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Amino Catalytic Oxidative Thioesterification Approach to α-Ketothioesters

Nagaraju Mupparapu,[†,‡] Manoj Khushwaha,[§] Ajai Prakash Gupta,[§] Parvindar Pal Singh,[†] and Qazi Naveed Ahmed*[,†,‡]

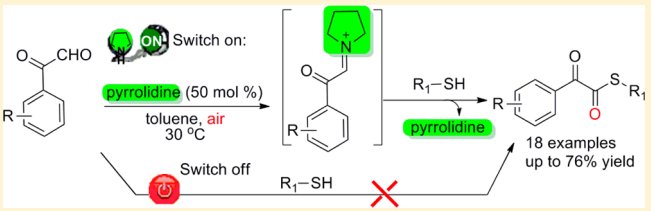
[†]Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-18001, India

[‡]Academy of Scientific and Innovative Research, Canal Road, Jammu-18001, India

[§]Quality Control and Quality Assurance, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-18001, India

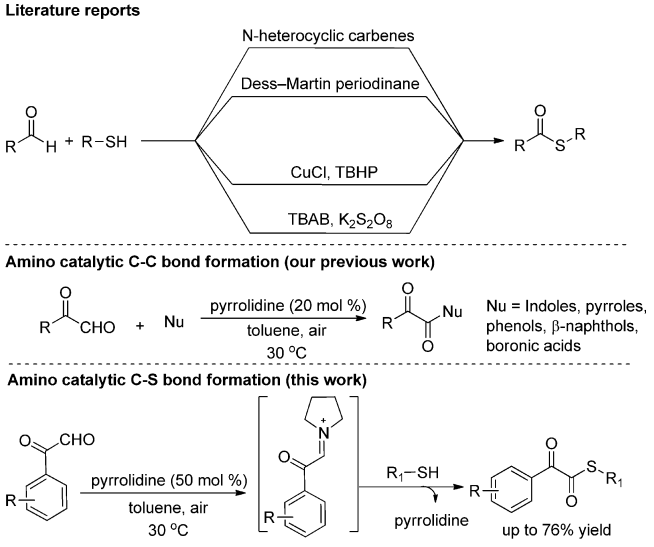
Supporting Information

ABSTRACT: An efficient metal-free method for the synthesis of α-ketothioesters is described for the first time. This reaction features the ability of pyrrolidine to fine-tune the reaction between 2-oxoaldehyde and thiols through iminium to the desired product in moderate to good yields. As an advantage, no external oxidants or metal catalysts are required in our method. Reactions performed under modified conditions lead to an apparent balance in reactivity of secondary amine and thiols toward 2-oxoaldehydes.



Thioesters are known for their important roles in various biological processes.[1] In addition, they act as versatile building blocks for the construction of various natural products.[2] Consequently, a good number of methods for the creation of this important component have been established (literature reports, Scheme 1).[3−8] Among these approaches, the oxidative thioesterification of aldehydes is not as commonly practiced as one might anticipate. To the best of our knowledge, there is no mild method reported to date on direct oxidative thioesterifications of 2-oxoaldehydes with thiols. As part of our continued interest in metal-free, amine-catalyzed oxidative coupling reactions,[9] we wished to develop a handy protocol to accomplish 2-oxothioesters from 2-oxoaldehydes. This could be established by fine-tuning the reactivity of thiols with secondary amines against 2-oxoaldehydes. Despite the competitive nature of amine and thiols toward nucleophilic addition reactions, we established an appropriate protocol that generated the oxidative coupled product in predominant quantity (Scheme 1).

Scheme 1. Summary of This Work



According to earlier work reported on an aminocatalytic cross-coupling approach to different C−C bonds, we performed a reaction between 4-methylphenylglyoxal (**1i**) and cyclohexanethiol (**3a**) in the presence of 20 mol % pyrrolidine (**2a**) in toluene at 80 °C. However, we failed to isolate α-ketothioesters **4i**, but instead, compound 2-(cyclohexylthio)-2-hydroxy-1-(*p*-tolyl)ethanone **5a** was obtained in 70% yield (Table 1, entry 1). The reason behind this was probably the predominant nucleophilc character of thiols over pyrrolidine. When the same reaction was run at different temperatures (entries 2−5), we successfully isolated **4i** in 35% yield when performed at 30 °C for 24 h (entry 5). This result encouraged us to further optimization reaction conditions to generate the desired product **4i** in maximum yield and avoid generation of **5a** and 1,2-dicyclohexyldisulfane as side products. In this direction, we performed different reactions with varied concentrations of pyrrolidine **3a** (entries 5−7). To our delight, we isolated the desired product in 76% yield when conducted with 50 mol % of pyrrolidine **3a**. This perhaps was the best conditions established for generation of 2-oxothioesters from 2-oxoaldehyde. Luckily, in each case, we did not observe α-

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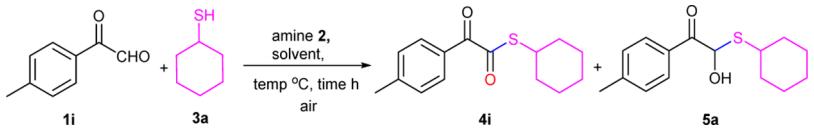
Table 1. Optimization for Oxidative Thioesterification of α-Ketoaldehydes[a]



1i 3a 4i 5a

entry	amine **2** (mol %)	solvent	temp (°C)	time (h)	yield **4i**/**5a** (%)[b]
1	pyrrolidine (20)	toluene	80	1	0/70
2	〃	〃	60	1.5	20/65
3	〃	〃	40	1.5	25/50
4	〃	〃	0	1.5	5/75
5	pyrrolidine (20)	〃	30	1.5	35/45
6	pyrrolidine (40)	〃	30	1.5	46/30
7	**pyrrolidine (50)**	〃	**30**	**1.5**	**76/15**
8	morpholine (50)	〃	30	1.5	10/80
9	piperidine (50)	〃	30	1.5	0/80
10	diethylamine (50)	〃	30	1.5	0/65
11	pyrrolidine (50)	DMSO	30	1.5	0/75
12	〃	MeOH	30	1.5	0/75
13	〃	MeCN	30	1.5	0/75
14	〃	THF	30	1.5	0/80

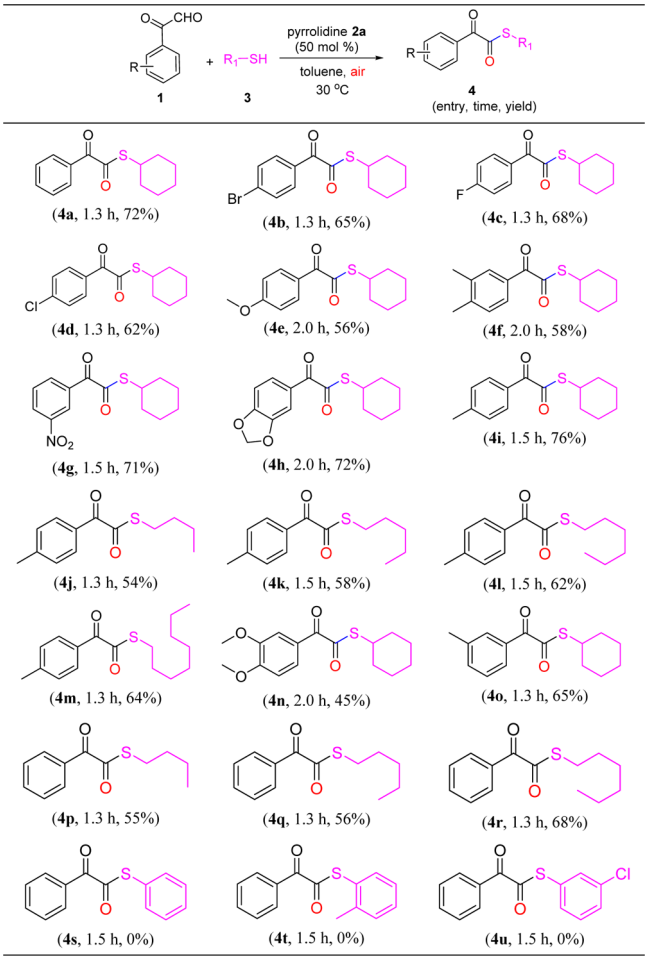
[a]Reaction conditions: 4-methylphenylglyoxal **1i** (0.592 mmol), cyclohexanethiol **3a** (0.888 mmol), and pyrrolidine **2a** (50 mol %) in toluene at 30 °C. [b]Isolated yields.

ketoamides as side product. As expected, the generation of the desired product in good yields is perhaps due to the increase in concentration of 2-oxoiminium. The same reactions, when tested with other amines, failed to generate the desired product in good yields (entries 8−10). Next, the same reaction when repeated in different solvent systems such as THF, MeOH, MeCN, and DMSO generated exclusively **5a** (entries 11−14). All of these observations revealed that reaction between 4-methylphenylglyoxal **1i** and cyclohexanethiol **3a** in the presence of pyrrolidine **2a** at 50 mol % in toluene at 30 °C are the best conditions for preparation of 2-oxothioesters **4i**.

Using the optimized conditions, we established the substrate scope of amino catalytic oxidative thioesterification. Reactions between different substituted arylglyoxals **1** and thiols **3** were carried out, and these results are summarized in Table 2. Primarily, different reactions were tested between aryl glyoxals **1** and cyclohexanethiol **3a** (entries **4a**−**4i**). Despite differences in substitution and variations in electronic nature, we successfully isolated the desired product in up to 76% yield. In parallel, we performed reactions between 2-oxo-2-(p-tolyl)acetaldehyde **1i** and various aliphatic thiols **3**. As evident, reactions with aliphatic thiols generated the desired product in good yields (entries **4i**−**4m**). In addition, different reactions were tested to cheek the general substrate scope of our reaction (entries **4n**−**4u**). Overall, we observed that our reaction has wide substrate scope. However, reactions with different thiophenols failed to produce the desired product (entries **4s**−**4u**). The reason behind this was the generation of dimerized product **8** in a pyrrolidine environment.

In order to better understand the possible reaction mechanism for the oxidative thioesterification of 2-oxoaldehyde, several controlled reactions were conducted (Figure 1). As anticipated, reaction between 2-oxo-2-(*p*-tolyl)acetaldehyde **1i** and cyclohexanethiol **3a** in the absence of pyrrolidine **2a** under standard reaction conditions failed to produce the desired product (experiment 1). This clearly indicates the importance of pyrrolidine **2a** as catalyst to generate the desired product through the 2-oxoiminium intermediate. Further, a

Table 2. Substrate Scope for Oxidative Thioesterification of α-Ketoaldehydes[a,b]



1 3 4
(entry, time, yield)

(**4a**, 1.3 h, 72%) (**4b**, 1.3 h, 65%) (**4c**, 1.3 h, 68%)
(**4d**, 1.3 h, 62%) (**4e**, 2.0 h, 56%) (**4f**, 2.0 h, 58%)
(**4g**, 1.5 h, 71%) (**4h**, 2.0 h, 72%) (**4i**, 1.5 h, 76%)
(**4j**, 1.3 h, 54%) (**4k**, 1.5 h, 58%) (**4l**, 1.5 h, 62%)
(**4m**, 1.3 h, 64%) (**4n**, 2.0 h, 45%) (**4o**, 1.3 h, 65%)
(**4p**, 1.3 h, 55%) (**4q**, 1.3 h, 56%) (**4r**, 1.3 h, 68%)
(**4s**, 1.5 h, 0%) (**4t**, 1.5 h, 0%) (**4u**, 1.5 h, 0%)

[a]Reaction conditions: Arylglyoxal **1** (0.592 mmol), thiol **3** (0.888 mmol), and pyrrolidine **2a** (50 mol %) in toluene at 30 °C. [b]Isolated yields.

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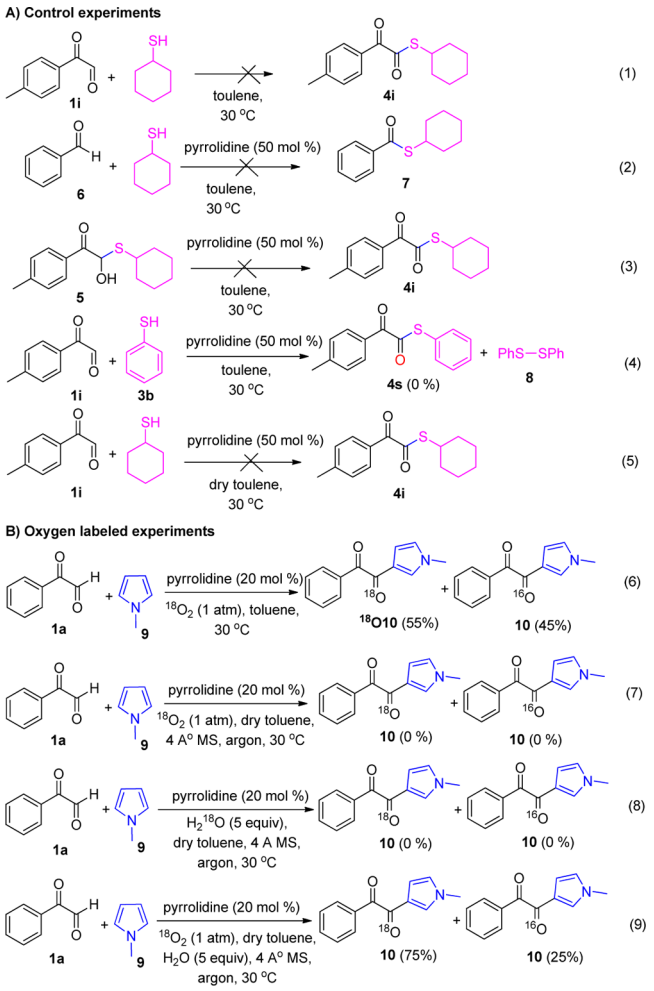

Figure 1. Control experiments and ^{18}O labeling experiments.

reaction between benzaldehyde **6** and cyclohexanethiol **3a** under standard condition also failed to produce thioester **7** (experiment 2). This result clearly demonstrates that the α-carbonyl group of 2-oxoaldehyde plays the crucial role as a directing group to facilitate this chemical reaction. Meanwhile, the absence of the desired product **4i** on reaction of hydroxyl compound **5** with 50 mol % pyrrolidine in toluene at 30 °C ruled out the role of **5** as intermediate in our reaction (experiment 3). As depicted in experiment 4 and Table 2, entries **4s**–**4u**, it is quite evident that, under a basic environment, aromatic thiols undergo dimerization and hence fail to generate thioesters. In experiment 5, the absence of the desired product under dry conditions undoubtedly highlighted the role of water in our reaction. In addition to control experiments, we performed oxygen labeled experiments. Thioesters as expected are labile structures and were successfully traced on an LC-MS instrument using APCI (atmospheric pressure chemical ionization) mode only. However, for carrying out the detailed LC analysis, we had to monitor our reaction system using LC-ESI-MS mode. For this, we preferred to test labeled experiments using *N*-methylpyrrole **9** as nucleophile (Figure 1). This could help us to validate in general the mechanism of our aminocatalytic cross-coupling reactions.[9a] In experiment 6, reaction was performed between **1a** and **9** under a labeled oxygen atmosphere in normal toluene (Supporting Information, page S3). In this case, we could easily trace the mass of ^{18}O labeled diketone product **10**. This clearly justifies the incorporation of C_1-oxygen in the product from air. The same reaction, when tried under argon in dry toluene with molecular sieves, failed to produce the desired product (experiment 7). In addition, the desired product **10** was not observed when our reaction was tested in the presence of $H_2{}^{18}O$ under an argon atmosphere in dry toluene (experiment 8). Experiments 7 and 8 obviously validate the role of moisture in promoting the reaction. Finally, we carried out a reaction between **1a** and **9** and 5 equiv of water under a labeled oxygen atmosphere in dry toluene and a argon atmosphere (experiment 9). Here, we obtained expected results that compare with experiment 6. These results absolutely justify that C_1-oxygen comes from air; however, moisture has a predominant role in oxidative thioesterification/amino catalytic cross-coupling reaction.

On the basis of the above observations and literature precedent, a plausible reaction mechanism for the oxidative thioesterification of 2-oxoaldehydes is depicted in Figure 2.

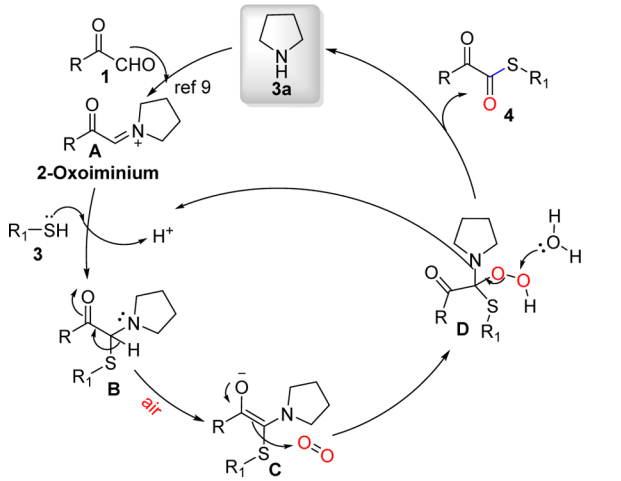

Figure 2. Plausible mechanism.

Primarily 2-oxoaldehyde reacts with pyrrolidine to form 2-oxoiminium **A**.[9] Later, thiol **3** attacks iminium intermediate **A** to generate **B**.[9a] Intermediate **B** subsequently undergoes base assisted enolization, followed by reaction with air, to form the intermediate **D**.[10] The unstable intermediate **D** generates the desired product through water assisted elimination of pyrrolidine.

In conclusion, we have developed a metal-free strategy for the oxidative thioesterification of 2-oxoaldehydes with aliphatic thiols for the first time. This method is compatible with a wide range of substrates and once again has meticulously established the strength of amino-catalytic oxidative coupling reactions toward generation of a C–S bond. In addition, we have established the mechanism of amino-catalytic cross-coupling reactions using different control experiments and oxygen labeled experiments.

EXPERIMENTAL SECTION

General Information. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates for monitoring the experiments. All chemicals used were of commercial grade and were used as such. ^1H NMR and ^{13}C NMR spectra were recorded on 500 and 400 MHz instruments. Chemical data for protons, carbons were reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton, carbon

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in the NMR solvents ($CDCl_3$: 7.26 ppm, ^{13}C NMR solvents $CDCl_3$: 77.0 ppm). The APCI-MS, ESI-MS, and LC-MS analysis were recorded on a triple-stage quadrupole mass spectrometer; the HRMS spectra were recorded as ESI-HRMS on a LC-Q-TOF (UHD) mass spectrometer. IR spectra were recorded on an FTIR spectrophotometer. Melting points were measured in a digital melting point apparatus.

General Procedure for Synthesis of α-Ketothioesters (4). A reaction vessel was charged with 2-oxoaldehyde **1** (0.592 mmol),[9b] pyrrolidine **2a** (50 mol %), and the respective thiol **3** (0.888 mmol) in 2 mL of toluene solvent. The reaction mixture was allowed to stir at room temperature (30 °C) for 2 h. After completion of the reaction, solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (100−200#) using hexane and ethyl acetate (99.5:0.5) as eluent. It afforded the corresponding product **4** in good yields (55−76%).

Analytical Data for Compound 4. *S-Cyclohexyl 2-Oxo-2-phenylethanethioate* ***4a***. Yellow gummy solid, yield: 105 mg (72%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11(d, J = 7.2 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 3.77 (m, 1H), 2.03 (m, 2H), 1.78 (m, 2H), 1.53 (m, 4H), 1.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 185.3, 133.3, 133.2, 129.29, 129.27, 127.37, 127.35, 41.2, 31.3, 24.4, 24.0; IR (CHCl3, cm-1) ν 1673, 1596; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{17}O_2S$ 249.0, found 249.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{17}O_2S$ 249.0944, found 249.0948.

S-Cyclohexyl 2-(4-Bromophenyl)-2-oxoethanethioate ***4b***. Yellow solid (mp: 80−83); yield: 124 mg (65%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 3.70 (m, 1H), 2.02−1.99 (m, 2H), 1.78−1.76 (m, 2H), 1.56−1.47 (m, 4H), 1.34−1.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 185.3, 131.97, 131.94, 130.3, 130.2, 42.5, 32.4, 25.6, 25.3. IR ($CHCl_3$, cm^{-1}) ν 1673, 1583; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}BrO_2S$ 327.0, found 327.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}BrO_2S$ 327.0049, found 327.0047.

S-Cyclohexyl 2-(4-Fluorophenyl)-2-oxoethanethioate ***4c***. Yellow gummy solid, yield: 106 mg (68%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 5.2, 7.6 Hz, 2H), 7.19 (t, J = 8.4 Hz, 2H), 3.70 (m, 1H), 2.02−1.99 (m, 2H), 1.77−1.75 (m, 2H), 1.56−1.47 (m, 4H), 1.34−1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 192.6, 184.9, 167.2, 165.7, 133.7, 133.6, 42.7, 32.7, 25.9, 25.4; IR ($CHCl_3$, cm^{-1}) ν 1679, 1597; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}FO_2S$ 267.0, found 267.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}FO_2S$ 267.0850, found 267.0852.

S-Cyclohexyl 2-(4-Chlorophenyl)-2-oxoethanethioate ***4d***. Yellow solid (mp: 73−75); yield: 103 mg (62%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 3.70 (m, 1H), 2.02−1.99 (m, 2H), 1.78−1.74 (m, 2H), 1.55−1.47 (m, 4H), 1.37−1.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 191.3, 184.2, 140.5, 131.0, 130.2, 128.1, 41.7, 31.7, 24.8, 24.0; IR (CHCl3, cm-1) ν 1674, 1587; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}ClO_2S$ 283.0, found 283.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}ClO_2S$ 283.0554, found 283.0562.

S-Cyclohexyl 2-(4-Methoxyphenyl)-2-oxoethanethioate ***4e***. Yellow gummy solid, yield: 91 mg (56%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.69−3.64 (m, 1H), 2.02−1.99 (m, 2H), 1.78−1.75 (m, 2H), 1.52−1.44 (m, 4H), 1.33−1.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 185.1, 164.9, 133.3, 124.5, 114.2, 55.6, 42.5, 32.8, 25.9, 25.9; IR ($CHCl_3$, cm^{-1}) ν 1672, 1596; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{15}H_{19}O_3S$ 279.0, found 279.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{15}H_{19}O_3S$ 279.1049, found 279.1054.

S-Cyclohexyl 2-(3,4-Dimethylphenyl)-2-oxoethanethioate ***4f***. Yellow gummy solid, yield: 93 mg (58%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 3.71 (m, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.02−2.00 (m, 2H), 1.75−1.73 (m, 2H), 1.52−1.44 (m, 4H), 1.37−1.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 186.7, 144.9, 137.3, 131.5, 130.0, 129.4, 128.6, 42.6, 32.8, 25.9, 25.4, 20.3, 19.7; IR ($CHCl_3$, cm^{-1}) ν 1664, 1599; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{16}H_{21}O_2S$ 277.0, found 277.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{16}H_{21}O_2S$ 277.1257, found 277.1262.

S-Cyclohexyl 2-(3-Nitrophenyl)-2-oxoethanethioate ***4g***. Yellow gummy solid, yield: 122 mg (71%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (m, 2H), 7.19 (t, 2H), 3.70 (m, 1H), 2.20 (m, 2H), 1.78 (m, 2H), 1.53 (m, 4H), 1.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 184.9, 167.8, 165.7, 133.72, 133.70, 133.65, 133.62, 116.26, 116.24, 116.08, 116.06, 42.7, 32.7, 25.8, 25.4; IR ($CHCl_3$, cm^{-1}) ν 1679, 1597; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}NO_4S$ 294.0, found 294.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{16}NO_4S$ 294.0795, found 294.0789.

S-Cyclohexyl 2-(Benzo[d][1,3]dioxol-5-yl)-2-oxoethanethioate ***4h***. Yellow solid (mp: 74−76); yield: 123 mg (72%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.07 (s, 2H), 3.66 (m, 1H), 2.01−1.99 (m, 2H), 1.77−1.74 (m, 2H), 1.54−1.46 (m, 4H), 1.36−1.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 184.9, 153.5, 148.4, 128.5, 126.1, 109.5, 108.3, 102.2, 42.6, 32.8, 25.9, 25.4; IR ($CHCl_3$, cm^{-1}) ν 1664, 1599; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{15}H_{17}O_4S$ 293.0, found 293.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{15}H_{17}O_4S$ 293.0842, found 293.0835.

S-Cyclohexyl 2-Oxo-2-(p-tolyl)ethanethioate ***4i***. Yellow gummy solid, yield: 116 mg (76%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.70 (m, 1H), 2.43 (s, 3H), 2.20−2.00 (m, 2H), 1.77−1.75 (m, 2H), 1.52−1.47 (m, 4H), 1.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 186.4, 146.1, 130.8, 129.5, 129.1, 42.6, 32.86, 32.82, 25.9, 25.4, 21.9; IR ($CHCl_3$, cm^{-1}) ν 1678, 1606; LC-MS (APCI) m/z $[M - H]^-$ Calcd for $C_{15}H_{19}O_2S$ 263.0, found 263.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{15}H_{19}O_2S$ 263.1100, found 263.1104.

S-Butyl 2-Oxo-2-(p-tolyl)ethanethioate ***4j***. Yellow gummy solid, yield: 75 mg (54%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.06 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.68 (m, 2H), 1.48 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 186.1, 146.1, 130.8, 129.5, 129.1, 31.1, 28.5, 22.0, 21.8, 13.5; IR (CHCl3, cm^{-1}) ν 1677, 1605; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{13}H_{17}O_2S$ 237.0, found 237.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{13}H_{17}O_2S$ 237.0944, found 237.0949.

S-Pentyl 2-Oxo-2-(p-tolyl)ethanethioate ***4k***. Yellow gummy solid, yield: 85 mg (58%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 1.72−1.65 (m, 2H), 1.43−1.33 (m, 4H), 0.93 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 186.1, 146.1, 130.8, 129.5, 129.1, 31.0, 28.85, 28.83, 22.1, 21.9, 13.9; IR ($CHCl_3$, cm^{-1}) ν 1679, 1606; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{19}O_2S$ 251.0, found 251.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{19}O_2S$ 251.1100, found 251.1112.

S-Hexyl 2-Oxo-2-(p-tolyl)ethanethioate ***4l***. Yellow gummy solid, yield: 96 mg (62%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 1.71 (m, 2H), 1.44 (m, 2H), 1.33 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 186.1, 146.1, 130.8, 129.5, 129.1, 31.2, 29.1, 28.8, 28.5, 22.5, 21.9,14.0; IR ($CHCl_3$, cm^{-1}) ν 1679, 1606; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{15}H_{21}O_2S$ 265.0, found 265.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{15}H_{21}O_2S$ 265.1257, found 265.1262.

S-Octyl 2-Oxo-2-(p-tolyl)ethanethioate ***4m***. Yellow gummy solid, yield: 110 mg (64%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 7.6 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.43 (s, 3H), 1.69 (m, 2H), 1.44 (m, 2H), 1.29 (m, 12H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 186.1, 146.1, 130.89, 130.88, 129.58, 129.56, 31.78, 31.76, 29.14, 29.12, 29.07, 29.05, 28.8, 22.64, 22.62, 14.1, 14.07, 14.06; IR ($CHCl_3$, cm^{-1}) ν 1679, 1606; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{17}H_{25}O_2S$ 293.0, found 293.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{17}H_{25}O_2S$ 293.1570, found 293.1578.

S-Cyclohexyl 2-(3,4-Dimethoxyphenyl)-2-oxoethanethioate ***4n***. Yellow gummy solid, yield: 81 mg (45%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 1.6, 6.8 Hz, 1H), 7.57 (s, 1H), 6.85 (d, J = 6.8,

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1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.62−3.58 (m, 1H), 2.08−2.05 (m, 1H), 1.95−1.93 (m, 1H), 1.71−1.69 (m, 2H), 1.49−1.40 (m, 4H), 1.29−1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 183.5, 153.2, 147.6, 125.2, 122.8, 109.9, 108.5, 54.5, 54.4, 40.9, 31.1, 24.2, 23.8; IR ($CHCl_3$, cm^{-1}) ν 1667, 1590; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{16}H_{21}O_4S$ 309.0, found 309.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{16}H_{21}O_4S$ 309.1155, found 309.1161.

S-Cyclohexyl 2-Oxo-2-(m-tolyl)ethanethioate ***4o***. Yellow gummy solid, yield: 99 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 5.6, Hz, 2H), 7.46 (d, J = 8.8 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 3.72 (m, 1H), 2.41 (s, 3H), 2.03 (m, 2H), 1.77 (m, 2H), 1.53 (m, 4H), 1.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.9, 187.1, 138.7, 135.6, 131.6, 131.0, 128.6, 128.0, 42.6, 32.8, 25.9, 25.4, 21.3; IR ($CHCl_3$, cm^{-1}) ν 1676, 1584; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{15}H_{19}O_2S$ 263.0, found 263.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{15}H_{19}O_2S$ 263.1102, found 263.1109.

S-Butyl 2-Oxo-2-phenylethanethioate ***4p***. Yellow gummy solid, yield: 72 mg (55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.6 Hz, 2H), 1.71 (m, 2H), 1.51 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 186.5, 134.8, 131.7, 130.7, 128.8, 31.2, 28.6, 22.0, 13.5; IR ($CHCl_3$, cm^{-1}) ν 1664, 1596; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{12}H_{15}O_2S$ 223.0, found 223.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{12}H_{15}O_2S$ 223.0787, found 223.0792.

S-Pentyl 2-Oxo-2-phenylethanethioate ***4q***. Yellow gummy solid, yield: 78 mg (56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 1.73 (m, 2H), 1.41 (m, 4H), 0.93 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 186.5, 134.8, 131.7, 130.7, 128.8, 31.0, 28.9, 28.8, 22.1, 13.9; IR ($CHCl_3$, cm^{-1}) ν 1672, 1593; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{13}H_{17}O_2S$ 237.0, found 237.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{13}H_{17}O_2S$ 237.0944, found 237.0952.

S-Hexyl 2-Oxo-2-phenylethanethioate ***4r***. Yellow gummy solid, yield: 99 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 1.72 (m, 2H), 1.45 (m, 2H), 1.33 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 186.5, 134.8, 131.7, 130.7, 128.8, 31.2, 29.1, 28.9, 28.5, 22.5, 14.0; IR ($CHCl_3$, cm^{-1}) ν 1675, 1596; LC-MS (APCI) m/z $[M + H]^+$ Calcd for $C_{14}H_{19}O_2S$ 251.0, found 251.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{14}H_{19}O_2S$ 251.1102, found 251.1108.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02176.

Copies of ^{1}H, ^{13}C NMR spectra, details for control experiments, and ^{18}O labeling experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: naqazi@iiim.ac.in.

Notes

The authors declare no competing financial interest.

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