1.2 equiv.) at room temperature for 48 h (Table 1, entry 1). The major product was identified as (*Z*)-2-benzylidene-5-(ethylthio)-4-(4-methoxyphenyl)thiophen-3(2*H*)-one **2a** by NMR, MS and further by X-ray crystallography(Figure 1).[16] Its isomer **3a** was also observed in a ratio of 8:2 (**2a**:**3a**) based on ^{1}H NMR analysis (entry 1). High temperature proved to benefit the process and the reaction was completed in 1.5 h at 130 °C (entry 2). Interestingly, the reaction afforded a mixture of **2a** and **3a** in 99% yield even in the presence of a less than a stoichiometric amount of iodine (entries 3–5). On elevating the temperature to 150 °C, the cyclization could be complete in 8 h with excellent yield and regioselectivity under the catalysis of 10 mol% of iodine (entry 6). Further decreasing the amount of I_2 led to longer reaction time and lower regioselectivity (entry 7). Additionally, other electrophilic catalysts, NIS and NBS, were found to be less efficient than I_2 for this cyclization (entries 8 and 9). A complex mixture was obtained with Br_2 as catalyst (entry 10). Finally, the reaction solvent was found to play an important role. The transformation of **1a** was very slow in DMF (entry 11).

Table 1. Screening reaction conditions.[a]



1a Ar = 4-MeOC$_6$H$_4$ **2a** **3a**

Entry	Cat. (equiv.)	Solvent	*T* [°C]	*t* [h]	Yield[b] **2a**+**3a**	Ratio[c] **2a**:**3a**
1	I_2 (1.2)	DMSO	r.t.	48	17%	80:20
2	I_2 (1.2)	DMSO	130	1.5	99%	94:6
3	I_2 (0.5)	DMSO	130	7	99%	89:11
4	I_2 (0.2)	DMSO	130	14	99%	90:10
5	I_2 (0.1)	DMSO	130	28	98%	85:15
6	***I_2 (0.1)***	***DMSO***	***150***	***8***	***98%***	***92:8***
7	I_2 (0.05)	DMSO	150	14	96%	87:13
8	NIS (0.1)	DMSO	150	16	96%	71:29
9	NBS (0.1)	DMSO	150	24	5%	77:23
10	Br_2 (0.1)	DMSO	150	6	–[d]	–
11	I_2 (0.1)	DMF	150	20	5%	60:40

[a] *Reaction conditions:* **1a** (0.2 mmol), solvent (2 mL).
[b] Isolated yields.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Complex mixture.

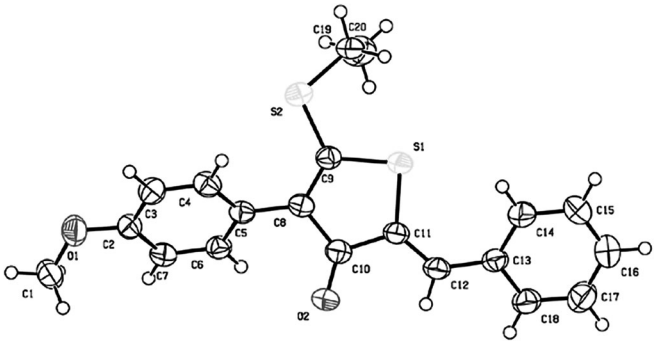
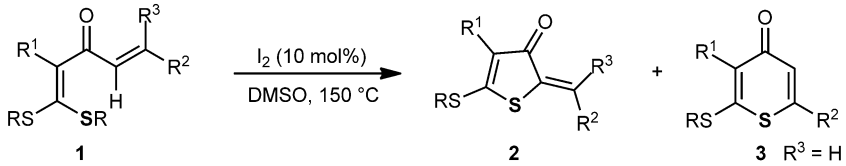


Figure 1. ORTEP diagram of **2a**.

Very recently, I_2-mediated/catalyzed C–H functionalization has been an area of intensive research due to its mild, low-cost, non-toxic, and unique catalytic properties.[17] The above reaction showed us a novel and efficient I_2-catalyzed oxidative sp^2C–H thiolation under neutral conditions. Thus, a set of ketene dithioacetals **1** was prepared to probe the scope of this process under the optimized reaction conditions (Table 1, entry 6). In generally, various ketene dithioacetals **1** could be selectively converted into the cyclic products in moderate to excellent yields (Table 2). For example, ketene diethyl thioacetals **1a**–**o** with both electron-rich and electron-deficient aromatic R^1 and R^2 groups effectively afforded a mixture of **2** and **3** in 60–99% isolated yields, respectively (entries 1–15). The reaction conditions were also compatible with **1p** and **1q** bearing dimethylthio and dibenzylthio functional groups (entries 16 and 17). Substrates **1r** and **1s** with aliphatic R^1 or R^2 substituents gave the corresponding cyclic products in good yields (entries 18 and 19). Additionally, **1t** with an electron-withdrawing benzoyl group at the α-position also worked well to give the desired mixture of **2t** and **3t**

Table 2. I_2-catalyzed cyclization of **1**.[a]



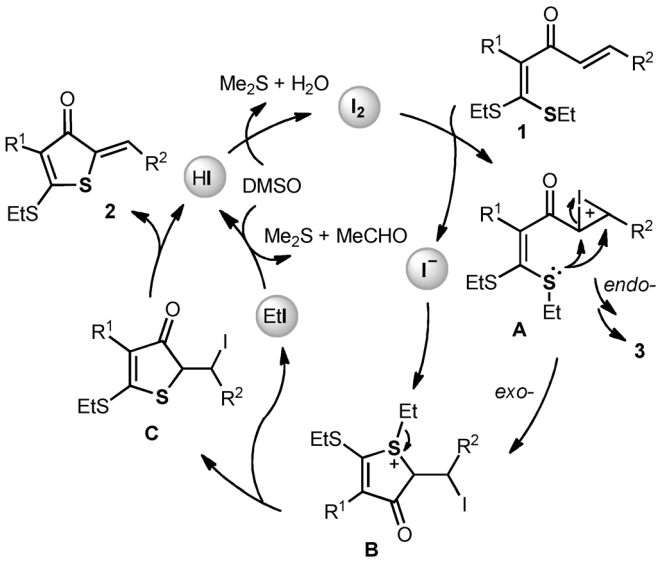
Entry	1	R	R^1	R^2	R^3	Time [h]	Yield of 2+3 [%][b]	Ratio 2:3[c]
1	**1a**	Et	4-$MeOC_6H_4$	Ph	H	8	98	92:8
2	**1b**	Et	4-$MeOC_6H_4$	4-MeC_6H_4	H	10	94	82:18
3	**1c**	Et	4-$MeOC_6H_4$	4-ClC_6H_4	H	10	90	97:3
4	**1d**	Et	4-$MeOC_6H_4$	2,3-$CH_2O_2C_6H_3$	H	18	68	95:5
5	**1e**	Et	4-$MeOC_6H_4$	2-ClC_6H_4	H	10	92	91:9
6	**1f**	Et	4-$MeOC_6H_4$	2-furyl	H	10	63	85:15
7	**1g**	Et	2-$MeOC_6H_4$	Ph	H	10	92	91:9
8	**1h**	Et	4-FC_6H_4	Ph	H	12	98	91:9
9	**1i**	Et	4-FC_6H_4	4-ClC_6H_4	H	26	96	95:5
10	**1j**	Et	4-FC_6H_4	4-$MeOC_6H_4$	H	23	64	97:3
11	**1k**	Et	4-FC_6H_4	2,3-$CH_2O_2C_6H_3$	H	12	85	94:6
12	**1l**	Et	4-ClC_6H_4	Ph	H	10	99	93:7
13	**1m**	Et	4-ClC_6H_4	4-ClC_6H_4	H	22	94	98:2
14	**1n**	Et	4-ClC_6H_4	2,3-$CH_2O_2C_6H_3$	H	16	94	95:5
15	**1o**	Et	4-BrC_6H_4	Ph	H	15	84	91:9
16	**1p**	Me	4-ClC_6H_4	Ph	H	11	97	98:2
17	**1q**	Bn	4-$MeOC_6H_4$	Ph	H	9	62	96:4
18	**1r**	Et	4-$MeOC_6H_4$	*t*-Bu	H	12	52	97:3
19	**1s**	Me	Me	Ph	H	7	73	92:8
20	**1t**	Et	PhCO	4-$MeOC_6H_4$	H	13	79	94:6
21	**1u**	Et	H	4-ClC_6H_4	H	12	–[d]	–
22	**1v**	Et	4-FC_6H_4	Ph	Ph	14	43	–
23	**1w**	-$(CH_2)_2$-	4-$MeOC_6H_4$	Ph	H	12	–[e]	–

[a] *Reaction conditions:* **1** (0.2 mmol), I_2 (0.02 mmol), DMSO (2 mL).
[b] Isolated yields.
[c] Determined by ^1H NMR spectroscopy.
[d] Complex mixture.
[e] No desired cyclic product was obtained. **1w** was recovered in 88% yield.

in 79% yield (entry 20). However, we found that the reaction is sensitive to the ketene dithioacetal **1u** without any substituent at the α-position and a complex mixture was often obtained on using the present protocol (entry 21). For the substrate **1v** bearing two substituents at the β-position, a diminished yield of **2v** was obtained likely due to the steric hindrance of the β-position (entry 22). The six-ring cyclic isomeric product could not be formed in this case. Finally, we investigated the cyclization of ketene cyclic dithioacetal **1w** under the catalysis of iodine. But no desired cyclic product was obtained after 12 h (entry 23).

On the basis of the experimental results and I_2-mediated transformations in DMSO reported in the literature,[17f,18] the reaction mechanism is understood in terms of the I_2-catalytic cycle shown in Scheme 2. Initially, iodonium **A** is formed from the substrates **1** in the presence of I_2. Thereby, the intramolecular attack of nucleophilic alkylthio on the iodonium moiety *via* an *exo* manner leads to cyclic intermediate **B**. Alkyl iodide is released with the assistance of iodide anion, resulting in iodocyclization product **C**. Finally, 2-methylene-3-thiophenones **2** are smoothly afforded *via* dehydroiodination. In this process, I_2 can be regenerated by the corresponding oxidation of both hydrogen iodide and alkyl iodide in DMSO to complete the catalytic cycle.[19]

During the reaction, we did not detect the iodocyclization products **C** in any of the cases. We postulate that the easier elimination of HI even under neutral conditions and at room temperature is likely due to the formation of the stable products **2** with an enone conjugate structure (**C**→**2**).[20] The regioselectivity of the cyclization is well in accordance with Baldwin's rule[21] and the *exo-trig* type of cyclization (**A**→**B**→**C**→**2**) is observed to be more highly favored than the *endo-trig* type of cyclization (**A**→→**3**). Each product **2** was also isolated as a stereoisomer with a *trans* relationship of the R^2 and carbonyl. No *cis*-isomers were detected from the crude products. This indicates



Scheme 2. Proposed mechanism for the cyclization of **1**.

a *trans*-elimination process of HI (**C**→**2**). Additionally, the alkylthio group as a sulfur nucleophile in our work can avoid the formation of disulfides as accompanying products. All of the above factors may contribute to the efficient conversions of ketene dithioacetals **1** to cyclic products **2**. Thus, we provide here a practical cyclization strategy for the synthesis of thiophenone derivatives **2** from easily prepared starting materials.

Encouraged by the above experimental results, we next tried to extend the cyclization to *ortho*-methylthiophenyl vinyl ketones for the synthesis of benzothiophenones (Table 3). As we expected, upon treatment of **4a** with 10 mol% of iodine in DMSO at 150 °C, the cyclization could took place to give the desired mixture of 2-methylenebenzothiophen-3-one **5a** and its isomer **6a** but only in 22% yield. The reaction yield was improved to 73% by increasing the amount of iodine to 50 mol% under otherwise identical conditions (entry 1). However, a stoichiometric amount of iodine decreased the reaction yield along with the formation of complex by-products. Thus, other substrates **4b–f** were selected toward the cyclization by using 50 mol% of iodine as catalyst. As shown in Table 3, the corresponding cyclic products **5b–f** along with their regioisomers **6b–f** were isolated in 40–62% yields (entries 2–6).

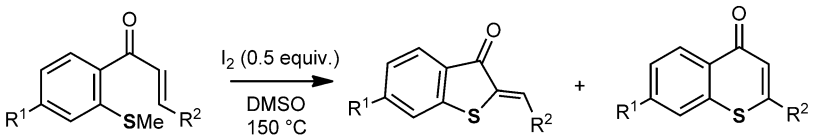
In conclusion, a transition metal-free vinylic C–H thiolation process has been developed. Under the catalysis of iodine (10 mol%), the cyclization of α-alkenoyl ketene dithioacetals *via* tandem iodocyclization and dehydroiodination occurs successfully in terms of the selectivity, product yields, and tolerance to a range of functional groups. The synthetic strategy provides an efficient and easy entry to polyfunctionalized 2-methylene-3-thiophenones and can be extended to the synthesis of 2-methylene-3-benzothiophenones *via* the cyclization of *ortho*-methylthiophenyl vinyl ketones. The alkylthio functional group retained in the products should enable potential transformations based on it.[22] Further investigations on applications are in progress in our research group.

Experimental Section

Typical Procedure

To a 25-mL round-bottom flask was added **1a** (77 mg, 0.2 mmol), I_2 (5.0 mg, 0.02 mmol) and DMSO (2 mL). The reaction mixture was stirred at 150 °C until **1a** was consumed under the monitoring of TLC. The resulting mixture was poured into dilute aqueous $Na_2S_2O_3$ solution (20 mL), and extracted with CH_2Cl_2 (3×10 mL). The combined organic

Table 3. Synthesis of benzothiophenones *via* I_2-catalyzed cyclization of **4**.[a]



Entry	**4**/R^1, R^2	Time [h]	Yield of **5**+**6** [%][b]	Ratio **5**:**6**[c]
1	**4a**/H, Ph	12	73	90:10
2	**4b**/H, 4-MeC_6H_4	12	58	90:10
3	**4c**/H, 4-$MeOC_6H_4$	11	56	81:19
4	**4d**/H, 2,3-$CH_2O_2C_6H_3$	10	62	94:6
5	**4e**/F, Ph	8	44	93:7
6	**4f**/F, 4-ClC_6H_4	10	40	73:27

[a] *Reaction conditions:* **4** (0.2 mmol), I_2 (0.5 equiv.), DMSO (2 mL).
[b] Isolated yields.
[c] Determined by ^{1}HNMR spectroscopy.

extracts were washed with water (3×10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent, petroleum ether/ethyl acetate: 50/1, v/v) to give a mixture of **2a** and **3a** as a yellow solid; yield: 68.5 mg (98%). Pure **2a** was obtained by an additional careful chromatography.

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[16] Crystal data for **2a**: $C_{20}H_{18}O_2S_2$, yellow, $M=354.46$, monoclinic, space group $P21/n$, $a=6.164(5)$ Å, $b=23.928(5)$ Å, $c=12.121(5)$ Å, $V=1765.5(16)$ Å^3, $\alpha=90.000(5)°$, $\beta=99.050(5)°$, $\gamma=90.000(5)°$, $Z=4$, $T=293(2)$ K, $F000=744$, 6666 reflections collected, 3103 unique with $R(\text{int})=0.0162$, $R_1=0.0336$, $wR_2=0.0825$ [$I>2\,s(I)$]. CCDC 947706 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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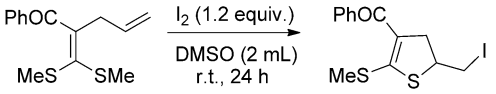
[20] In order to get more information on the mechanism, we examined the I_2-catalyzed cyclization of α-benzoyl, α-allyl ketene dimethyl thioacetal. It was found that



the iodocyclization product could be isolated in 37% yield along with the recovery of starting material in 51% yield when the reaction was performed in DMSO in the presence of 1.2 equivalents of I_2 at room temperature. The reaction mixture became complex at 150 °C with 0.1 equivalent of I_2 as catalyst. For details, please see the Supporting Information.

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