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Metal-Free Catalytic Synthesis of Thiocarbamates Using Sodium Sulfinates as the Sulfur Source

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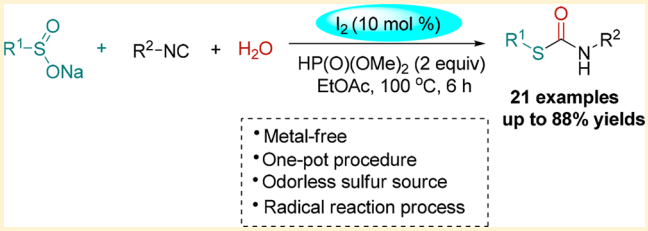
Supporting Information

ABSTRACT: A novel molecular iodine-catalyzed protocol for the construction of thiocarbamates from readily available sodium sulfinates, isocyanides, and water has been described. The present methodology offers a facile and practical route to a variety of thiocarbamates in moderate to good yields with favorable functional group tolerance by use odorless sodium sulfinates as the sulfur source. The mechanistic studies suggest the present transformation involves a radical process.



Thiocarbamates are recognized as an important class of biologically active molecules, with widespread use as herbicides[1] (e.g., molinate, thiobencarb, orbencarb), fungicides,[2] pesticides,[3] anesthetics,[4] and antiviral[5] agents. In the past decades, significant efforts have been made toward the construction of substituted thiocarbamates in term of their pharmacological effects and important biological activities. Traditional synthetic methods mainly involve the two-step operation reactions of amines with phosgene and thiols[6] or the reactions of amine with gaseous carbonyl sulfide followed by alkylation with alkyl halides.[7] Other strategies such as the palladium-catalyzed thiocarboxylation of amines with CO and S_8 or ArSSAr[8] and the reaction of thiols with isocyanates have also been developed.[9] However, multistep operations and the utilization of hazardous phosgene, CO, or isocyanates as the substrate limit their applications.[10] Recently, some efficient methods have been established to avoid the use of these hazardous starting materials,[11] including the Boc-Oxyma-promoted coupling reaction of hydroxamic acid with thiophenol,[12] the reaction of CBZ(Boc)-protected amines and thiophenols,[13] and iodine-catalyzed synthesis of secondary thiocarbamates from isocyanides and preformed thiosulfonates.[14] Very recently, the groups of He[15] and Sawant[16] and our group[17] also reported a strategy for direct one-pot synthesis of thiocarbamates via cross-coupling of isocyanides and thiols in the presence of water. Nevertheless, most of these methods also suffer from some drawbacks such as the use of metal reagents and air-sensitive, awful-smelling thiols or their derivatives. This is particularly problematic for large-scale synthesis in synthetic chemistry. Therefore, searching for alternative metal-free methods to construct thiocarbamates by using of odorless and easy-to-handle sulfuration agents is still an interesting and practical issue.

Sodium sulfinates are stable, odorless, and readily accessible reagents that have usually been employed as sulfone sources for the construction of organic sulfone compounds.[18] Recently, sodium sulfinates have emerged as promising thiolating reagents to construct the C−S bond through reductive sulfenylation reactions.[19−22] For example, Deng' group reported elegant methods for the synthesis of sulfenylated indoles and phenols via direct sulfenylation of indoles and phenols with sodium sulfinates.[20] Wu and Jiang presented copper-catalyzed oxysulfenylation of enolates with sodium sulfinates leading to sulfenylated cyclic ethers.[21] The Yi group described sulfenylation strategies with sodium sulfinates via an arylsulfenyl radical process using PPh_3 as a reducing reagent.[22] To the best of our knowledge, direct sulfenylation of isocyanides with sodium sulfinates has not yet been reported. In continuation of our ongoing research in the construction of sulfur-containing compounds[23] and green organic synthesis,[24] herein, we report a novel and efficient molecular iodine-catalyzed protocol for the direct synthesis of thiocarbamates from sodium sulfinates, water, and isocyanides (Scheme 1). This metal-free protocol, which simply utilizes readily available sodium sulfinates as the thiolating reagent and $HP(O)(OMe)_2$ as the reducing agent, provides an alternative and highly attractive approach to a series of biologically important thiocarbamate derivatives in moderate to good yields with favorable functional group tolerance.

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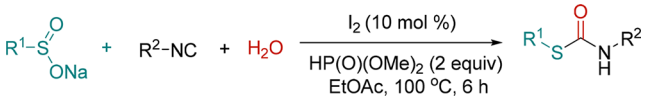
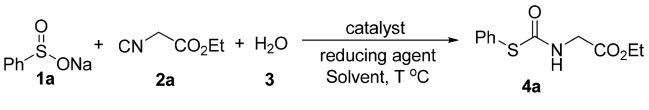
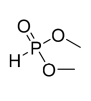
Scheme 1. Synthesis of Thiocarbamates Using Sodium Sulfinates as the Sulfur Source



Initially, sodium benzenesulfinate (**1a**), ethyl 2-isocyanoacetate (**2a**), and water were utilized as the model substrates to optimize various reaction conditions. A series of iodide-containing catalysts (5 mol %) were investigated using $HP(O)(OMe)_2$ as the reducing agent in DCE at 100 °C. As a result, none of the desired product **4a** was detected when KI, TBAI, NaI, and I_2O_5 were screened (Table 1, entries 1−4). To our delight, molecular iodine could catalyze efficiently the reaction to give the desired product **4a** in 70% yield (Table 1, entry 5). The reaction efficiency was further improved with an increase of the loading of molecular iodine to 10 mol % (Table 1, entries 6 and 7). No transformation was observed in the absence of molecular iodine catalyst (Table 1, entry 8). Among various reducing agents such as $HP(O)(OMe)_2$, $HP(O)(OEt)_2$, $HP(O)(OiPr)_2$, and PPh_3 examined, $HP(O)(OMe)_2$ was found to be the best one to promote this reaction (Table 1, entry 6 vs entries 9−11). It should be noted that no reaction occurred when the reaction was performed without reducing agent, indicating that $HP(O)(OMe)_2$ is essential for this reaction (Table 1, entry 12). Subsequent investigation on the effect of various solvents found that EtOAc was the optimized reaction medium to give the corresponding product **4a** in 88% yield (Table 1, entry 15). The optimized reaction temperature is 100 °C. A higher temperature (110 °C) or a lower temperature (80 or 90 °C) led to a slightly lower yield (Table 1, entries 19−21). No conversion was observed when the reaction was conducted at room temperature or 60 °C (Table 1, entries 22 and 23).

Table 1. Optimization of the Reaction Conditions[a]

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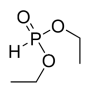
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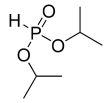
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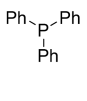
P4

entry	catalyst	reducing agent	solvent	T (°C)	yield[b] (%)
1	KI (5)	**P1**	DCE	100	0
2	TBAI (5)	**P1**	DCE	100	0
3	NaI (5)	**P1**	DCE	100	0
4	I_2O_5 (5)	**P1**	DCE	100	0
5	I_2 (5)	**P1**	DCE	100	70
6	I_2 (10)	**P1**	DCE	100	85
7	I_2 (15)	**P1**	DCE	100	75
8		**P1**	DCE	100	0
9	I_2 (10)	**P2**	DCE	100	76
10	I_2 (10)	**P3**	DCE	100	60
11	I_2 (10)	**P4**	DCE	100	9
12	I_2 (10)		DCE	100	0
13	I_2 (10)	**P1**	CH_3CN	100	83
14	I_2 (10)	**P1**	1,4-dioxane	100	73
15	I_2 (10)	**P1**	EtOAc	100	88
16	I_2 (10)	**P1**	DMSO	100	trace
17	I_2 (10)	**P1**	DMF	100	0
18	I_2 (10)	**P1**	EtOH	100	0
19	I_2 (10)	**P1**	EtOAc	110	68
20	I_2 (10)	**P1**	EtOAc	90	81
21	I_2 (10)	**P1**	EtOAc	80	59
22	I_2 (10)	**P1**	EtOAc	60	0
23	I_2 (10)	**P1**	EtOAc	25	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), H_2O (0.6 mmol), catalyst (5−15 mol %), reducing agent (0.4 mmol), solvent (1.5 mL), 25−100 °C, 6 h. [b]Isolated yields based on **1a**.

Under the established reaction conditions, we then examined the scope of this transformation. As summarized in Table 2, a series of substituted sodium benzenesulfinates including some electron-rich groups or some electron-poor groups were found to be suitable substrates for this reaction, and the corresponding thiocarbamates (**4b−h**) were obtained in moderate to good yields. Notably, halo substituents (F, Cl, and Br), trifluoromethyl and nitro groups were also compatible with this transformation, providing the chance for further modification. It was found that the reaction efficiency was significantly affected by the steric effect. The reaction failed to yield the desired product **4i** when sterically hindered sulfinate such as sodium 2,6-diisopropylbenzenesulfinate was used in this reaction system. When sodium 2-naphthalenesulfinate was employed as the substrate, the desired product **4j** was obtained in 73% yield. It is noteworthy that heterocycle sodium sulfinate such as sodium thiophene-2-sulfinate was also well tolerated in this transformation leading to the expected product **4k** in 67% yield. Unfortunately, none of the desired products were detected when alkyl sodium sulfinates such as sodium methylsulfonate and sodium trifluoromethanesulfinate were used as substrates. With respect to the isocyanides, in addition to **2a**, cyclohexyl isocyanide, *tert*-butyl isocyanide, and methyl isocyanoacetate were all suitable substrates and generated the corresponding products **4l−t** in good yields. Moreover, tosylmethyl isocyanide (TosMIC reagent) could also be utilized in the process to give the desired products **4u** and **4v** in 70% and 78% yields, respectively. Unfortunately, when an aromatic isocyanide such as 2,6-dimethylphenyl isocyanide was investigated under the standard conditions, none of the desired product **4w** was detected.

Furthermore, several control experiments were carried out to gain some insights into the possible reaction mechanism. Initially, when TEMPO (well-known radical-capturing species) was added into the reaction system of **1b** and **2a** under the standard conditions, the present reaction was completely inhibited and TEMPO-trapped thiyl radical complex was detected by LC−MS analysis. The above result suggested that the present transformation might proceed via a radical process (Scheme 2, (a)). When sodium benzenesulfinate (**1a**) was added independently in this reaction system, only a trace amount of PhSSPh was detected (Scheme 2, (b)). Furthermore, treatment of 1,2-diphenyl disulfide with **2a** under standard conditions did not give the desired product **4a** (Scheme 2, (c)). These results indicated that the disulfide should not be the intermediate in this reaction. When the model reaction was carried out in the absence of water, only a trace amount of product **4a** was detected (Scheme 2, (d)). Moreover, isotope-labeling experiments using $H_2{}^{18}O$ revealed that the oxygen atom of thiocarbamates originated from water (Scheme 2, (e)). In addition, when the model reaction was

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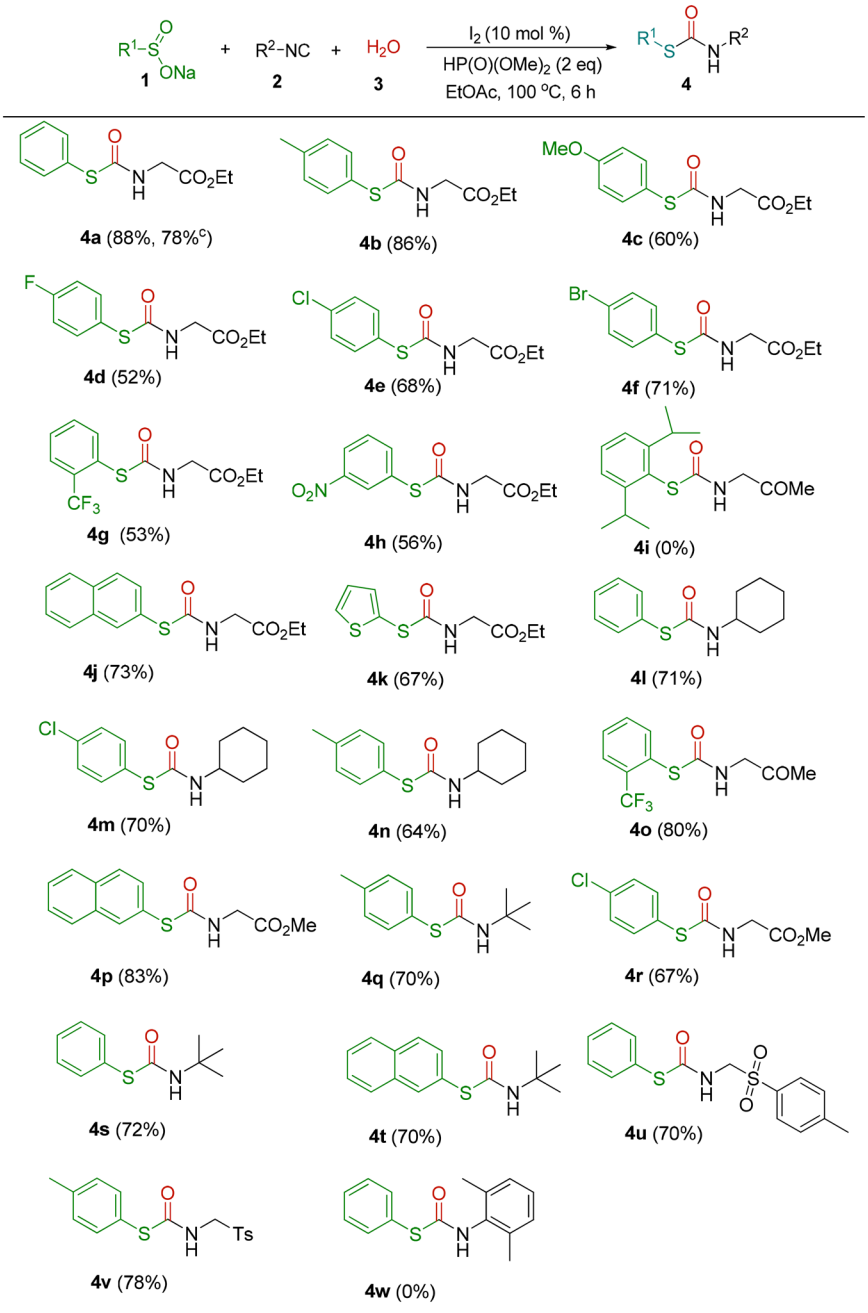
Table 2. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.6 mmol), I_2 (10 mol %), $HP(O)(OMe)_2$ (0.4 mmol), EtOAc (1.5 mL), air, 100 °C, 6 h. [b]Isolated yields based on **1**. [c]**1** (2 mmol), **2** (4 mmol), **3** (6 mmol).

conducted under N_2, the reaction was dramatically inhibited and only 9% yield of the desired product **4a** was isolated, which suggested air (oxygen) is necessary for this reaction (Scheme 2, (f)).

Based on the above experiments and previous related reports,[15−17,20−22] the possible reaction pathway is described in Scheme 3. Initially, sodium sulfinate **1** was converted into sulfenyl iodide **5** by a combination of I_2−$HP(O)(OMe)_2$.[20,22] Subsequently, sulfenyl iodide **5** might undergo homolytic cleavage to form sulfenyl radical **6** andiodine radical.[22,25] Then, the addition of sulfenyl radical **6** to isocyanide **2** produced C-radical intermediate **7**.[14,16,17] The interaction of C-radical intermediate **7** with iodine radical gave intermediate **8**, which was attacked by water leading to the desired product **4** with the release of HI.[16,26] Finally, the generated HI would be oxidized by air (O_2) into I_2 to complete the catalytic cycle.[27]

In summary, we have developed a facile and efficient metal-free protocol for the preparation of thiocarbamates from sodium sulfinates, isocyanides, and water. Control experiments suggest that the present transformation proceeds via a radical process. The present protocol opens up a new door to construct various thiocarbamates by using stable and odorless

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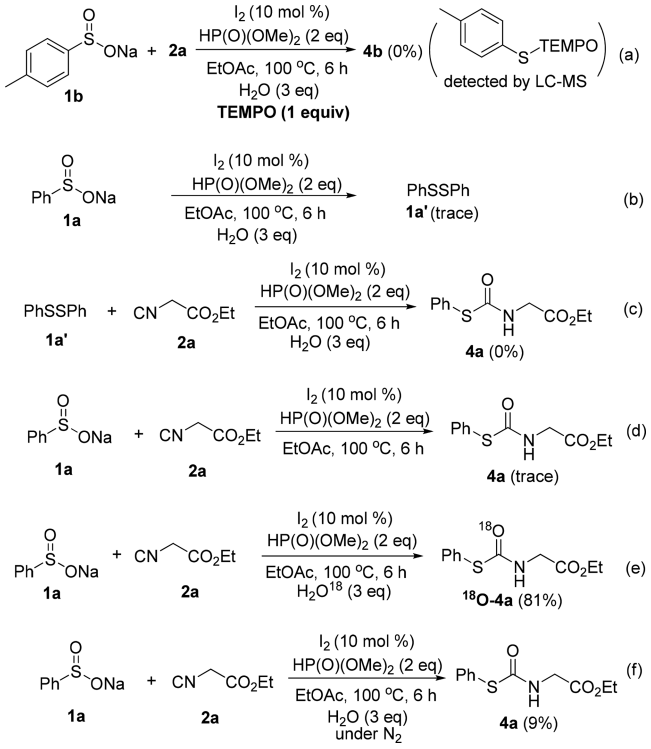
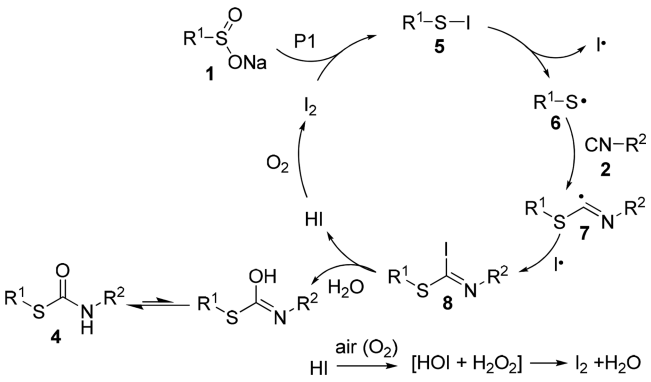
Scheme 2. Control Experiments



Scheme 3. Possible Reaction Pathway



sodium sulfinates as the sulfur source, in which molecular iodine and $HP(O)(OMe)_2$ was simply employed as the catalyst and reducing agent, respectively.

EXPERIMENTAL SECTION

General Information. All commercially available reagent-grade chemicals were purchased from Aldrich, Acros, Alfa Aesar, and Energy Chemical Co. and used as received without further purification unless otherwise stated. ^1H NMR and $^{13}C\{1H\}$ NMR were recorded in $CDCl_3$ on a Bruker Avance III spectrometer with TMS as internal standard (500 MHz ^1H, 125 MHz ^{13}C) at room temperature, the chemical shifts (δ) were expressed in ppm, and J values were given in Hz. The following abbreviations are used to indicate the multiplicity: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m). Mass analyses and HRMS were obtained on a Finnigan-LCQDECA mass spectrometer and a Bruker Daltonics Bio-TOF-Q mass spectrometer by the ESI method, respectively. Column chromatography was performed on silica gel (200−300 mesh).

General Experimental Procedure. In a tube (25 mL), sodium sulfinate **1** (0.2 mmol), isocyanide **2** (0.4 mmol), H_2O **3** (0.6 mmol, 10.8 μL), I_2 (0.02 mmol, 5 mg), $HP(O)(OMe)_2$ (0.4 mmol, 36.7 μL), and EtOAc(1.5 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, 3 mL of water was added to the reaction system. The mixture was extracted by ethyl acetate. The combined organic layers were concentrated under reduced pressure, and the crude mixtures were purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired product **4**.

Experimental Procedure for Model Reaction (2 mmol). In a tube (50 mL), sodium benzenesulfinate **1** (2 mmol), ethyl 2-isocyanoacetate **2** (4 mmol), H_2O **3** (6 mmol, 108 μL), I_2 (0.2 mmol, 50 mg), $HP(O)(OMe)_2$ (4 mmol, 367 μL), and EtOAc (10 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, 5 mL of water was added to the reaction system. The mixture was extracted by ethyl acetate. The combined organic layers were concentrated under reduced pressure, and the crude mixtures were purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent (PE/EtOAc = 5:1) to give the desired product **4a** in 78% yield (0.37g).

Radical-Trapping Experiment with TEMPO. In a tube (25 mL), sodium 4-methylbenzenesulfinate **1a** (35.6 mg), ethyl 2-isocyanoacetate **2a** (43.5 μL), H_2O **3** (0.6 mmol, 10.8 μL), I_2 (0.02 mmol, 5 mg), $HP(O)(OMe)_2$ (0.4 mmol, 36.7 μL), TEMPO (31.2 mg), and EtOAc(1.5 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, none of the desired product **4b** was detected and TEMPO-trapped thiyl radical complex (p-MePhS−TEMPO) was detected by LC−MS experiment (see the Supporting Information).

Reaction of PhSSPh with Isocyanide under Standard Conditions. In a tube (25 mL), PhSSPh **1a'**(43.6 mg), ethyl 2-isocyanoacetate **2a**(43.5 μL), H_2O **3** (0.6 mmol, 10.8 μL), I_2 (0.02 mmol, 5 mg), $HP(O)(OMe)_2$ (0.4 mmol, 36.7 μL), and EtOAc(1.5 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, none of the desired product **4a** was detected.

The model reaction was carried out in the absence of water. In a tube (25 mL), sodium 4-methylbenzenesulfinate **1a** (35.6 mg), ethyl 2-isocyanoacetate **2a** (43.5 μL), 4 Å molecular sieves (20 mg), I_2 (0.02 mmol, 5 mg), $HP(O)(OMe)_2$ (0.4 mmol, 36.7 μL), and EtOAc (1.5 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, only a trace amount of the desired product **4a** was detected.

Isotope Labeling Experiment Using $H_2{}^{18}O$. In a tube (25 mL), sodium 4-methylbenzenesulfinate **1a** (35.6 mg), ethyl 2-isocyanoacetate **2a** (43.5 μL), H_2O^{18} (0.6 mmol, 12 μL), I_2 (0.02 mmol, 5 mg), $HP(O)(OMe)_2$ (0.4 mmol, 36.7 μL), and EtOAc (1.5 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, the desired product O^{18}-**4a** was obtained in 81% yield (38.7 mg).

The model reaction was carried out under N_2. In a tube (25 mL), sodium 4-methylbenzenesulfinate **1a** (35.6 mg), ethyl 2-isocyanoacetate **2a** (43.5 μL), H_2O **3** (0.6 mmol, 10.8 μL), I_2 (0.02 mmol, 5 mg), $HP(O)(OMe)_2$ (0.4 mmol, 36.7 μL), and EtOAc (1.5 mL) were added. Then the tube was sealed, and the reaction vessel was allowed to stir at 100 °C (oil bath) for 6 h. After completion of the reaction, 3 mL of water was added to the reaction system. The mixture was extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure and the crude mixtures were purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate (PE/EtOAc = 5:1) as eluent to give the desired product **4a** in 9% yield (4.3 mg).

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Ethyl 2-(Phenylthiocarbonylamino)acetate. Compound **4a** was obtained in 88% yield (42.1 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 101.2−101.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61−7.59 (m, 2H), 7.47−7.42 (m, 3H), 6.00 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 4.04 (d, J = 5.1 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.3, 166.9, 135.6, 130.0, 129.6, 128.0, 61.7, 42.7, 14.1; HRMS calcd for $C_{11}H_{14}NO_3S$ $(M + H)^+$ 240.0694, found 240.0697.

Ethyl 2-(p-Tolylthiocarbonylamino)acetate. Compound **4b** was obtained in 86% yield (43.5 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 72.8−73.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 5.96 (s, 1H), 4.18 (d, J = 7.1 Hz, 2H), 4.01 (d, J = 5.2 Hz, 2H), 2.38 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.3, 167.4, 140.4, 135.6, 130.4, 124.5, 61.7, 42.7, 21.4, 14.1; HRMS calcd for $C_{12}H_{16}NO_3S$ $(M + H)^+$ 254.0851, found 254.0852.

Ethyl 2-((4-Methoxyphenylthio)carbonylamino)acetate. Compound **4c** was obtained in 58% yield (31.2 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 60.2−61.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 6.96−6.93 (d, J = 8.6 Hz, 2H), 5.91 (s, 1H), 4.19 (m, J = 7.1 Hz, 2H), 4.01 (d, J = 5.1 Hz, 2H), 3.83 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.3, 167.8, 161.1, 137.4, 118.6, 115.2, 61.7, 55.4, 42.6, 14.1; HRMS calcd for $C_{12}H_{16}NO_4S$ $(M + H)^+$ 270.0800, found 270.0803.

Ethyl 2-((4-Fluorophenylthio)carbonylamino)acetate,. Compound **4d** was obtained in 52% yield (26.7 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 79.7−80.9 °C, ^{1}H NMR (500 MHz, $CDCl_3$) 7.57−7.52 (m, 2H), 7.14−7.07 (m, 2H), 5.92 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.04 (d, J = 5.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.3, 166.5, 163.7 (d, J = 248.8 Hz), 137.7 (d, J = 8.8 Hz), 123.2, 116.7 (d, J = 21.3 Hz), 61.8, 42.8, 14.1; HRMS calcd for $C_{11}H_{13}FNO_3S$ $(M + H)^+$ 258.0600, found 258.0603.

Ethyl 2-((4-Chlorophenylthio)carbonylamino)acetate. Compound **4e** was obtained in 68% yield (37.1 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 86.0−86.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 5.98 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 4.04 (d, J = 5.1 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.2, 166.0, 136.7, 136.3, 129.6, 126.4, 61.8, 42.8, 14.1; HRMS calcd for $C_{11}H_{13}ClNO_3S$ $(M + H)^+$ 274.0305, found 274.0309.

Ethyl 2-((4-Bromophenylthio)carbonylamino)acetate. Compound **4f** was obtained in 71% yield (44.9 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 67.6−68.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 6.02 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.04 (d, J = 5.1 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.3, 165.9, 136.9, 132.6, 127.0, 124.5, 61.8, 42.8, 14.1; HRMS calcd for $C_{11}H_{13}BrNO_3S$ $(M + H)^+$ 317.9800, found 317.9801.

Ethyl 2-((2-(Trifluoromethyl)phenylthio)carbonylamino)acetate. Compound **4g** was obtained in 53% yield (32.5 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 83.4−84.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−7.75 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 6.04 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.05 (d, J = 5.1 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.2, 165.1, 139.9, 133.8 (q, J = 30.0 Hz), 132.4, 130.1, 127.1 (q, J = 5.5 Hz), 126.5, 121.06 (q, J = 272.5 Hz), 61.9, 42.9, 14.1; HRMS calcd for $C_{12}H_{13}F_3NO_3S$ $(M + H)^+$ 308.0568, found 308.0571.

Ethyl 2-((3-Nitrophenylthio)carbonylamino)acetate. Compound **4h** was obtained in 56% yield (31.8 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 6.15 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.09 (d, J = 5.1 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.1, 164.5, 148.3, 141.0, 130.3, 129.8, 124.2, 62.0, 43.0, 14.1; HRMS calcd for $C_{11}H_{13}N_2O_5S$ $(M + H)^+$ 285.0545, found 285.0547.

Ethyl 2-((Naphthalen-2-ylthio)carbonylamino)acetate. Compound **4j** was obtained in 73% yield (42.2 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 104.8−106.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.87−7.83 (m, 3H), 7.61−7.60 (m, 1H), 7.55−7.49 (m, 2H), 6.05 (s, 1H), 4.19−4.11 (m, 2H), 4.00 (d, J = 5.2 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.3, 167.0, 135.6, 133.6, 133.5, 131.7, 129.3, 128.1, 127.8, 127.5, 126.8, 125.2, 61.7, 42.7, 14.1; HRMS calcd for $C_{15}H_{16}NO_3S$ $(M + H)^+$ 290.0851, found 290.0855.

Ethyl 2-((Thiophene-2-ylthio)carbonylamino)acetate. Compound **4k** was obtained in 67% yield (31.5 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 7:1): white solid; mp = 64.1−64.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61−7.59 (m, 1H), 7.35−7.33 (m, 1H), 7.15−7.12 (m, 1H), 6.04 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.02 (d, J = 5.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.1, 166.4, 137.9, 133.4, 128.5, 125.6, 61.8, 42.7, 14.1; HRMS calcd for $C_9H_{12}NO_3S_2$ $(M + H)^+$ 246.0259, found 246.0263.

S-Phenyl Cyclohexylcarbamothioate. Compound **4l** was obtained in 71% yield (33.4 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 7:1): white solid; mp = 56.6−57.8 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.21 (d, J = 7.4 Hz, 1H), 7.45−7.42 (m, 2H), 7.40−7.38 (m, 3H), 3.51−3.49 (m, 1H), 1.69−1.66 (m, 2H), 1.55−1.53 (m, 1H), 1.26−1.17 (m, 4H), 1.13−1.07 (m, 1H); ^{13}C{1H} NMR (125 MHz, DMSO) δ 162.9, 135.4, 129.5, 129.3, 129.1, 50.8, 32.8, 25.5, 25.0; HRMS calcd for $C_{13}H_{18}NOS$ $(M + H)^+$ 236.1109, found 236.1112.

S-4-Chlorophenyl Cyclohexylcarbamothioate. Compound **4m** was obtained in 70% yield (37.7 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 7:1): white solid; mp = 60.0−61.8 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.29 (d, J = 7.4 Hz, 1H), 7.45 (s, 4H), 3.51−3.50 (m, 1H), 1.78−1.76 (m, 2H), 1.69−1.66 (m, 2H), 1.55−1.53 (m, 1H), 1.27−1.18 (m, 4H), 1.13−1.08 (m, 1H); ^{13}C{1H} NMR (125 MHz, DMSO) δ 162.4, 137.0, 134.1, 129.3, 128.6, 50.9, 32.8, 25.5, 25.0; HRMS calcd for $C_{13}H_{17}ClNOS$ $(M + H)^+$ 270.0719, found 270.0721.

S-p-Tolyl Cyclohexylcarbamothioate. Compound **4n** was obtained in 64% yield (31.9 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 7:1): white solid; mp = 61.6−62.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 5.28 (s, 1H), 3.73−3.71 (m, 1H), 2.37 (s, 3H), 1.88−1.86 (m, 2H), 1.63−1.54 (m, 3H), 1.35−1.26 (m, 2H), 1.16−1.05 (m, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 165.5, 139.9, 135.4, 130.3, 125.4, 50.4, 32.9, 25.4, 24.6, 21.3; HRMS calcd for $C_{14}H_{20}NOS$ $(M + H)^+$ 250.1266, found 250.1267.

S-2-(Trifluoromethyl)phenyl 2-Oxopropylcarbamothioate. Compound **4o** was obtained in 80% yield (44.3 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 121.5−122.1 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 5.94 (s, 1H), 4.07 (d, J = 5.1 Hz, 2H), 3.77 (s, 3H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 169.6, 165.2, 139.9, 133.7, 133.5 (d, J = 12.5 Hz), 132.4, 130.1, 127.2 (q, J = 6.3 Hz), 123.2 (d, J = 272.5 Hz), 52.6, 42.8; HRMS calcd for $C_{11}H_{11}F_3NO_2S$ $(M + H)^+$ 278.0463, found 278.0465.

Methyl 2-((Naphthalen-2-ylthio)carbonylamino)acetate. Compound **4p** was obtained in 83% yield (45.7 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 102.7−103.2 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.81 (t, J = 5.8 Hz, 1H), 8.12 (s, 1H), 7.97−7.93 (m, 3H), 7.61−7.55 (m, 2H), 7.54−7.52 (m, 1H), 3.95 (d, J = 5.9 Hz, 2H), 3.65 (s, 3H); ^{13}C{1H} NMR (125 MHz, DMSO) δ 170.3, 165.7, 134.9, 133.5, 133.1, 132.3, 128.8, 128.2, 128.1, 127.6, 127.1, 126.2, 52.3, 42.7; HRMS calcd for $C_{14}H_{14}NO_3S$ $(M + H)^+$ 276.0694, found 276.0697.

S-p-Tolyl tert-Butylcarbamothioate. Compound **4q** was obtained in 70% yield (31.2 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 119.0−119.6 °C;, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.1 Hz, 2H), 7.20 (d, J =

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8.1 Hz, 2H), 5.19 (s, 1H), 2.36 (s, 3H), 1.31 (s, 9H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.5, 139.7, 135.4, 130.1, 125.7, 53.4, 28.8, 21.3; HRMS calcd for $C_{12}H_{18}NOS$ $(M + H)^+$ 224.1109, found 224.1113.

Methyl 2-((4-Chlorophenylthio)carbonylamino)acetate. Compound **4r** was obtained in 67% yield (34.7 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 98.6−99.9 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 5.97 (s, 1H), 4.06 (d, J = 5.2 Hz, 2H), 3.76 (s, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.7, 166.1, 136.7, 136.3, 129.7, 126.3, 52.6, 42.6; HRMS calcd for $C_{10}H_{11}ClNO_3S$ $(M + H)^+$ 260.0148, found 260.0151.

S-Phenyl tert-Butylcarbamothioate. Compound **4s** was obtained in 72% yield (30.1 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 10:1): white solid; mp = 110.3−110.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58−7.50 (m, 2H), 7.43−7.36 (m, 3H), 5.22 (s, 1H), 1.32 (s, 9H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.0, 135.4, 129.3, 129.3, 129.1, 53.5, 28.9; HRMS calcd for $C_{11}H_{16}NOS$ $(M + H)^+$ 210.0953, found 210.0955.

S-Naphthalen-2-yl tert-Butylcarbamothioate. Compound **4t** was obtained in 70% yield (36.3 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 10:1): white solid; mp = 110.3−110.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.90−7.77 (m, 3H), 7.58−7.56 (m, 1H), 7.54−7.47 (m, 2H), 5.27 (s, 1H), 1.33 (s, 9H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.1, 135.2, 133.6, 133.3, 131.8, 128.9, 128.0, 127.8, 127.2, 126.6, 126.4, 53.6, 28.9; HRMS calcd for $C_{15}H_{18}NOS$ $(M + H)^+$,260.1109, found 260.1106.

S-Phenyl Tosylmethylcarbamothioate. Compound **4u** was obtained in 70% yield (44.9 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 10:1): white solid; mp = 98.2−98.9 °C; ^1H NMR (500 MHz, $CDCl_3$): ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.42−7.36 (m, 6H), 6.35 (t, J = 6.3 Hz, 1H), 4.62 (d, J = 6.7 Hz, 2H), 2.45 (s, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.6, 145.7, 135.4, 133.6, 130.2, 130.1, 129.6, 129.0, 126.9, 61.3, 21.8; HRMS calcd for $C_{15}H_{16}NO_3S_2$ $(M + H)^+$ 322.0572, found 322.0575.

S-p-Tolyl Tosylmethylcarbamothioate. Compound **4v** was obtained in 78% yield (52.3 mg) according to the general procedure (0.2 mmol, eluent: PE/EtOAc = 5:1): white solid; mp = 91.3−92.4 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.06 (t, J = 6.3 Hz, 1H), 4.59 (d, J = 6.7 Hz, 2H), 2.47 (s, 3H), 2.38 (s, 3H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.0, 145.7, 141.0, 135.5, 133.5, 130.6, 130.1, 129.0, 61.1, 21.6, 21.4; HRMS calcd for $C_{16}H_{18}NO_3S_2$ $(M + H)^+$ 336.0728, found 336.0731.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02844.

^1H and $^{13}C\{^1H\}$NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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