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Synthesis of α-Keto Thioamides by Metal-Free C=C Bond Cleavage in Enaminones Using Elemental Sulfur

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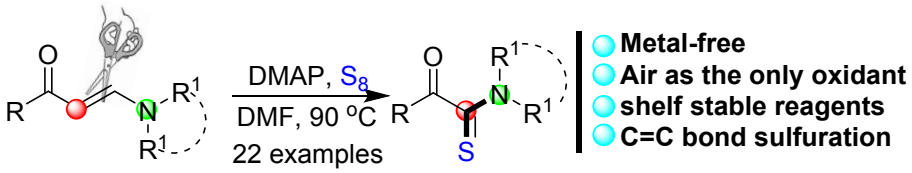


Abstract An unprecedented way of cleaving the C=C bond in *N,N*-disubstituted enaminones in the presence of elemental sulfur and *N,N*-dimehtyl-4-aminopyridine (DMAP) is disclosed. Without using any metal catalyst or additive, the cascade functionalization of both C=C and C-H bonds takes place to enable the formation of new C=S and C-N bonds, thus providing a facile and practical method for the synthesis of *N,N*-disubstituted α-keto thioamides.

The carbon-sulfur bonds are ubiquitous as characteristic moiety in natural products, polymeric materials, pharmaceuticals and biologically valuable lead compounds.[1] According to the chemical valence of the sulfur atom, the carbon-sulfur bonds usually present in two different forms: the C-S single bond and the C=S double bond. Because of the features of high stability and enriched pathways of bond formation, the construction of singe C-S bond is accessible via a large number of different synthetic

approaches such as cross coupling, substitution and addition reactions etc.[2] On the contrary, as the other form of carbon-sulfur bond, the C=S double bond has received much less advances in terms of synthetic methodology. However, because the C=S double bond is known as featured fragment in a large number of organic compounds possessing valuable biological profiles as well as pharmaceutical activities, devising synthetic routes enabling the construction of C=S double bond is thus highly critical work. Traditionally, the Lawessons' reagent is a reliable option in the C=S double bond forming reaction by transforming the carbonyl group into thiocaronyl group.[3] The high cost and production of phosphorus waste, however, are restrictions preventing the widespread application of this reagent. Thanks to the efforts been made by researchers, some more easily available and environmentally friendly sulfurating reagents, such as alkali sulfide and elemental sulfur have been found as practical alternatives in several sulfuration reactions. For example, the coupling reactions of amine, elemental sulfur with an alkyne,[4] amine,[5] aldehyde,[6] and active methyl C-H bonds[7] have been reported as effective methods in the synthesis of thioamides via C=S bond construction. In addition, the decarboxylation of arylacetic and cinnamic acids has also been developed for the synthesis of thioamides by reacting with elemental sulfur and amines.[8] On the other hand, the reactions of alkali sulfide, aldehyde with amines/amides,[9] amines/haloalkynes,[10] or aryl nitriles[11] can provide divergent thioamides, too. Recently, novel synthetic methods towards thioamides have been established by employing various other sulfur sources such as methylene thiols, isothiocyanates, 2-thioxothiazolidinone, P_4S_{10} and tetramethylthiuram disulfide

etc.[12]

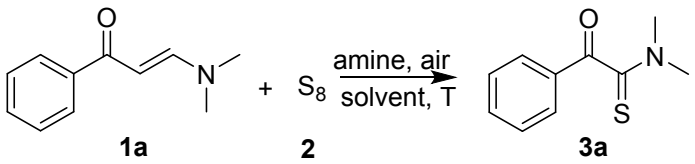
Generally, all the formation of C=S double bond in these presently known methods involve the transformation of C=O, C-H or C≡C triple bonds. It is interesting that a reaction transforming C=C double bond to C=S bond is not yet known. Recently, the functionalization on the C=C double bond in enaminones has been revealed as robust tool in the designation of enriched organic syntheses by us and other groups.[13] In view of our previous works on and continuous interests in the synthetic chemistry based on enaminones,[14] we envisage that it is possible to achieve the generation of a C=S bond by functionalizing the C=C double bond of enaminones, which may provide α-keto thioamide as products resulting from such transformation.

As a class of typical thioamide derivatives, the α-keto thioamides are reported with important functions in organic synthesis and biological studies.[15] Previously, the synthesis of α-keto thioamides can be accessed via the reactions of methyl ketones with various thiol amide reagents such as (*N,N*-dimethylthiocarbamoyl)lithium,[16] amine/sodium hydrosulfide,[17] elemental sulfur/amine,[18] or elemental sulfur/amide.[19] In other cases, arylglyoxal hydrates have been used as more active equivalents of methyl ketones for the synthesis of similar products.[20] The overall availability for α-keto thioamides, however, is yet inadequate for diversity oriented α-keto thioamide synthesis. In this background, devising reactions initiated by unprecedented transformation models is highly demanding. Herein, we report a new approach for the metal-free synthesis of α-keto thioamides via the reactions of elemental sulfur[21] and enaminones under aerobic condition, which is also hitherto the first example of

carbon-carbon bond cleavage-based synthesis of α-keto thioamides.

Initially, the model reaction of enaminone **1a** with elemental sulfur **2** was first run in DMF by heating at 90 °C, but no reaction took place (entry 1, Table 1). Interestingly, the employment of DMAP as additive led to the formation of product **3a** with good yield (entry 2, Table 1). In parallel entries, other organic bases such as *N*-methylmorpholine (NMM) and DABCO could not promote this reaction (entries 3-4, Table 1). Subsequently, reducing the amount of elemental sulfur was found to be negative, and considerably lower yield of **3a** was afforded (entries 5-6, Table 1). Later on, toluene, dioxane and DMSO were employed as alternative reaction medium, respectively (entries 7-9, Table 1), but none was practical. In the experiments conducted at different temperature, 90 °C was proved to be most favorable (entries 10-11, Table 1). In addition, decreasing the loading of DMAP undermined the yield of **3a** (entry 12, Table 1). Subsequently, a control entry performed under nitrogen atmosphere gave **3a** in only trace amount, indicating that the oxygen in air was indispensable for this reaction (entry 13, Table 1). As further comparison, the reaction using 2,6-ludine as base additive didn't lead to the synthesis of **3a**, indicating the specific function of DMAP for this reaction (entry 14, Table 1). Conducting the same reaction with catalytic amount of DMAP in the present of 1 equiv NaOH was not practical, either (entry, 15, Table 1). Finally, the parallel reaction using K_2S as the alternative sulfur source with **1a** gave only trace amount of **3a** with the optimal parameters in entry 2.

Table 1 Optimization on the reaction conditions for α-keto thioamide synthesis[a]



1a **2** **3a**

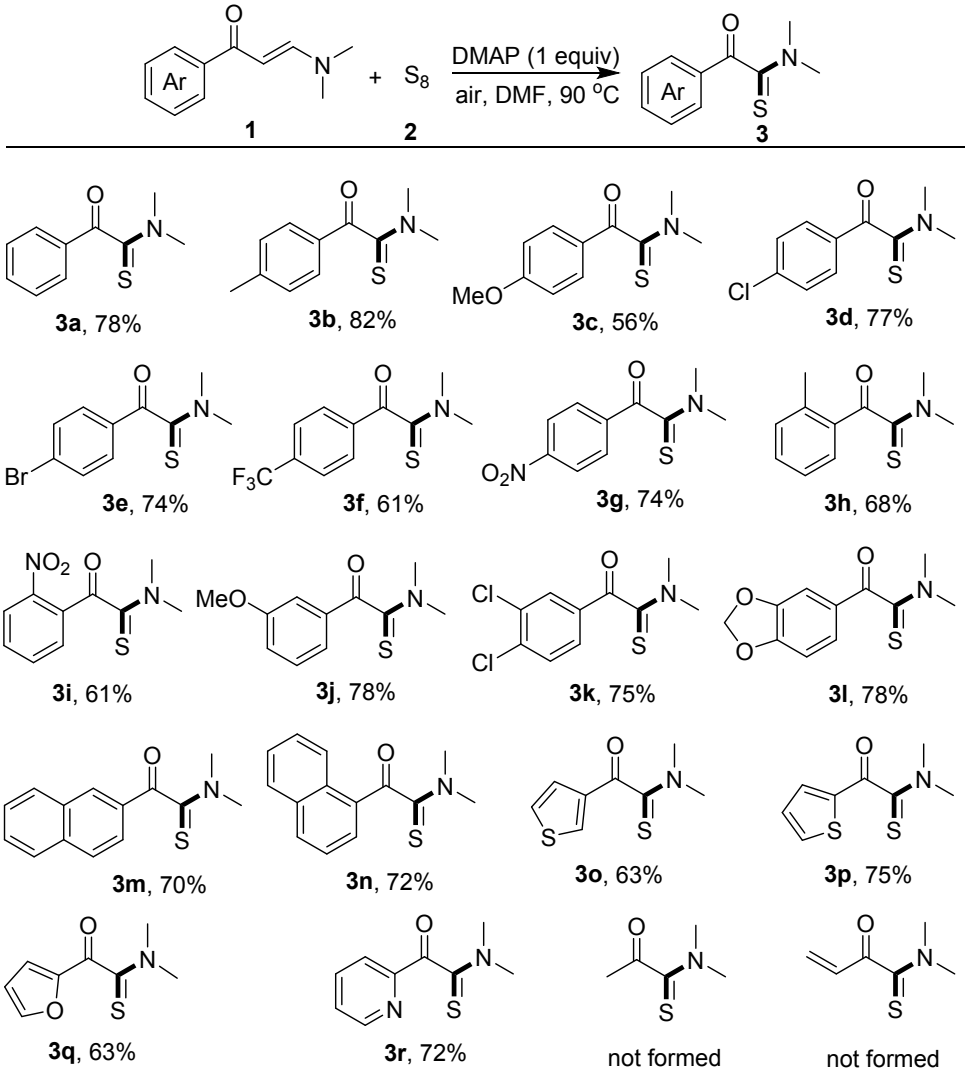
entry	additive	solvent	T (°C)	yield (%)[b]
1	-	DMF	90	0
2	DMAP	DMF	90	78
3	NMM	DMF	90	0
4	DABCO	DMF	90	0
5[c]	DMAP	DMF	90	trace
6[d]	DMAP	DMF	90	10
7	DMAP	toluene	90	0
8	DMAP	dioxane	90	0
9	DMAP	DMSO	90	trace
10	DMAP	DMF	80	trace
11	DMAP	DMF	100	64
12[e]	DMAP	DMF	90	47
13[f]	DMAP	DMF	90	trace
14	2,6-lutidine	DMF	90	0
15[g]	DMAP	DMF	90	5

[a]The general conditions: **1a** (0.2 mmol), **2** (0.8 mmol) and additive (0.2 mmol) in 2 mL of solvent, stirred at 90 °C for 24 h under air atmosphere. [b]Yield of isolated product based on **1a**. [c]The loading of sulfur was 0.2 mmol. [d]The loading of sulfur was 0.4 mmol. [e]The loading of DMAP was 0.1 mmol. [f]Reaction under N_2. [g]20 mol% DMAP and 1 equiv NaOH were used.

Following the optimization experiments, the application scope of this C=C bond cleavge-based sulfuration was then examined. The reactions employing different enaminones to react with elemental sulfur were executed, and the results in synthesizing different α-keto thioamides **3** via the reactions of *N,N*-dimethyl tertiary enaminones were shown in Table 2. According to the acquired results, the present method was generally applicable for the synthesis of α-aroyl thioamides via the reactions of corresponding aryl functionalized enaminones. In the reactions of *N,N*-dimethyl amino-based enaminones, the substrates with phenyl ring containing

alkyl, halogen, nitro, alkoxyl, and trifluoromethyl substitution displayed fine compatibility to the titled reaction regardless the site and property of the substituents, and no fixed impact of these substituents to the product yield was reflected in the present data (**3a-3l**, Table 2). Additionally, the naphthyl (**3m** and **3n**, Table 1) and heteroaryl (**3o-3r**, Table 2) functionalized α-keto thiomamides were also smoothly synthesized with moderate to good yields via the same

Table 2 Scope on the synthesis of *N,N*-dimethyl α-keto thioamides[a,b]

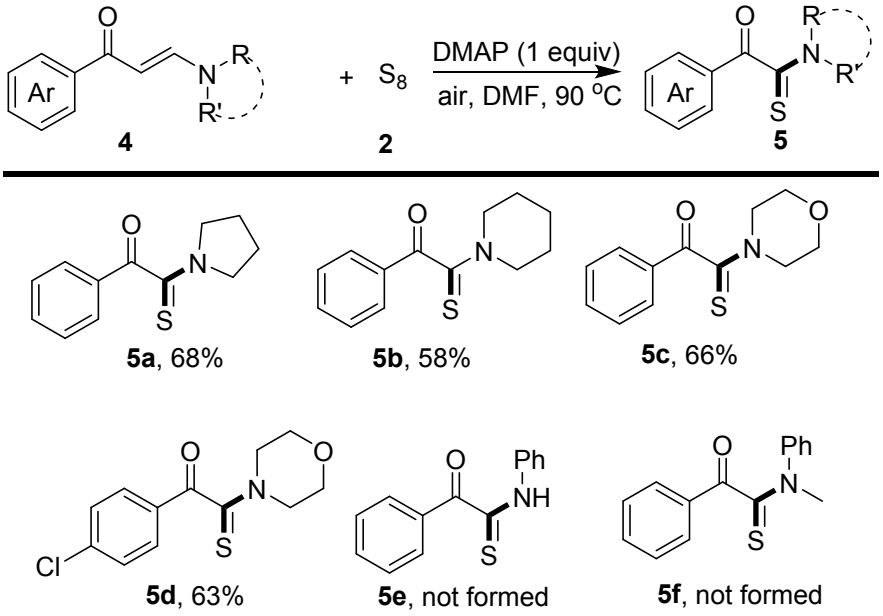


[a]The general conditions: **1** (0.2 mmol), **2** (0.8 mmol) and DMAP (0.2 mmol) in 2 mL of DMF, stirred at 90 °C for 24 h under air atmosphere. [b]Yield of isolated product based on **1**.

transformation, demonstrating that this method was generally applicable for the aryl functionalized enaminones. The reaction employing an enaminone functionalized with methyl instead of the aryl in **1** did not provide the target product. Similarly, the reation employing a *N,N*-dimethyl vinyl enaminone under the present conditions did not give rise to the expected product, either.

Next, for further expanding the scope on the synthetic protocols, the tertiary enaminones functionalized with varied *N,N*-substitution[22] were employed to the standard reactions conditions with elemental sulfur. As outlined in Table 3, the enaminones functionalized with pyrrolidine, piperidine as well as morpholine were found to be identically practical in the individual synthesis of α-keto thioamides **5a**-**5d**. The successful synthesis of these products confirmed the satisfactory application scope of the present method in the synthesis of *N,N*-disubstituted α-keto thioamide. However, the attempts in synthesizing *NH*-α-keto thioamide **5e** and *N*-methyl, *N*-phenyl α-keto thioamide **5f** were not successful by this method. Analyzing the reaction synthesizing **5a** led to the simultaneous isolation of **3a** as side product in 28% yield, indicating that DMF was also an active amino source in the formation of products **3**. The result also explained the relatively lower product yields of **5**.

Table 3 Scope on the synthesis of α-keto thioamides with varied *N,N*-disubstitution[a,b]



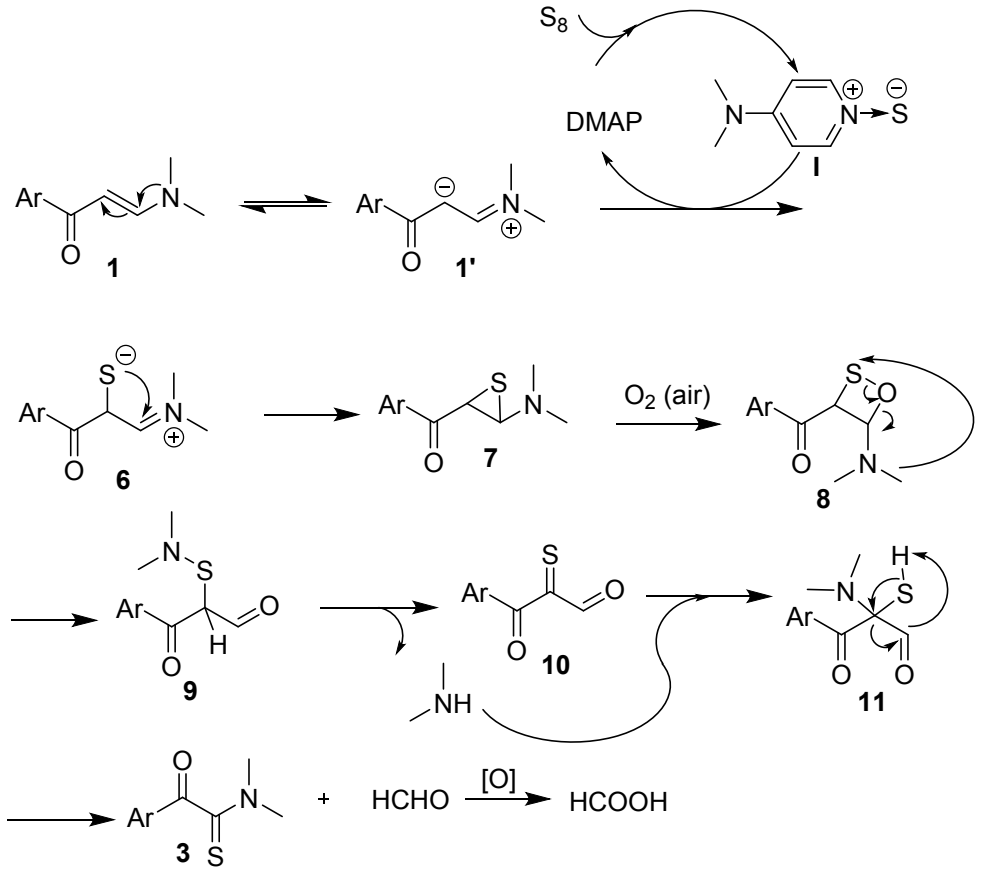
[a]The general conditions: **4** (0.2 mmol), **2** (0.8 mmol) and DMAP (0.2 mmol) in 2 mL of DMF, stirred at 90 °C for 24 h under air atmosphere. [b]Yield of isolated product based on **4**.

While different intermediates such as 1,2-dioxetane[23] or 1,2-oxathietane resulting from the oxidation of molecular oxygen to the C=C double bond were possible for this reaction, we analyzed the crude mixture of the model reaction by GC. The results showed clearly that formaldehyde was formed during the reaction (see SI),

On the basis of the result from control experiments (entry 13, Table 1) and previous reports on the enaminone C=C bond cleavage, the possible mechanism of the present sulfuration reaction is proposed (Scheme 1). Originally, the elemental sulfur incorporates the nucleophilic DMAP[24] to form the active pyridine N-S species **I** which mediates the transfer of the sulfur atom to enaminones and provides intermediate **6** via the enaminone's isomeric version **1'**. Subsequently, the intramolecular cyclization of **6** leads to the formation of thiirane intermediate **7**. The oxidative insertion of molecular oxygen[25] to **7** produces 1,2-oxathietane intermediate **8**. The ring opening of **8** via the migration of the amino group to the sulfur atom

enables the formation of **9** which undergoes quick elimination of the secondary amine to generate intermediate **10**. Successively, the nucleophilic attack of the amine to the thiocarbonyl site provides *N,S*-acetal intermediate **11**. The decomposition of **11** then yields products **3** and releases formaldehyde. Further oxidation on the formaldehyde giving formic acid may take place to consume part of DMAP, which is also positive to the formation of the target product.

Scheme 1 The proposed reaction mechanism



In conclusion, we have identified a novel protocol for the synthesis of α-keto thioamides via the sulfuration based on enaminone C=C double bond cleavage. The reactions of easily available tertiary enaminones and elemental sulfur take place efficiently in air atmosphere without using any metal catalyst or additional oxidant.

Owing to the special mode of bond transformation, simple operation as well as the broad substrate tolerance, the present method will be a useful complementary option in the synthesis of α-keto thioamides.

Experimental section

General information

All experiments were carried out under air atmosphere. Enaminones **1**[26] and **4**[22] were prepared following literature processes. Other chemicals and solvents used in the experiments were acquired from commercial sources and used directly without further treatment. ^{1}H and ^{13}C NMR were recorded in 400 MHz spectrometer by using $CDCl_3$ as solvent and TMS as internal standard. The chemical shifts were reported in ppm, and the frequencies for ^{1}H and ^{13}C NMR test were 400 MHz and 100MHz, respectively. High resolution mass spectrometry (HRMS) data for all new products were obtained under ESI model in an apparatus equipped with TOF analyzer. The melting points of solid samples were tested in an X-4A apparatus without correcting the temperature.

General procedure for the synthesis of α-keto thioamides 3 and 5

To a 25 mL round-bottom flask were added enaminone **1** or **4** (0.2 mmol), sulfur powder (0.8 mmol), DMAP (0.2 mmol) and DMF (2 mL). Then the resulting mixture was heated up to 90 ^{o}C with oil bath, and stirred at the same temperature for 24 hours (TLC). After cooling down to room temperature, 5 mL of water was added, and the suspension was extracted with ethyl acetate (3 × 10 mL). The organic phases were collected and washed with small amount of water for three times. After drying with

anhydrous Na_2SO_4, the solid was filtered and the acquired solution was employed to reduced pressure to remove the solvent. The residue obtained therein was then subjected to flash silica gel column chromatography to provide pure products with the elution of mixed petroleum ether/ethyl acetate (v/v = 10:1).

***N,N*-Dimethyl-2-oxo-2-phenylethanethioamide** (**3a**).[19] Yield 78%, 30 mg; pale yellow solid; mp 80-81°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.3 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 2 H), 3.55 (s, 3 H), 3.23 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.8, 188.4, 134.2, 133.2, 129.9, 128.8, 42.4, 40.4.

***N,N*-Dimethyl-2-oxo-2-(*p*-tolyl)ethanethioamide** (**3b**).[19] Yield 82%, 34 mg; yellow solid; mp 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 2 H), 7.28 (d, *J* = 7.6 Hz, 2 H), 3.54 (s, 3 H), 3.21 (s, 3 H), 2.42 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.0, 188.4, 145.5, 130.6, 130.0, 129.6, 42.5, 40.5, 21.9.

2-(4-Methoxyphenyl)-*N,N*-dimethyl-2-oxoethanethioamide (**3c**).[19] Yiled 56%, 25 mg; yellow solid; mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 9.2Hz, 2 H), 6.95 (d, *J* = 8.8Hz, 2H), 3.88(s, 3 H), 3.54(s, 3 H), 3.22(s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 197.3, 187.8, 164.5, 132.3, 126.0, 114.2, 55.6, 42.4, 40.5.

2-(4-Chlorophenyl)-*N,N*-dimethyl-2-oxoethanethioamide (**3d**).[4] Yield 77%, 35 mg; yellow solid; mp 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 3.55 (s, 3 H), 3.23 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.0, 186.9, 140.8, 131.7, 131.3, 129.2, 42.5, 40.5.

2-(4-Bromophenyl)-N,N-dimethyl-2-oxoethanethioamide (**3e**). Yield 74%, 40 mg; yellow solid; mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2 H),

7.63 (d, *J* = 8.4 Hz, 2 H), 3.55 (s, 3 H), 3.23 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 196.0, 187.1, 132.2, 131.3, 129.8, 129.6, 42.5, 40.5; HRMS (ESI) m/z calcd for $C_{10}H_{11}BrNOS$ $(M + H)^+$ 271.9739, found 271.9737.

***N,N*-Dimethyl-2-oxo-2-(4-(trifluoromethyl)phenyl)ethanethioamide (3f)**.[15a] Yield 61%, 32 mg; yellow solid; mp 70-71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 2 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 3.57 (s, 3 H), 3.26 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.5, 186.3, 136.3, 135.0, 130.2, 125.8, 124.8 (q, $J_{c\text{-}F}$ = 271 Hz), 42.5, 40.5.

2-(4-Nitrophenyl)-N,N-dimethyl-2-oxoethanethioamide (3g).[19] Yield 74%, 35 mg; yellow solid; mp 148-150 °C;1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.2Hz, 2H), 8.16 (d, *J* = 9.2 Hz, 2 H), 3.59(s, 3 H), 3.28(s, 3 H); 13C$\{^{1}H\}$ NMR (100 MHz, CDCl3) δ 194.8, 184.9, 150.7, 138.4, 130.9, 123.9, 42.5, 40.5.

***N,N*-Dimethyl-2-oxo-2-(o-tolyl)ethanethioamide (3h)**.[19] Yield 68%, 28 mg; pale yellow solid; mp137-138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.31-7.24 (m, 2 H), 3.56 (s, 3 H), 3.29 (s, 3 H), 2.69 (s, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)δ 198.2, 189.7, 141.8, 133.2, 132.6, 132.1, 131.9, 125.9, 42.5, 40.7, 21.9.

2-(2-Nitrophenyl)-*N,N*-dimethyl-2-oxoethanethioamide (3i). Yield 61%, 29 mg; yellow solid; mp 114-115 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03(d, *J* = 8.0Hz, 1H), 7.87(d, *J* = 7.6Hz, 1H), 7.74 (t, *J* = 7.6Hz, 1H), 7.63 (t, *J* = 7.8Hz, 1H), 3.62(s, 3 H), 3.47(s, 3 H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.9, 183.3, 134.8, 133.8, 132.4,131.6, 123.7,77.3, 43.1, 42.6; HRMS (ESI) m/z calcd for $C_{10}H_{11}N_2O_3S$ (M +

H)$^+$ 239.0485, found 239.0483.

2-(3-Methoxyphenyl)-N,N-dimethyl-2-oxoethanethioamide (**3j**).[19] Yield 78%, 35 mg; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.54 (m, 1 H), 7.50 (d, *J* = 7.7 Hz, 1 H), 7.37 (t, *J* = 7.9 Hz 1 H), 7.16-7.13 (m, 1 H), 3.86 (s, 3 H), 3.55 (s, 3 H), 3.22 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.8, 188.2, 160.0, 134.6, 129.9, 122.8, 120.9, 113.6, 77.4, 77.0, 76.7, 55.5, 42.4, 40.4.

2-(3,4-Dichlorophenyl)-N,N-dimethyl-2-oxoethanethioamide (**3k**). Yield 75%, 39 mg; yellow solid; mp 106-108 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.81 (d, *J* = 8.3 Hz, 1 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 3.55 (s, 3 H), 3.24 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.1, 185.4, 138.8, 133.6, 133.1, 131.5, 131.0, 128.8, 42.5, 40.5; HRMS (ESI) m/z calcd for $C_{10}H_{10}Cl_2NOS$ $(M+H)^+$ 261.9855, found 261.9854.

2-(Benzo[d][1,3]dioxol-5-yl)-N,N-dimethyl-2-oxoethanethioamide (**3l**). Yield 78 %, 37 mg; brown solid; mp 128-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 1 H), 7.45 (s, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.07 (s, 2 H), 3.54 (s, 3 H), 3.22 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.9, 187.3, 152.9, 148.4, 127.8, 127.1, 109.0, 108.4, 102.2, 42.5, 40.5; HRMS (ESI) m/z calcd for $C_{11}H_{12}NO_3S$ $(M+H)^+$ 238.0532, found 238.0534.

***N,N*-Dimethyl-2-(naphthalen-2-yl)-2-oxoethanethioamide** (**3m**). Yield 70%, 34 mg; yellow solid; mp 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1 H), 8.04 (d, *J* = 8.6 Hz, 1 H), 7.96-7.87 (m, 3 H), 7.65-7.54 (m, 2 H), 3.61 (s, 3 H), 3.26 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.9, 188.6, 136.1, 132.5, 132.4, 130.6, 129.8, 129.2, 128.9, 127.9, 127.1, 124.4, 42.5, 40.6; HRMS (ESI) m/z calcd for $C_{14}H_{14}NOS$

$(M + H)^+$ 244.0791, found 244.0789.

***N,N*-Dimethyl-2-(naphthalen-1-yl)-2-oxoethanethioamide** (**3n**). Yield 72%, 35 mg; yellow solid; mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, *J* = 8.7 Hz, 1 H), 8.07 (d, *J* = 8.1 Hz, 1 H), 7.98 (d, *J* = 7.2 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 7.69 (t, *J* = 7.7 Hz, 1 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.49 (t, *J* = 7.7 Hz, 1 H), 3.59 (s, 3 H), 3.32 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.9, 189.9, 135.3, 134.2, 132.9, 131.5, 129.2, 129.1, 128.7, 126.9, 126.1, 124.3, 42.7, 40.8; HRMS (ESI) m/z calcd for $C_{14}H_{14}NOS$ $(M + H)^+$ 244.0791, found 244.0786.

***N,N*-Dimethyl-2-oxo-2-(thiophen-3-yl)ethanethioamide** (**3o**). Yield 63%, 25 mg; yellow solid; mp 71-72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.57 (d, *J* = 5.1 Hz, 1 H), 7.37-7.28 (m, 1 H), 3.53 (s, 3 H), 3.24 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.5, 182.7, 138.2, 135.7, 127.6, 127.0, 42.5, 40.6; HRMS (ESI) m/z calcd for $C_8H_{10}NOS_2$ $(M + H)^+$ 200.0198, found 200.0194.

***N,N*-Dimethyl-2-oxo-2-(thiophen-2-yl)ethanethioamide** (**3p**).[19] Yield 75%, 30 mg; yellow solid; mp 92-93 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, J = 8.0 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 7.18-7.12 (m, 1 H), 3.52 (s, 3 H), 3.27 (s, 3 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 195.3, 181.6, 140.2, 135.9, 135.6, 128.5, 42.6, 40.7.

***N,N*-Dimethyl-2-oxo-2-(furan-2-yl)ethanethioamide** (**3q**). Yield 63%, 23 mg; brown liquid; ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 7.61 (s, 1 H), 7.24 (s, 1 H), 6.52 (s, 1 H), 3.44 (s, 3 H), 3.20 (s, 3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.7, 176.5, 149.8, 148.2, 121.5, 112.8, 42.4, 40.8; HRMS (ESI) m/z calcd for $C_8H_{10}NO_2S$ $(M + H)^+$ 184.0427, found 184.0424.

***N,N*-Dimethyl-2-oxo-2-(pyridin-2-yl)ethanethioamide** (**3r**). Yield 72%, 28 mg; black solid; mp 113-114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (dd, *J* = 3.6, 1.2 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 7.91-7.89 (m, 1 H), 7.50-7.48 (m, 1 H), 3.58 (s, 3 H), 3.28 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ :197.5, 186.8, 152.1, 149.6, 137.2, 127.5, 124.0, 42.6, 40.2; HRMS (ESI) m/z calcd for $C_9H_{11}N_2OS$ $(M + H)^+$ 195.0587, found 195.0583.

1-Phenyl-2-(pyrrolidin-1-yl)-2-thioxoethan-1-one (**5a**).[18] Yield 68%, 30 mg; yellow solid; mp 45-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.5 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 2 H), 3.96 (t, *J* = 6.7 Hz, 2 H), 3.55 (t, *J* = 6.4 Hz, 2 H), 2.11-2.04 (m, 4 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 192.8, 188.8, 134.2, 132.9, 130.1, 128.8, 51.3, 51.1, 26.1, 23.9.

1-Phenyl-2-(piperidin-1-yl)-2-thioxoethan-1-one (**5b**).[17] Yield 58%, 27 mg; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.2 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.48 (t, *J* = 7.7 Hz, 2 H), 4.25 (t, *J* = 5.6 Hz, 2 H), 3.54 (t, *J* = 5.6 Hz, 2 H), 1.86-1.74 (m, 4 H), 1.62 (s, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 194.5, 187.9, 134.1, 133.5, 129.8, 128.8, 53.0, 48.1, 26.4, 25.3, 24.1.

2-Morpholino-1-phenyl-2-thioxoethan-1-one (**5c**).[17] Yield 66%, 31 mg; yellow solid; mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.2 Hz, 2 H), 7.62 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.8 Hz, 2 H), 4.34 (t, *J* = 5.0 Hz, 2 H), 3.91 (t, *J* = 5.0 Hz, 2 H), 3.70 (t, *J* = 4.8 Hz, 2 H), 3.60 (t, *J* = 4.8 Hz, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 195.8, 187.9, 134.4, 133.3, 129.8, 128.9, 66.5, 66.4, 51.9, 47.1.

1-(4-Chlorophenyl)-2-morpholino-2-thioxoethan-1-one (**5d**).[17] Yield 63%, 34 mg;

yellow solid; mp 137–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 4.32 (t, *J* = 4.8 Hz, 2 H), 3.91 (t, *J* = 4.8 Hz, 2 H), 3.70 (t, *J* = 4.6 Hz, 2 H), 3.59 (t, *J* = 4.6 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 195.0, 186.4, 141.0, 131.8, 131.2, 129.3, 66.5, 66.4, 52.0, 47.2.

Scale-up synthesis of α-keto thioamides 3a

To a 50 mL round-bottom flask were charged with enaminone **1a** (1 mmol), sulfur powder (4 mmol), DMAP (1 mmol) and DMF (5 mL). The resulting mixture was stirred at 90 °C with oil bath heating for 24 hours. After cooling down to room temperature, 15 mL of water was added, and the suspension was extracted with ethyl acetate (3 × 15 mL). The organic phases were collected and washed with small amount of water for three times. After drying with anhydrous Na_2SO_4, the solid was filtered, and the acquired solution was employed to reduced pressure to remove the solvent. The residue obtained therein was then subjected to flash silica gel column chromatography to provide pure product **3a** (50%, 95.8 mg) with the elution of mixed petroleum ether/ethyl acetate (v/v = 10:1).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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