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# Thioesterifications Free of Activating Agent and Thiol: A Three-Component Reaction of Carboxylic Acids, Thioureas, and Michael Acceptors

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**Abstract:** An amine-catalyzed, one-pot synthesis of thioesters directly from carboxylic acids, thioureas, and Michael acceptors is described. This process was further improved by use of 1-[2-(methylamino)ethyl]-3-phenylthiourea (**4**) as the catalyst. Aromatic and aliphatic carboxylic acids with functional groups are compatible with this process, and both α,β-unsaturated esters and ketones can be the Michael acceptors for this reaction. The progress of this reaction was monitored by $^1$H NMR, and a reaction mechanism is proposed.

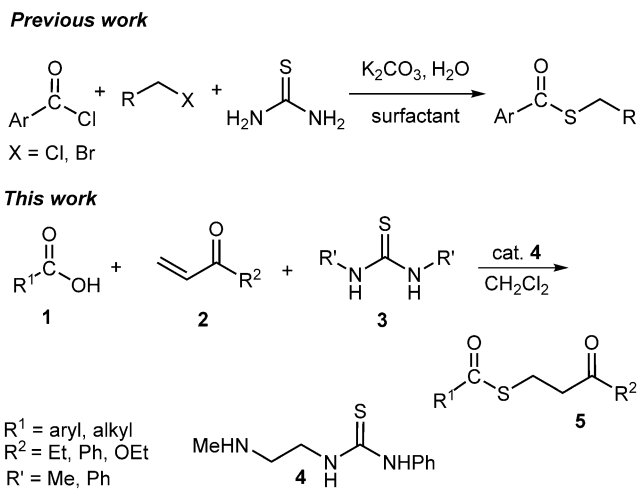
**Keywords:** Michael addition; multicomponent reaction; organic catalysis; thioesterification

Thioesters (thiol esters) are useful building blocks for organic synthesis[1,2] and the chemical synthesis of proteins.[3] They serve as activated carboxylic acids and are often used as acyl transfer agents for various nucleophiles, or precursors to generate radicals.[4,5] For example, native chemical ligation (NCL), a powerful chemical method to synthesize proteins, employs the reaction between an *N*-terminal cysteine peptide and a *C*-terminal peptide thioester.[3,6] In addition, α,β-unsaturated thioesters are often good substrates in asymmetric 1,4-addition reactions.[7] Some thioesters also possess biological activities and medicinal potential.[8,9]

The conventional methods for generating thioesters are: (i) the activation of carboxylic acids with carbodiimides or *N*-acylbenzotriazoles followed by the addition of thiols[10] and (ii) the reaction of acyl halides with thiols.[11] Recent progress in the preparation of thioesters includes the acid-catalyzed, direct condensation of carboxylic acids and thiols,[12] and various coupling reactions, mainly mediated by metal complexes.[13–15] An interesting development, recently reported by Cai et al., demonstrated that thioesters could be produced from a one-pot, three-component reaction of organic halides, aromatic acyl halides, and thiourea as the source of the sulfur atom (Scheme 1).[16]

Herein, we report a new thioesterification of carboxylic acids in which the adducts of thioureas and Michael acceptors activate the carboxylic acids and also provide the corresponding thiolate to generate the thioesters. This one-pot, three-component reaction is performed under mild conditions and is free of the use of reactive, often foul-smelling thiols and the activating reagents frequently required for the thioesterification of carboxylic acids. We have found that the efficiency of this process is further improved by addition of a catalytic amount of compound **4**, a conjugate of a thiourea and a secondary amine.

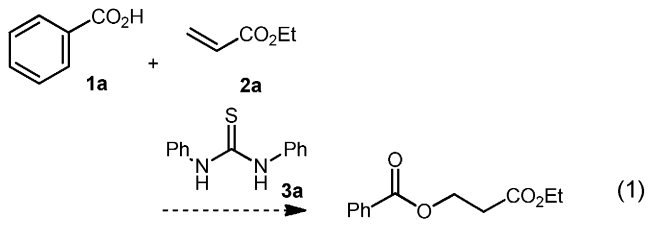
Thiourea and its derivatives have been widely applied as powerful catalysts in organocatalytic reactions.[17] However, when various thioureas, such as *N,N′*-diphenylthiourea (**3a**), were screened in an at-



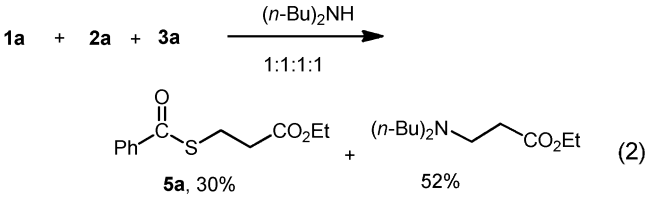

**Scheme 1.** Synthesis of thioesters using thiourea.

tempt to prepare the Michael adduct of benzoic acid (**1a**) and ethyl acrylate (**2a**) [Eq. (1)], the results were unsatisfactory. We felt that this addition process might be improved by the addition of amines to give the more nucleophilic benzoate anion. Thus, a mixture of **1a**, **2a**, **3a** and dibutylamine was heated at 40 °C for 24 h [Eq. (2)]. We were pleased to find that the thioester **5a** was isolated in 30% yield along with the aza-Michael adduct, ethyl 3-(dibutylamino)propanoate (52%).[18] The thioester **5a** was unambiguously characterized by NMR and IR spectroscopy and mass analysis.[19]




(1)

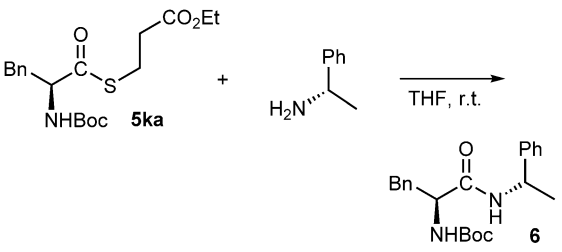



(2)

We were intrigued by the unexpected formation of **5a**, and the results of optimizing this thioesterification are summarized in Table 1. We observed that the thioesters were unstable and often lost during their isolation, so the reported yields were determined by $^1$H NMR analysis of the crude products with an internal standard (anisole); isolated yields, shown in parentheses, were obtained after column chromatography. Varying the stoichiometry of the reagents or dibutylamine gave very limited improvements in yields (entries 1–4). The idea of constraining the role of the secondary amine as a basic catalyst, rather than as the nucleophile, prompted us to explore the conjugate of an amine and a thiourea to facilitate this reaction. Indeed, the yield of **5a** increased to 72% when we used **4**, derived from addition of *N*-methylethylenediamine to phenyl isothiocyanate, in place of dibutylamine and thiourea **3a** as the 2° amine base and the source of the sulfur atom, respectively (entry 5). The yield rose further to 81% when the acrylate **2a** was the limiting reagent (entry 6). We subsequently found that the same result could be obtained by using a catalytic amount of **4** (20 mol%), accompanied with excess thiourea **3a** (entry 7). However, further reducing the quantity of **4** to 10 mol% was not productive (entry 8). In addition to $CH_2Cl_2$, other polar, aprotic solvents such as toluene and DMF were compatible with this reaction (entries 9 and 10), and the reaction time could be shortened to 10 h by increasing the reaction temperature, by using solvents with higher boiling points (entries 9 and 11). However, the reaction failed in THF, methanol, or aqueous DMF solution (entries 12–14). *N,N′*-Dimethylthiourea (**3b**), commercially available as is **3a**, was also a suitable source of the sulfur atom (entries 15 and 16). The low yield for the reaction involving **3b** in $CH_2Cl_2$ (entry 15) is likely due to its low solubility at the reaction temperature (40 °C) used.

The scope of the reaction is summarized in Table 2. *o*-Toluic acid (**1b**), 3,4- and 2,6-dimethylbenzoic acids (**1c** and **1d**) gave satisfactory yields (entries 1–3). Both electron-rich and electron-deficient benzoic acids can be the substrates for this reaction, as shown for 4-methoxy- and 4-nitrobenzoic acids (**1e** and **1f**, entries 4 and 5). 2-Iodobenzoic acid (**1g**) gave a moderate yield (entry 6). Both 1- and 2-naphthoic acids are also good substrates (entries 7 and 8). The results obtained from the naphthoic acids **1h** and **1i** and the dimethylbenzoic acids **1c** and **1d** suggest that the steric environment around the carboxyl group has little influence on the reaction. The thioesterification also proceeded well for 4-methoxyphenylacetic acid (**1j**) and Boc-L-phenylalanine (**1k**), in both of which the carboxyl groups are not conjugated to the aromatic systems (entries 9 and 10). Aliphatic carboxylic acids, such as **1l** and **1m**, were also compatible with the reaction, although the yields were lower (entries 11 and 12). In addition to the acrylates **2a** and **2b**, other Michael acceptors including the α,β-unsaturated ketones **2c** and **2d** and dimethyl fumarate (**2e**) provided the corresponding thioesters (entries 13–16). Phenyl vinyl ketone[20] (**2c**) provided the best yields among the Michael acceptors screened, and also resulted in increased yields of the thioesters derived from the aliphatic carboxylic acids **1l** and **1m** (entries 17 and 18) as compared those obtained with **2a** (entries 11 and 12). The successful thioesterification of **1n** and **1k** suggests that biomolecules with the amide or carbamate functional groups, for example, protected peptides, could be potential substrates for this reaction.

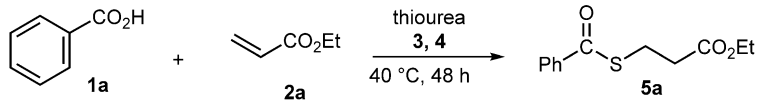
When the thioester **5ka** was further reacted with (*S*)-1-phenylethanamine, amide **6** was obtained as




(3)

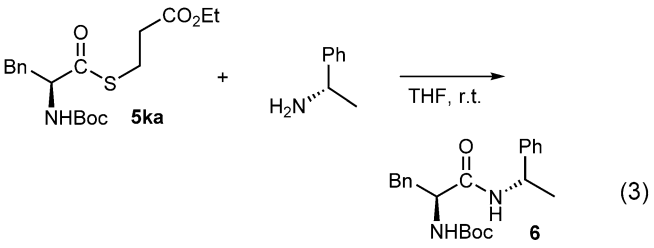
**Table 1.** Reaction optimizations for the thioesterification of **1a**




| Entry | **1a** [a] | **2a** [a] | **3a** [a] | $(n\text{-Bu})_2NH$ [a] | **4** [a] | Solvent | Yield [%][b] |
|---|---|---|---|---|---|---|---|
| 1 | 1.0 | 1.0 | 1.0 | 1.0 | – | $CH_2Cl_2$ | 30 (15) |
| 2 | 1.0 | 1.0 | 1.5 | 1.0 | – | $CH_2Cl_2$ | 31 (15) |
| 3 | 1.0 | 1.5 | 1.0 | 1.0 | – | $CH_2Cl_2$ | 25 (10) |
| 4 | 1.0 | 1.5 | 1.5 | 0.2 | – | $CH_2Cl_2$ | 20 (5) |
| 5 | 1.0 | 1.0 | – | – | 1.5 | $CH_2Cl_2$ | 72 (50) |
| 6 | 1.5 | 1.0 | – | – | 1.5 | $CH_2Cl_2$ | 81 (55) |
| 7 | 1.5 | 1.0 | 1.5 | – | 0.2 | $CH_2Cl_2$ | 80 (55) |
| 8 | 1.0 | 1.0 | 1.0 | – | 0.1 | $CH_2Cl_2$ | 45 (25) |
| 9[c] | 1.5 | 1.0 | 1.5 | – | 0.2 | toluene | 78 |
| 10 | 1.5 | 1.0 | 1.5 | – | 0.2 | DMF | 80 |
| 11[d] | 1.5 | 1.0 | 1.5 | – | 0.2 | toluene | 81 |
| 12 | 1.5 | 1.0 | 1.5 | – | 0.2 | THF | 0 |
| 13 | 1.5 | 1.0 | 1.5 | – | 0.2 | MeOH | 0 |
| 14 | 1.5 | 1.0 | 1.5 | – | 0.2 | $DMF_{(aq)}$[e] | 0 |
| 15 | 1.0 | 1.0 | 1.0[f] | – | 0.2 | $CH_2Cl_2$ | 25 |
| 16[g] | 1.5 | 1.0 | 1.5[f] | – | 0.2 | toluene | 80 |

[a] Equivalents of the reagent used.
[b] As calculated from $^1$H NMR spectra utilizing anisole as an internal standard; isolated yields shown in parentheses.
[c] Reaction conducted at 50 °C, 24 h.
[d] Reaction conducted at 90 °C, 10 h.
[e] DMF/$H_2O$, v/v = 1:1.
[f] *N,N′*-Dimethylthiourea was used.
[g] 80 °C.

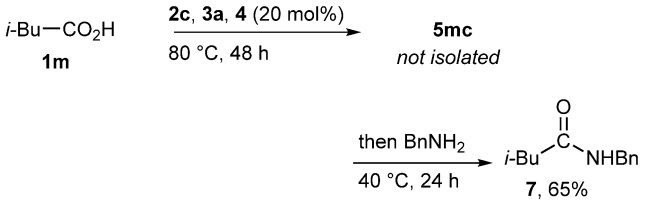
a single product and no diastereomeric isomer was observed in $^{13}$C NMR. This result suggests that the optical purity of **1k** was preserved during this thioesterification [Eq. (3)].



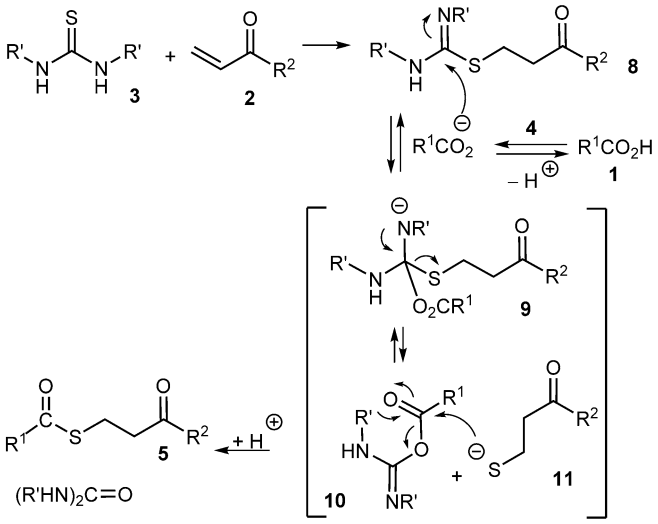

(3)

The effectiveness of this methodology was shown by the gram-scale synthesis of **5ba** (1.45 g, 56% yield) and the one-pot synthesis of *N*-benzyl-3-methylbutanamide (**7**) in 65% isolated yield (Scheme 2).

The proposed mechanism for the reaction is shown in Scheme 3 and is consistent with the following observations. Monitoring of the reaction of **1m**, **2c**, **3a**, and **4** by $^1$H NMR spectroscopy showed that an intermediate was first generated and reached its highest concentration in 6 h (Figure 1). Then the formation of




**Scheme 2.** One-pot synthesis of amide **12**.




**Scheme 3.** A plausible reaction mechanism for the thioesterification.

**Table 2.** Thioesterification of carboxylic acids [a]

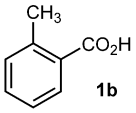
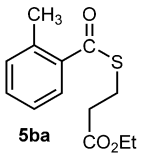
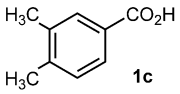
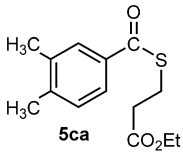
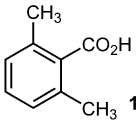
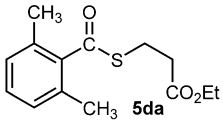
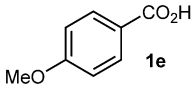
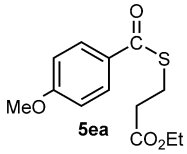
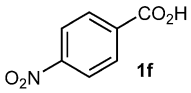
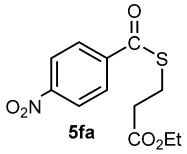
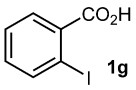
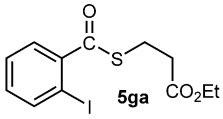
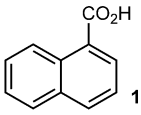
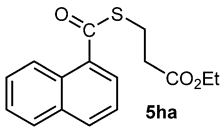
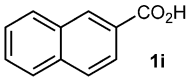
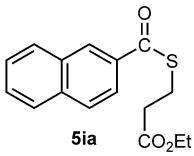
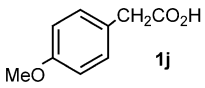
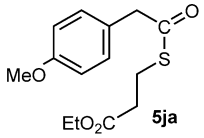
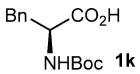
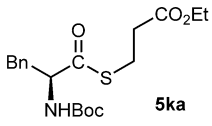
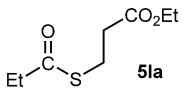
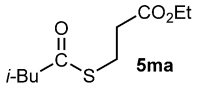
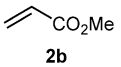
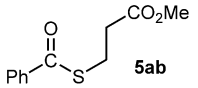
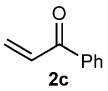
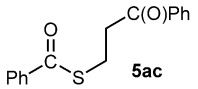
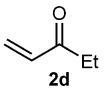
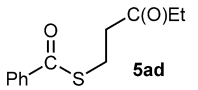
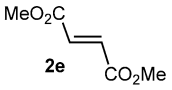
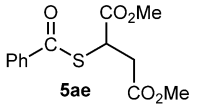
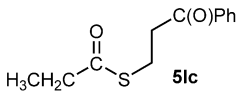
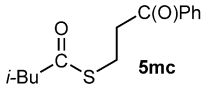
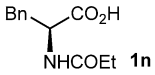
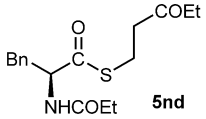
| entry | Carboxylic acid | Michael acceptor | Thioester | Yield [%][b] |
|---|---|---|---|---|
| 1 |  **1b** | **2a** |  **5ba** | 84 (60) |
| 2 |  **1c** | **2a** |  **5ca** | 72 (55) |
| 3 |  **1d** | **2a** |  **5da** | 68 (52) |
| 4 |  **1e** | **2a** |  **5ea** | 81 (62) |
| 5 |  **1f** | **2a** |  **5fa** | 60 (41) |
| 6 |  **1g** | **2a** |  **5ga** | 52 (30) |
| 7[c] |  **1h** | **2a** |  **5ha** | 70 (46) |
| 8[c] |  **1i** | **2a** |  **5ia** | 75 (52) |
| 9[c] |  **1j** | **2a** |  **5ja** | 80 (58) |
| 10[c] |  **1k** | **2a** |  **5ka** | 65 (40) |
| 11 |  **1l** | **2a** |  **5la** | 50 (25) |

**Table 2.** (Continued)

| entry | Carboxylic acid | Michael acceptor | Thioester | Yield [%][b] |
|---|---|---|---|---|
| 12 | *i*-Bu—$CO_2$H **1m** | **2a** |  **5ma** | 64 (40) |
| 13 | **1a** |  **2b** |  **5ab** | 75 (51) |
| 14[d] | **1a** |  **2c** |  **5ac** | 85 (62) |
| 15[d] | **1a** |  **2d** |  **5ad** | 60 (42) |
| 16[c] | **1a** |  **2e** |  **5ae** | 46 (20) |
| 17[d] | **1l** | **2c** |  **5lc** | 70 (45) |
| 18 | **1m** | **2c** |  **5mc** | 85 (66) |
| 19 |  **1n** | **2d** |  **5nd** | 55 (35) |

[a] Thiourea **3a** was applied; reaction in toluene, 80 °C, 24 h.
[b] Yields determined by $^1$H NMR spectroscopic analysis; isolated yields shown in parentheses.
[c] Reaction in toluene, 80 °C, 48 h.
[d] Reaction in $CH_2Cl_2$, 40 °C, 48 h

the product **5mc** was observed, accompanied with a decrease in the intermediate. The intermediate was isolated and characterized as compound **8** ($R^2 = R' =$ Ph) through its synthesis by addition of thiourea **3a** to phenyl vinyl ketone (**2c**).[19,21] Subsequent addition of isovaleric acid (**1m**) and **4** (20 mol%) to the solution of **8** also provided thioester **5mc**. In this mechanism, the addition/substitution of the carboxylate to **8** gives carbamimidate **10** and thiolate **11**, which further react to produce thioesters and stable ureas.

In summary, this new method for preparing thioesters is free of the troublesome thiols and activating reagents generally required for the thioesterification of carboxylic acids. Instead, both the thioureas and the α,β-unsaturated esters are easy to handle, inexpensive and commercially available. Both aromatic and aliphatic carboxylic acids with functional groups are compatible with this process. The proposed reaction mechanism is supported by the identified reaction intermediate. Thus, this reaction provides a metal-free, convenient synthesis of thioesters of biological or chemical interest.

## Experimental Section

### Typical Procedure for the Synthesis of Thioesters

To a solution of benzoic acid (**1a**, 184.4 mg, 1.51 mmol), ethyl acrylate (**2a**, 100.9 mg, 1.01 mmol), and *N,N′*-diphenylthiourea (**3a**, 1.51 mmol, 1.5 equiv.) in toluene (5.0 mL) was added thiourea catalyst **4** (42.3 mg, 0.20 mmol). The reaction was heated in an oil bath (80 °C) for 24 h, and then the excess solvent was evaporated under vacuum. The crude product was purified by column chromatography ($SiO_2$: EtOAc/*n*-hexane, 1:5; $R_f = 0.76$) to give thioester **5a** as a colorless oil; yield: 131.2 mg (0.55 mmol, 55%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.93$ (d, $J = 7.2$ Hz, 2H), 7.54 (t, $J =$ 7.3 Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.29 (t, $J = 6.9$ Hz, 2H), 2.69 (t, $J = 6.9$ Hz, 2H), 1.21 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 191.5$,

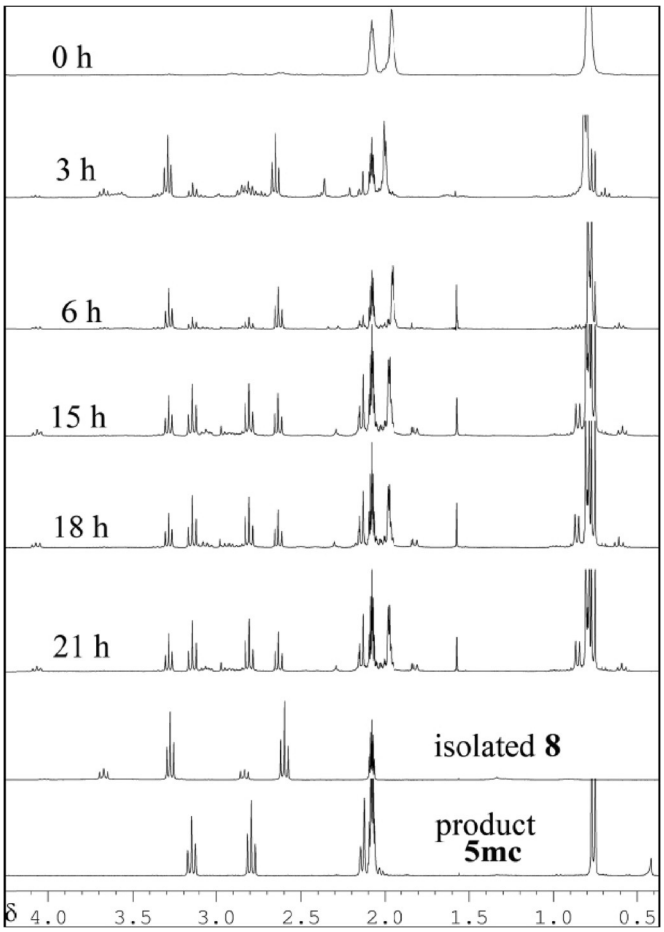



**Figure 1.** Reaction progress of the thioesterification monitored by $^1$H NMR spectroscopy (80 °C, 300 MHz);[19] **1m** (1.0 mmol), **2c** (1.0 mmol), **3a** (1.0 mmol) and **4** (0.2 mmol in toluene-$d_8$ (1.0 mL).

171.7, 136.7, 133.4, 128.6, 127.2, 60.7, 34.4, 24.0, 14.1; IR (neat): $\nu$ = 2981 (m), 2360 (m), 1735 (s), 1664 (s), 1207 (s), 912 (s), 690 (s) cm$^{-1}$; HR-MS (ESI$^+$): $m/z$ = 261.0556, calcd. for $[M+Na]^+$ ($C_{12}H_{14}O_3NaS$): 261.0561.

### 1-(2-(Methylamino)ethyl)-3-phenylthiourea (4)

To a solution of *N*-methylethane-1,2-diamine (15.2 mg, 3.24 mmol), and phenyl isothiocyanate (438.5 mg, 3.24 mmol) in THF (5.0 mL) was added triethylamine (328.3 mg, 3.24 mmol). The reaction mixture was stirred at room temperature for 18 h, and then the excess solvent was evaporated under vacuum. The crude product was purified by column chromatography ($SiO_2$: MeOH/EtOAc, 1:4; $R_f$ = 0.35) to give compound **4** as a white solid; yield: 549.5 mg (2.62 mmol, 81%); mp 161.0–163.0 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.33–7.32 (m, 4H), 7.21–7.18 (m, 1H), 7.09 (s, 1H), 4.39 (s, 1H), 3.65 (t,, $J$ = 6.3 Hz, 2H), 3.01 (t,, $J$ = 6.3 Hz, 2H), 2.44 (s, 3H), 2.01 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 184.1, 140.9, 129.1, 123.3, 122.8, 49.5, 40.4, 32.6; HR-MS (ESI$^-$); $m/z$ = 208.0909, calcd. for $[M-H]^-$ ($C_{10}H_{14}N_3S$): 208.0908.

### *N*-Benzyl-3-methylbutanamide (7)[22]

To a solution of isovaleric acid **1m** (58.2 mg, 0.57 mmol), 1-phenylprop-2-en-1-one **2c** (50.2 mg, 0.38 mmol), and *N,N′*-diphenylthiourea **3a** (130.1 mg, 0.57 mmol) in toluene (1.5 mL) was added thiourea catalyst **4** (16.5 mg, 0.08 mmol). The reaction mixture was heated in an oil bath (80 °C) for 24 h, cooled to room temperature, treated with benzylamine **11** (61.1 mg, 0.57 mmol) and then heated in an oil bath (40 °C) for 24 h. Then excess solvent was evaporated under vacuum. The crude product was purified by column chromatography ($SiO_2$: EtOAc/*n*-hexane, 1:2; $R_f$ 0.42) to give **12** as a light yellow solid; yield: 47.5 mg (0.25 mmol, 65%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.31–7.25 (m, 5H), 5.69 (s, 1H), 4.43 (d, $J$ = 5.7 Hz, 2H), 2.17–2.09 (m, 1H), 2.06 (d, $J$ = 7.2 Hz, 2H), 0.95 (d, $J$ = 7.2 Hz, 6H). The spectroscopic data are consistent with the reported values.[22]

### 3-Oxo-3-phenylpropyl *N,N′*-Diphenylcarbamimidothioate (8)

To a solution of 1-phenylprop-2-en-1-one **2c** (15.2 mg, 0.115 mmol) in toluene (0.5 mL) was added *N,N′*-diphenylthiourea **3a** (26.2 mg, 0.115 mmol). The reaction mixture was heated in an oil bath (80 °C) for 5 h, and then the excess solvent was evaporated under vacuum. The crude product was purified by column chromatography ($SiO_2$: EtOAc/*n*-hexane, 1:4; $R_f$ = 0.62) to give compound **8** as a yellow solid; yield: 29.5 mg (0.081 mmol, 71%); mp 104.0–105.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.90–7.89 (m, 3H), 7.53–7.41 (m, 5H), 7.19–7.15 (m, 3H), 6.74–6.64 (m, 4H), 3.61 (t, $J$ = 6.0 Hz, 2H), 3.27 (t, $J$ = 6.0 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 199.1, 147.3, 136.6, 133.2, 129.5, 129.2, 128.5, 127.9, 117.8, 113.2, 38.8, 37.4; HR-MS (FAB$^+$): $m/z$ = 360.1293, calcd. for $[M]^+$ ($C_{22}H_{20}N_2OS$): 360.1296.

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