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Direct synthesis of α-ketothioamides from aryl methyl ketones and amines via I_2-promoted sp^3 C–H functionalization

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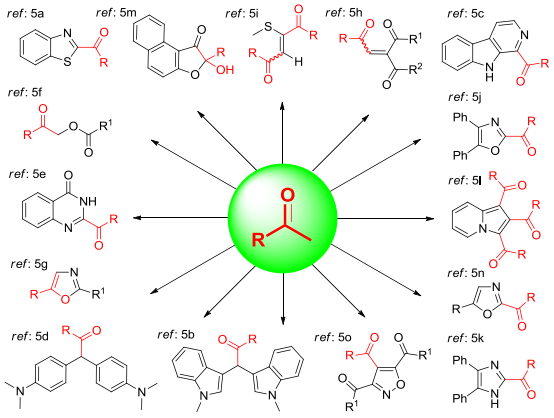
ABSTRACT

A domino reaction that involves the formation of C=S and C–N bonds in one process via sp^3 C–H functionalization strategy has been developed. This reaction affords an efficient and direct method for the synthesis of α-ketothioamides from aryl methyl ketones, amines, and sodium hydrosulfide under the promotion of iodine.

1. Introduction

As an important transformation in synthetic chemistry, C–H bond functionalization has been extensively pursued and widely examined by organic chemists.[1] In recent years, numerous methods have been established for the conversion of a C–H bond to a C–Z bond (such as C–C, C–N, and C–O), with particularly impressive results achieved through transition-metal-catalyzed strategies.[2] In addition, iodine and iodides have emerged as effective mediums to promote the C–H bond functionalization process and have been utilized in the construction of diversified molecules.[3] These methods exhibit many advantages in providing metal-free, low cost, and facile reaction conditions.[4] Due to its efficacy in realizing C–H bond functionalization, iodine has drawn general interests. In our previous work, it was discovered that acetyl compounds, such as acetophenone, could easily be activated by iodine to achieve the sp^3 C–H bond functionalization. Readily available acetophenone was therefore utilized to construct various organic scaffolds in one pot under facile conditions (Scheme 1).[5] On account of the extensive application of iodine in activating acetyl substrates to realize the sp^3 C–H bond functionalization, we tried to employ more examples to enrich this reaction system.

Thioamides are an important class of functional skeletons, which widely exist in bioactive molecules.[6] They have been used as valuable building blocks to construct sulfur-containing compounds[7] and natural products.[8] Moreover, thioamides have been applied to a wide range of fields, including organocatalysis,[9] peptide chemistry,[10] and medical chemistry.[11] So far, various methods have been reported for the synthesis of thioamides, these methods can be mainly classified into two categories according to their synthetic strategy. One cluster of methodology emphasizes the use of sulfur reagents to replace the oxygen atom of amide (Scheme 2, (A)).[12] Another cluster of methodology focuses attention on the direct synthesis of thioamides from ketone, amine, and sulfur powder (Scheme 2, (B)). Among these approaches, Willgerodt–Kindler reaction is widely accepted as the traditional choice for the transformation of acetophenone to 2-phenylacetamide.[13] More recently, researchers have shifted their



Scheme 1. The compounds derived from acetyl substrates in one pot.

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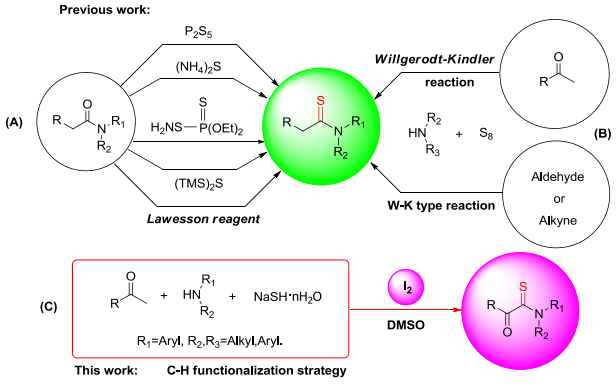


Scheme 2. Strategies for the synthesis of thioamides and α-ketothioamides.

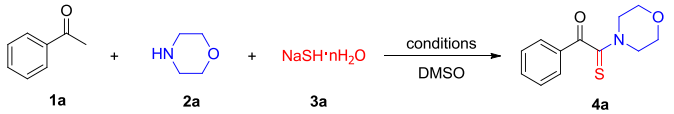
attention to wider methods based on the Willgerodt–Kindler reaction for the synthesis of thioamides and α-ketothioamides.[14] However, neither the Willgerodt–Kindler reaction nor its analogies have been able to achieve the direct and efficient conversion of acetophenone to α-ketothioamide. Herein, a highly efficient I_2-promoted sp^3 C–H functionalization strategy is reported for the direct construction of α-ketothioamides (Scheme 2, (C)).

2. Results and discussion

The reaction of acetophenone (**1a**), morpholine (**2a**) and sodium hydrosulfide (**3a**) with I_2 at 120 °C was initially selected as the model reaction for optimization of the reaction conditions. First, different solvents were screened, it was found that DMSO is the most efficient solvent for the conversion (Table 1, Entries 1–6). Higher and lower temperature were shown to decrease the yield of the desired product, 120 °C was thus selected as the optimum temperature (Table 1, Entries 7–8). The target product could not be obtained when the substrates were heated at 120 °C in the absence of I_2 (Table 1, Entry 9), which implied that I_2 played a crucial role in the reaction. To our delight, an increase in the amount of I_2 to 1.5 equiv led to the production of 2-morpholino-1-phenyl-2-thioxoethanone (**4a**) in good yield (Table 1, Entry 10). However, additional amounts of I_2 failed to promote this reaction further (Table 1, Entry 11). Next, **3a** was replaced by various sulfur reagents, such as sulfur sublimed, sulfur powder, and sodium sulfide (Table 1, Entries 12–14), but all demonstrated dissatisfying results. Sodium hydrosulfide was thus selected as the source of sulfur for this conversion. The amount of sodium hydrosulfide was subsequently investigated, where 2 equiv of $NaSH \cdot nH_2O$ were confirmed as the preferential ratio for this reaction. Following the experimental optimizations, the suitable reaction conditions were determined as acetophenone (**1a**, 1.0 mmol), morpholine (**2a**, 1.0 mmol), and $NaSH \cdot nH_2O$ (**3a**, 2.0 mmol) with I_2 (1.5 mmol) at 120 °C in the presence of DMSO (Table 1, Entry 10).

With the optimal conditions in hand, different sets of experiments were performed to investigate the scope of this protocol. As shown in Table 2, the reaction proceeded smoothly as acetophenone reacted with secondary amine (Table 2, **4a**–**d**) and aliphatic amine (Table 2, **4e**). Another set of examples were carried out between a wide range of substituted aryl methyl ketones and morpholine, where it was found that the desired products could be obtained in moderate to good yields (61–95%). It should be noted that the electron-donating substituents attached to the phenyl rings, such as *para*-Me, *para*-OMe, *meta*-OMe, and *para*-OEt exhibited good reactivity in the reaction (Table 2, **4f**–**i**). The yields showed a slight decrease while the electron-withdrawing groups, such as F and Cl, were situated at the *para*-position of the phenyl ring (**4j**–**k**). In addition, the strong electron-withdrawing group NO_2 was also unfavorable for the transformation (**4l**). However, the substitution of the benzene ring with aryls or heteroaryls, such as phenyl (**4m**), naphthyl (**4n** and **4o**), furanyl (**4p**), thiophenyl (**4q**) or benzofuryl (**4r**), was found favorable for the reaction and excellent

Table 1
Optimization of the reaction conditions[a]

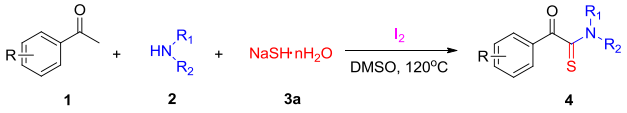


1a 2a 3a 4a

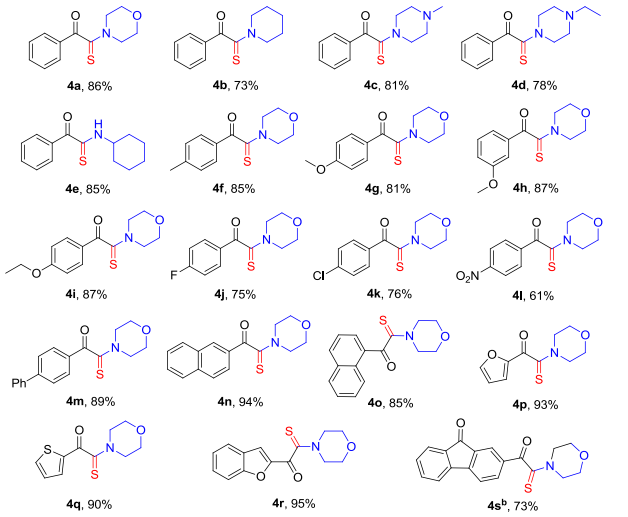
Entry	Solvent (3 mL)	I_2 (equiv)	S source (equiv)	T (°C)	Yield (%)[d]
1[a]	CH_3OH	1.0	$NaSH \cdot nH_2O$	Reflux	31
2[a]	Glycol	1.0	$NaSH \cdot nH_2O$	120	33
3[a]	CH_3CN	1.0	$NaSH \cdot nH_2O$	Reflux	—[e]
4[a]	DMF	1.0	$NaSH \cdot nH_2O$	120	35
5[a]	DMSO	1.0	$NaSH \cdot nH_2O$	120	72
6[a]	Dioxane	1.0	$NaSH \cdot nH_2O$	Reflux	—[e]
7[a]	DMSO	1.0	$NaSH \cdot nH_2O$	100	57
8[a]	DMSO	1.0	$NaSH \cdot nH_2O$	140	68
9[a]	DMSO	0	$NaSH \cdot nH_2O$	120	—[e]
10[a]	DMSO	1.5	$NaSH \cdot nH_2O$	120	**86**
11[a]	DMSO	2.0	$NaSH \cdot nH_2O$	120	78
12[a]	DMSO	1.5	S	120	<5
13[a]	DMSO	1.5	S_8	120	<5
14[a]	DMSO	1.5	$Na_2S \cdot 9H_2O$	120	46
15[b]	DMSO	1.5	$NaSH \cdot nH_2O$	120	80
16[c]	DMSO	1.5	$NaSH \cdot nH_2O$	120	84

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), and **3a** (2.0 mmol) in 3 mL solvent for 5 h.
[b] Reaction was performed with 1.0 mmol of $NaSH \cdot nH_2O$ for 5 h.
[c] Reaction was performed with 1.5 mmol $NaSH \cdot nH_2O$ for 5 h.
[d] Isolated yields.
[e] No desired product was obtained.

Table 2
Reaction scope of aryl methyl ketones and alkylamines[a]



1 2 3a 4



[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) and **3a** (2.0 mmol) with I_2 (1.5 mmol) in DMSO (3 mL) at 120°C for 5-10h.
[b] The compound **4s** was prepared from 1-(9H-fluoren-2-yl)ethanone, but the methylene was iodide by I_2 and subsequently oxidized by DMSO (see details in Supporting Information) .

reactivity was achieved. On the other hand, 1-(9*H*-fluoren-2-yl) ethanone provided the corresponding product in moderate yield (**4s**). The structure of the product was confirmed by an X-ray crystallographic study of **4q** (Fig. 1).[15]

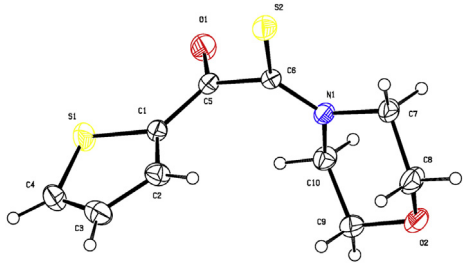
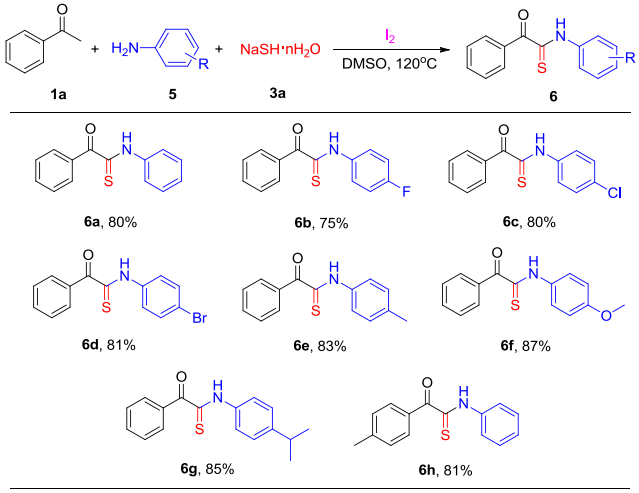


Fig. 1. X-ray crystal structure of compound **4q**.

Subsequently, various arylamines, which show weaker nucleophilicity were examined to further expand the scope of the substrates. To our delight, aniline and the anilines with electron-withdrawing substituents, such as F, Cl, and Br, proceeded smoothly (Table 3, **6a**–**d**). Furthermore, the electron-donating groups, including methyl, methoxyl, and isopropyl also furnished the corresponding products in good yields (**6e**–**g**). The structure of the target molecule was confirmed by the X-ray crystallographic analysis of **6h** (Fig. 2).[15]

Table 3
Reaction scope of arylamines[a]



[a] Reaction conditions: **1a** (1.0 mmol), **5** (1.0 mmol), and **3a** (2.0 mmol) with I_2 (1.5 mmol) in DMSO (3 mL) at 120°C for 15-20h.

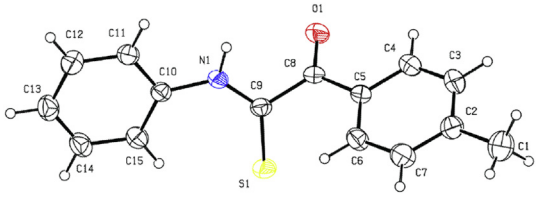
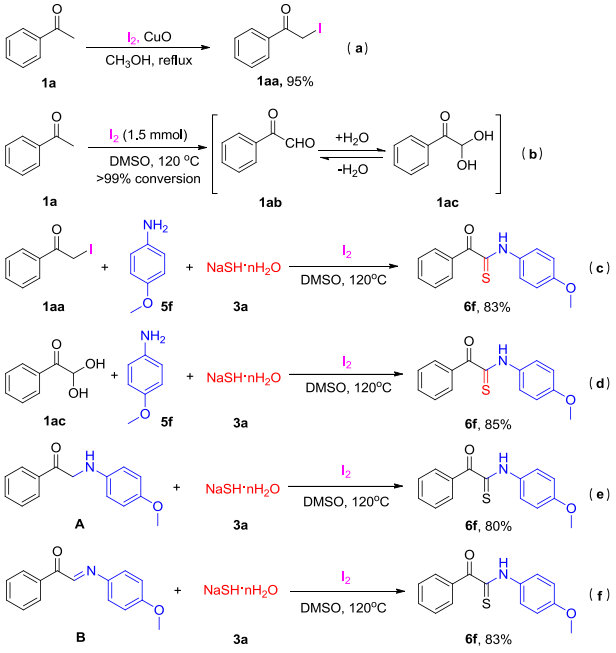


Fig. 2. X-ray crystal structure of compound **6h**.

A series of control experiments were performed to gain some insights into the reaction mechanism. Firstly, it was found that α-iodo acetophenone (**1aa**) could form in 95% yield under the I_2/CuO system (Scheme 3(a)).[16] When acetophenone was added into the I_2/DMSO, the phenylglyoxal (**1ab**) or hemiacetal (**1ac**) could be obtained in quantitative transformation (Scheme 3(b)). Then α-iodo acetophenone **1aa**, 4-methoxyaniline **5f**, and NaSH·nH$_2$O were subjected to the standard conditions for 3 h, and the desired product (**6f**) was subsequently obtained in 83% yield. This indicated that α-iodo acetophenone could be an important intermediate in this reaction (Scheme 3(c)). To our satisfaction, the use of phenylglyoxal (**1ac**) as a substitute for acetophenone led to the production of the target product in 85% yield (Scheme 3(d)). This result strongly proved that phenylglyoxal could also be a key intermediate in this reaction. Finally, 2-((4-methoxyphenyl)amino)-1-phenylethanone **A** and 2-((4-methoxyphenyl)imino)-1-phenylethanone **B** were synthesized to further study the reaction details.[17] To our surprise, both **A** and **B** could transform to **6f** in good yields under the standard conditions (Scheme 3(e), (f)). This suggest that **A** and **B** were possible key intermediates.

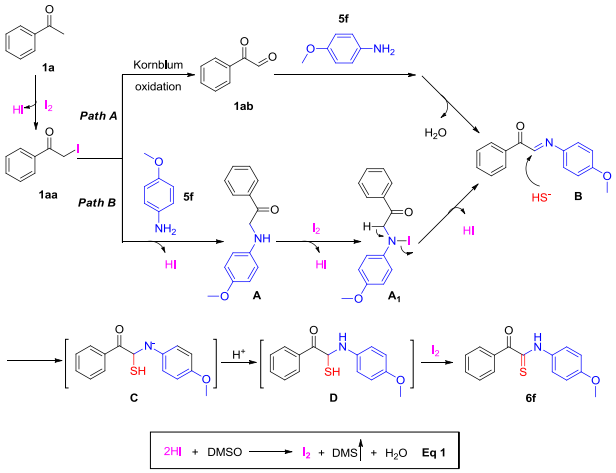


Scheme 3. Controlled experiments to prove the mechanism.

Based on the aforementioned results and our previous work,[5] a proposed reaction mechanism was presented as follows using acetophenone (**1a**) and 4-methoxyaniline (**5f**) as examples (Scheme 4). First, **1a** was substituted by iodine to afford **1aa**. The reaction subsequently underwent two possible pathways to achieve the transformation. In the main path A, **1aa** was converted into phenylglyoxal **1ab** through Kornblum Oxidation. The in situ generated **1ab** was immediately trapped by **5f** to afford imine **B**. In path B, a substitution occurred between **1aa** and **5f** to provide intermediate **A**, which was followed by iodination to afford $\mathbf{A_1}$. Next, $\mathbf{A_1}$ underwent the oxidative dehydrogenation to generate imine **B**.[18] Next, HS^- attacked intermediate **B** to afford **D** under an acid atmosphere. Finally, the target molecule **6f** was then produced from **D** via the oxidation of I_2.[19] In this process, the previously formed byproduct HI could be oxidized by DMSO to regenerate I_2 (Eq. 1).[5a,m]

3. Conclusion

In summary, an efficient I_2-promoted sp^3 C–H functionalization strategy has been developed for the direct synthesis of α-ketothioamides from readily available aryl methyl ketones and amines.



Scheme 4. The proposed mechanism for the present reaction.

This three-component reaction conveniently achieved the formation of C=S and C–N bonds through several mechanistically different reactions (iodination, nucleophilic substitution, and Kornblum Oxidation). Further applications of this I_2-promoted sp^3 C–H functionalization strategy will be reported in due course.

4. Experimental

4.1. General

All substrates and reagents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). IR spectra were recorded on a Perkin–Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H spectra were recorded in $CDCl_3$ on 400/600 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet), coupling constants (Hertz), and integration. ^{13}C spectra were recorded in $CDCl_3$ on 100 MHz NMR spectrometers and resonances (δ) are given in ppm. HRMS were obtained on an apex-Ultra MS spectrometer. MS was recorded using EI (70 eV). Melting points were determined using an electrothermal capillary melting point apparatus and not corrected. The X-ray crystal-structure determinations were obtained on a Bruker SMART APEX CCD system.

4.2. General procedure for synthesis of 4a (4a as an example)

A mixture of acetophenone **1a** (120 mg, 1.0 mmol), morpholine **2a** (87 mg, 1.0 mmol), $NaSH\cdot nH_2O$ **3a** (278 mg, 2.0 mmol), and iodine (381 mg, 1.5 mmol) in DMSO (3 mL) was stirred at 120 °C for 5 h. After disappearance of the reactant (monitored by TLC), and added 50 mL water to the mixture, then extracted with EtOAc three times (3×50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4, and evaporation. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc=8:1) to yield the desired product **4a** as a yellow solid (202.2 mg, 86% yield).

4.3. Characterization data

*4.3.1. 2-Morpholino-1-phenyl-2-thioxoethanone (**4a**).*[14b] Yield 86%; yellow solid; mp 113–116 °C; IR (KBr): 2973, 2856, 1657, 1595, 1505, 1445, 1285, 1265, 1104, 950, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.00 (d, J=8.4 Hz, 2H), 7.65–7.60 (m, 1H), 7.50 (t, J=7.8 Hz, 2H), 4.34 (t, J=4.8 Hz, 2H), 3.91 (t, J=4.8 Hz, 2H), 3.67–3.72 (m, 2H), 3.60 (t, J=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6, 187.8, 134.4, 133.2, 129.8, 128.9, 66.4, 66.3, 51.9, 47.1; MS (EI): m/z 236.13 (M+1, 5.88), 235.09 (M, 53.20), 177.12 (34.09), 150.11 (5.27), 130.05 (100.00), 105.06 (86.03).

*4.3.2. 1-Phenyl-2-(piperidin-1-yl)-2-thioxoethanone (**4b**).*[14b] Yield 73%; light yellow solid; mp 70–74 °C; IR (KBr): 2942, 2920, 2855, 1665, 1595, 1506, 1441, 1273, 1250, 1221, 1123, 1003, 805, 690, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03–7.94 (m, 2H), 7.56–7.64 (m, 1H), 7.49 (t, J=7.8 Hz, 2H), 4.25 (t, J=5.4 Hz, 2H), 3.54 (t, J=5.6 Hz, 2H), 1.88–1.70 (m, 4H), 1.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.3, 187.9, 134.1, 133.3, 129.7, 128.8, 53.0, 48.1, 26.4, 25.3, 24.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}NOS$: 234.0947; found: 234.0948.

*4.3.3. 2-(4-Methylpiperazin-1-yl)-1-phenyl-2-thioxoethanone (**4c**).* Yield 81%; yellow solid; mp 95–98 °C; IR (KBr): 2984, 2940, 2853, 2799, 2744, 1671, 1591, 1511, 1444, 1292, 1255, 1222, 1163, 1139, 1031, 994, 949, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.00–7.94 (m, 2H), 7.64–7.57 (m, 1H), 7.49 (t, J=7.8 Hz, 2H), 4.32 (t, J=4.8 Hz, 2H), 3.59 (t, J=5.0 Hz, 2H), 2.63 (t, J=5.2 Hz, 2H), 2.43 (t, J=4.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.9, 187.6, 134.1, 132.9, 129.5, 128.7, 54.3, 53.7, 51.1, 46.4, 45.3; HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{13}H_{17}N_2OS$: 249.1056; found: 249.1055.

*4.3.4. 2-(4-Ethylpiperazin-1-yl)-1-phenyl-2-thioxoethanone (**4d**).* Yield 78%; yellow solid; mp 73–76 °C; IR (KBr): 2965, 2928, 2870, 2810, 2772, 1667, 1596, 1515, 1446, 1292, 1264, 1238, 1017, 703, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01–7.94 (m, 2H), 7.65–7.57 (m, 1H), 7.49 (t, J=7.8 Hz, 2H), 4.33 (t, J=4.6 Hz, 2H), 3.60 (t, J=5.0 Hz, 2H), 2.67 (t, J=5.2 Hz, 2H), 2.53–2.41 (m, 4H), 1.10 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.8, 187.8, 134.2, 133.0, 129.6, 128.7, 52.2, 51.6(3), 51.6(1), 51.3, 46.6, 11.8; HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{14}H_{19}N_2OS$: 263.1212; found: 263.1211.

*4.3.5. N-Cyclohexyl-2-oxo-2-phenylethanethioamide (**4e**).* Yield 85%; yellow solid; mp 128–132 °C; IR (KBr): 3290, 2939, 2853, 1661, 1595, 1548, 1447, 1413, 1271, 1240, 1064, 886, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.39 (s, 1H), 7.96 (d, J=7.8 Hz, 2H), 7.55 (t, J=7.2 Hz, 1H), 7.40 (t, J=7.8 Hz, 2H), 4.50–4.40 (m, 1H), 2.15 (d, J=10.8 Hz, 2H), 1.80 (d, J=13.2 Hz, 2H), 1.69 (d, J=13.2 Hz, 1H), 1.51–1.32 (m, 4H), 1.31–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 192.7, 188.2, 133.7, 133.4, 130.4, 128.0, 53.5, 30.9, 25.2, 24.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}NOS$: 248.1104; found: 248.1102.

*4.3.6. 2-Morpholino-2-thioxo-1-(p-tolyl)ethanone (**4f**).* Yield 85%; yellow solid; mp 115–117 °C; IR (KBr): 2958, 2921, 2854, 1659, 1601, 1506, 1438, 1271, 1232, 1114, 1032, 948, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.88 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 4.32 (t, J=4.8 Hz, 2H), 3.90 (t, J=4.8 Hz, 2H), 3.68 (d, J=4.2 Hz, 2H), 3.59 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.8, 187.8, 145.6, 130.6, 129.8, 129.6, 66.4, 66.3, 51.8, 47.0, 21.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{16}NO_2S$: 250.0896; found: 250.0897.

*4.3.7. 1-(4-Methoxyphenyl)-2-morpholino-2-thioxoethanone (**4g**).*[14b] Yield 81%; yellow solid; mp 120–123 °C; IR (KBr): 3066, 2977, 2937, 2848, 1652, 1594, 1511, 1441, 1324, 1264, 1165, 1103, 1025, 938, 853, 685, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.8 Hz, 2H), 4.32 (t, J=4.8 Hz, 2H), 3.98–3.80 (m, 5H), 3.68 (s, 2H), 3.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.9, 187.1, 164.5, 132.2, 125.8, 114.2, 66.4, 66.3,

55.6, 51.8, 47.0; MS (EI): *m/z* 266.05 (M+1, 3.04), 265.02 (M, 19.61), 180.05 (1.40), 135.02 (100.00), 107.04 (5.86).

*4.3.8. 1-(3-Methoxyphenyl)-2-morpholino-2-thioxoethanone (**4h**).*[14b] Yield 87%; yellow solid; mp 86–89 °C; IR (KBr): 2973, 2924, 2862, 1659, 1601, 1583, 1509, 1438, 1292, 1268, 1113, 1026, 968, 875, 731, 526 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.58–7.49 (m, 2H), 7.39 (t, *J*=7.8 Hz, 1H), 7.16 (d, *J*=7.8 Hz, 1H), 4.36–4.28 (m, 2H), 3.93–3.87 (m, 2H), 3.85 (s, 3H), 3.68 (d, *J*=4.2 Hz, 2H), 3.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.2, 187.5, 159.8, 134.3, 129.8, 122.5, 120.9, 113.2, 66.2, 66.1, 55.3, 51.7, 46.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{16}NO_3S$: 266.0845; found: 266.0846.

*4.3.9. 1-(4-Ethoxyphenyl)-2-morpholino-2-thioxoethanone (**4i**).* Yield 87%; yellow solid; mp 131–134 °C; IR (KBr): 2976, 2901, 2856, 1649, 1600, 1571, 1504, 1261, 1236, 1170, 1114, 1034, 951, 854, 749, 661, 526 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J*=8.4 Hz, 2H), 6.94 (d, *J*=9.0 Hz, 2H), 4.32 (t, *J*=4.8 Hz, 2H), 4.14–4.08 (m, 2H), 3.89 (t, *J*=4.8 Hz, 2H), 3.68 (s, 2H), 3.59 (s, 2H), 1.44 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.1, 187.2, 164.0, 132.2, 125.6, 114.6, 66.4, 66.3, 63.9, 51.8, 47.0, 14.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{18}NO_3S$: 280.1002; found: 280.1000.

*4.3.10. 1-(4-Fluorophenyl)-2-morpholino-2-thioxoethanone (**4j**).* Yield 75%; yellow solid; mp 130–135 °C; IR (KBr): 2979, 2916, 2856, 1658, 1594, 1502, 1277, 1236, 1112, 1029, 951, 849, 744, 659, 606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.08–7.98 (m, 2H), 7.17 (t, *J*=8.6 Hz, 2H), 4.33 (t, *J*=5.0 Hz, 2H), 3.91 (t, *J*=5.0 Hz, 2H), 3.71 (t, *J*=4.8 Hz, 2H), 3.60 (t, *J*=4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.1, 186.3, 167.6, 165.1, 132.6, 132.5, 130.0, 116.3, 116.1, 66.4, 66.3, 51.9, 47.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}FNO_2S$: 254.0646; found: 254.0650.

*4.3.11. 1-(4-Chlorophenyl)-2-morpholino-2-thioxoethanone (**4k**).*[14b] Yield 76%; yellow solid; mp 137–139 °C; IR (KBr): 2966, 2921, 2854, 1660, 1584, 1500, 1266, 1234, 1112, 1029, 949, 738, 523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94 (d, *J*=8.4 Hz, 2H), 7.47 (d, *J*=8.4 Hz, 2H), 4.32 (t, *J*=4.8 Hz, 2H), 3.91 (t, *J*=4.8 Hz, 2H), 3.71 (t, *J*=4.8 Hz, 2H), 3.60 (t, *J*=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.8, 186.4, 141.0, 131.6, 131.1, 129.3, 66.5, 66.3, 51.9, 47.1; MS (EI): *m/z* 270.21 (M+1, 1.82), 269.03 (M, 34.52), 211.04 (13.43), 183.98 (5.26), 139.06 (38.43), 130.06 (100.00), 111.07 (30.19).

*4.3.12. 2-Morpholino-1-(4-nitrophenyl)-2-thioxoethanone (**4l**).* Yield 61%; yellow solid; mp 177–181 °C; IR (KBr): 2976, 2925, 2855, 2361, 1663, 1600, 1519, 1441, 1346, 1267, 1231, 1107, 1029, 951, 809, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.32 (d, *J*=8.8 Hz, 2H), 8.17 (d, *J*=8.8 Hz, 2H), 4.34 (t, *J*=4.8 Hz, 2H), 3.93 (t, *J*=5.0 Hz, 2H), 3.75 (t, *J*=4.8 Hz, 2H), 3.64 (t, *J*=4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.5, 184.4, 150.6, 138.2, 130.7, 123.9, 66.4, 66.3, 52.0, 47.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_2O_4S$: 281.0591; found: 281.0589.

*4.3.13. 1-([1,1′-Biphenyl]-4-yl)-2-morpholino-2-thioxoethanone (**4m**).* Yield 89%; yellow solid; mp 169–172 °C; IR (KBr): 2968, 2852, 1657, 1598, 1511, 1441, 1263, 1104, 1007, 944, 739, 693 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.06 (d, *J*=8.4 Hz, 2H), 7.70 (d, *J*=7.8 Hz, 2H), 7.61 (d, *J*=7.8 Hz, 2H), 7.51–7.44 (m, 2H), 7.42 (t, *J*=7.2 Hz, 1H), 4.37–4.31 (m, 2H), 3.94–3.88 (m, 2H), 3.71 (d, *J*=4.2 Hz, 2H), 3.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.6, 187.5, 147.1, 139.4, 131.9, 130.4, 129.0, 128.5, 127.5, 127.3, 66.5, 66.3, 51.9, 47.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{18}NO_2S$: 312.1053; found: 312.1053.

*4.3.14. 2-Morpholino-1-(naphthalen-2-yl)-2-thioxoethanone (**4n**).* Yield 94%; yellow solid; mp 150–154 °C; IR (KBr): 2963, 2920, 2852, 1643, 1623, 1509, 1272, 1223, 1111, 1028, 931, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.51 (s, 1H), 8.03 (d, *J*=8.4 Hz, 1H), 7.95 (d, *J*=8.4 Hz, 1H), 7.92 (d, *J*=8.4 Hz, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.66–7.60 (m, 1H), 7.59–7.53 (m, 1H), 4.42–4.42 (m, 2H), 3.93 (t, *J*=4.8 Hz, 2H), 3.68 (d, *J*=3.6 Hz, 2H), 3.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.7, 188.0, 136.1, 132.4, 132.3, 130.5, 129.7, 129.3, 128.9, 127.8, 127.1, 124.2, 66.5, 66.3, 51.9, 47.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}NO_2S$: 286.0896; found: 286.0898.

*4.3.15. 2-Morpholino-1-(naphthalen-1-yl)-2-thioxoethanone (**4o**).* Yield 85%; brown solid; mp 121–124 °C; IR (KBr): 2978, 2918, 2859, 1651, 1501, 1439, 1270, 1227, 1112, 1024, 931, 781, 500 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.20 (d, *J*=8.4 Hz, 1H), 8.06 (d, *J*=8.4 Hz, 1H), 8.01 (d, *J*=6.6 Hz, 1H), 7.88 (d, *J*=7.8 Hz, 1H), 7.70–7.64 (m, 1H), 7.57 (t, *J*=7.2 Hz, 1H), 7.49 (t, *J*=7.8 Hz, 1H), 4.35 (t, *J*=4.8 Hz, 2H), 3.91 (t, *J*=4.8 Hz, 2H), 3.69 (d, *J*=4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.6, 189.3, 135.5, 134.0, 132.9, 131.3, 129.1, 129.0, 128.6, 126.9, 125.9, 124.2, 66.4, 66.3, 51.9, 47.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}NO_2S$: 286.0896; found: 286.0898.

*4.3.16. 1-(Furan-2-yl)-2-morpholino-2-thioxoethanone (**4p**).* Yield 93%; yellow solid; mp 97–100 °C; IR (KBr): 2974, 2854, 1640, 1503, 1460, 1394, 1274, 1241, 1108, 1028, 962, 775, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (s, 1H), 7.34 (d, *J*=3.2 Hz, 1H), 6.62 (t, *J*=1.6 Hz, 1H), 4.27 (t, *J*=4.4 Hz, 2H), 3.87 (t, *J*=4.6 Hz, 2H), 3.71 (d, *J*=4.8 Hz, 2H), 3.66 (d, *J*=4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.1, 175.6, 149.3, 148.2, 121.5, 112.7, 66.1, 65.8, 51.6, 47.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{12}NO_3S$: 226.0532; found: 226.0533.

*4.3.17. 2-Morpholino-1-(thiophen-2-yl)-2-thioxoethanone (**4q**).* Yield 90%; yellow solid; mp 166–167 °C; IR (KBr): 2986, 2860, 1634, 1502, 1440, 1406, 1269, 1237, 1107, 1027, 925, 779, 744, 721, 523 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.80 (s, 1H), 7.77 (s, 1H), 7.17 (d, *J*=4.2 Hz, 1H), 4.30 (d, *J*=3.6 Hz, 2H), 3.89 (d, *J*=4.2 Hz, 2H), 3.71 (s, 2H), 3.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.2, 181.0, 140.2, 136.2, 135.6, 128.6, 66.5, 66.3, 52.0, 47.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{12}NO_2S_2$: 242.0304; found: 242.0305.

*4.3.18. 1-(Benzofuran-2-yl)-2-morpholino-2-thioxoethanone (**4r**).* Yield 95%; yellow solid; mp 152–155 °C; IR (KBr): 3009, 2961, 2857, 1646, 1548, 1503, 1298, 1271, 1163, 1111, 1029, 976, 748, 527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (d, *J*=7.6 Hz, 1H), 7.66 (d, *J*=1.6 Hz, 1H), 7.57 (d, *J*=8.4 Hz, 1H), 7.49 (t, *J*=7.8 Hz, 1H), 7.31 (t, *J*=7.2 Hz, 1H), 4.30 (t, *J*=4.2 Hz, 2H), 3.89 (t, *J*=4.0 Hz, 2H), 3.70 (d, *J*=5.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 192.7, 177.0, 155.9, 149.3, 128.9, 126.4, 124.0, 123.3, 117.3, 112.1, 66.1, 65.8, 51.7, 47.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_3S$: 276.0689; found: 276.0690.

*4.3.19. 2-(2-Morpholino-2-thioxoacetyl)-9H-fluoren-9-one (**4s**).* Yield 73%; yellow solid; mp 197–200 °C; IR (KBr): 2915, 2855, 2361, 2338, 1717, 1660, 1612, 1511, 1433, 1263, 1236, 1180, 1112, 1029, 977, 739, 662, 529 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.17 (d, *J*=7.8 Hz, 1H), 8.12 (s, 1H), 7.66 (d, *J*=7.8 Hz, 1H), 7.62–7.51 (m, 3H), 7.38 (t, *J*=7.2 Hz, 1H), 4.35 (t, *J*=4.8 Hz, 2H), 3.93 (t, *J*=4.8 Hz, 2H), 3.76–3.71 (m, 2H), 3.65 (d, *J*=4.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.4, 191.8, 185.8, 149.2, 142.5, 136.3, 135.0, 134.4, 134.1, 133.9, 130.5, 125.0, 124.4, 121.4, 120.6, 66.4, 66.2, 51.9, 47.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_3S$: 338.0845; found: 338.0857.

*4.3.20. 2-Oxo-N,2-diphenylethanethioamide (**6a**).* Yield 80%; yellow solid; mp 87–91 °C; IR (KBr): 3258, 1651, 1594, 1531, 1391, 1266, 943, 764, 699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.19 (s, 1H), 8.06–8.01 (m, 2H), 8.01–7.97 (m, 2H), 7.60–7.55 (m, 1H),

7.49–7.40 (m, 4H), 7.35–7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.7, 187.4, 137.6, 133.8, 133.2, 130.6, 128.9, 128.0, 127.1, 122.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{12}NOS$: 242.0634; found: 242.0634.

*4.3.21. N-(4-Fluorophenyl)-2-oxo-2-phenylethanethioamide (**6b**).* Yield 75%; yellow solid; mp 120–124 °C; IR (KBr): 3267, 3151, 3072, 1656, 1549, 1507, 1388, 1265, 1227, 1106, 926, 835, 691, 513 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.37 (s, 1H), 8.05–7.90 (m, 4H), 7.63–7.51 (m, 1H), 7.39 (t, J=7.8 Hz, 2H), 7.11 (t, J=8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.4, 187.5, 161.9, 159.4, 134.0, 133.8, 133.4, 130.8, 128.1, 124.3, 124.2, 116.0, 115.8; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{11}FNOS$: 260.0540; found: 260.0539.

*4.3.22. N-(4-Chlorophenyl)-2-oxo-2-phenylethanethioamide (**6c**).* Yield 80%; yellow solid; mp 124–125 °C; IR (KBr): 3314, 1636, 1544, 1488, 1390, 1265, 1093, 833, 713, 686, 664, 512 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.32 (s, 1H), 7.98 (d, J=7.8 Hz, 2H), 7.95 (d, J=9.0 Hz, 2H), 7.60–7.54 (m, 1H), 7.43–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 189.7, 187.0, 136.3, 133.9, 133.5, 132.3, 130.9, 129.2, 128.1, 123.3; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}ClNNaOS$: 298.0064; found: 298.0066.

*4.3.23. N-(4-Bromophenyl)-2-oxo-2-phenylethanethioamide (**6d**).* Yield 81%; yellow solid; mp 126–129 °C; IR (KBr): 3314, 1636, 1591, 1543, 1485, 1387, 1265, 1072, 1005, 830, 813, 709, 685, 663, 510 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.27 (s, 1H), 7.99 (d, J=6.6 Hz, 2H), 7.90 (d, J=6.0 Hz, 2H), 7.61–7.48 (m, 3H), 7.45–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.0, 187.1, 136.8, 133.9, 133.5, 132.1, 130.8, 128.1, 123.6, 120.1; MS (EI): m/z 318.98 (M, 9.10), 215.95 (12.23), 155.00 (6.15), 135.07 (9.20), 105.01 (100.00). Anal. Calcd for $C_{14}H_{10}BrNOS$: C, 52.51; H, 3.15; N, 4.37; S, 10.01. Found: C, 52.74; H, 3.39; N, 4.33; S, 10.23.

*4.3.24. 2-Oxo-2-phenyl-N-(p-tolyl)ethanethioamide (**6e**).* Yield 83%; yellow solid; mp 98–101 °C; IR (KBr): 3301, 3206, 3135, 1639, 1591, 1545, 1507, 1396, 1266, 1103, 942, 817, 692, 660, 511 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.32 (s, 1H), 7.99–7.95 (m, 2H), 7.86–7.80 (m, 2H), 7.55–7.49 (m, 1H), 7.39–7.34 (m, 2H), 7.23–7.18 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 189.9, 187.4, 137.3, 135.2, 133.7, 133.6, 130.7, 129.5, 128.0, 122.2, 21.1; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}NOS$: 256.0791; found: 256.0791.

*4.3.25. N-(4-Methoxyphenyl)-2-oxo-2-phenylethanethioamide (**6f**).* Yield 87%; yellow solid; mp 106–111 °C; IR (KBr): 3290, 2361, 2338, 1653, 1595, 1540, 1504, 1395, 1264, 1244, 1170, 1028, 943, 830, 700, 526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.26 (s, 1H), 7.99 (d, J=8.0 Hz, 2H), 7.88 (d, J=8.8 Hz, 2H), 7.54 (t, J=7.0 Hz, 1H), 7.39 (t, J=7.4 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 189.8, 187.6, 158.0, 133.7, 133.4, 130.7, 130.6, 128.0, 123.8, 113.9, 55.31; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}NO_2S$: 272.0740; found: 272.0736.

*4.3.26. N-(4-Isopropylphenyl)-2-oxo-2-phenylethanethioamide (**6g**).* Yield 85%; yellow solid; mp 56–60 °C; IR (KBr): 3208, 2958, 1664, 1593, 1529, 1398, 1264, 949, 835, 694, 549 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.18 (s, 1H), 8.02 (d, J=8.4 Hz, 2H), 7.91 (d, J=7.8 Hz, 2H), 7.56 (t, J=7.8 Hz, 1H), 7.42 (t, J=7.8 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 2.99–2.88 (m, 1H), 1.27 (d, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 189.5, 187.3, 148.2, 135.5, 133.7, 130.8, 128.0, 127.5, 127.0, 122.1, 33.8, 23.8, 23.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{18}NOS$: 284.1104; found: 284.1103.

*4.3.27. 2-Oxo-N-phenyl-2-(p-tolyl)ethanethioamide (**6h**).* Yield 81%; yellow solid; mp 90–93 °C; IR (KBr): 3308, 2361, 2338, 1636, 1600, 1488, 1395, 1265, 1179, 1101, 939, 759, 691, 509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.39 (s, 1H), 7.87 (d, J=8.0 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H), 7.29 (t, J=7.8 Hz, 2H), 7.17 (t, J=7.4 Hz, 1H), 7.03 (d, J=8.0 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.4, 187.5, 145.1, 137.7, 130.8, 130.5, 128.8, 127.0, 123.7, 122.1, 21.7; HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{15}H_{14}NOS$: 256.0791; found: 256.0789.

*4.3.28. 2-((4-Methoxyphenyl)amino)-1-phenylethanone (intermediate **A**).* Yield 93%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J=7.2 Hz, 2H), 7.62 (t, J=7.4 Hz, 1H), 7.51 (t, J=7.6 Hz, 2H), 6.83 (d, J=8.8 Hz, 2H), 6.68 (d, J=8.8 Hz, 2H), 4.92 (s, 1H), 4.59 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.4, 152.2, 141.4, 134.9, 133.8, 128.8, 127.7, 114.9, 114.2, 55.7, 51.2.

*4.3.29. (E)-2-((4-Methoxyphenyl)imino)-1-phenylethanone (intermediate **B**).*[17b] Yield 95%; brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.35 (s, 1H), 8.29 (d, J=7.6 Hz, 2H), 7.60 (t, J=7.4 Hz, 1H), 7.49 (t, J=7.6 Hz, 2H), 7.40 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.8, 160.4, 154.0, 141.5, 135.4, 133.3, 130.5, 128.3, 123.5, 114.5, 55.4.

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Supplementary data

The general experimental methods and the characterizing data including ^{1}H NMR, ^{13}C NMR for products are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.045.

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