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KI-catalyzed synthesis of *S*-Thiocarbamates by cross-coupling of cyclohexyl isocyanide with sulfonyl chlorides

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Abstract

A simple and efficient process for direct generation of various *S*-thiocarbamates is developed by cross-coupling of readily available sulfonyl chlorides with cyclohexyl isocyanide. The yields are excellent and the structures of the generated *S*-thiocarbamates are characterized by nuclear magnetic resonance spectroscopy, infrared spectroscopy, and high-resolution mass spectrometry together with X-ray crystallographic analysis. The protocol has the advantages of using easily available reagents, employs inexpensive KI as the reagent, demonstrates good functional group tolerance, and utilizes mild reaction conditions.

Keywords

isocyanides, potassium iodide, *S*-Thiocarbamates, sulfonyl chlorides, water

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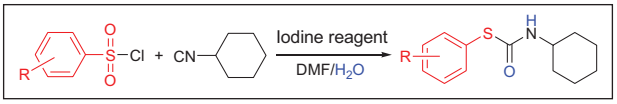

Introduction

In the past few decades, the synthesis and study of organic sulfur chemicals has become a popular research topic.[1–6] *S*-Thiocarbamates represent key building blocks that are common in many synthetic pharmaceuticals and natural biologically active compounds.[7] They have numerous biological applications in the manufacture of pharmaceuticals and agrochemicals including the HIV-1 nucleocapsid protein NCp7 inhibitor[8] and bactericidal,[9] anesthetic,[10] fungicidal,[11] pesticidal,[12] and herbicidal[13] substances. Therefore, the development of new methods for the synthesis of *S*-thiocarbamates is of widespread interest. Classic methods for the synthesis of *S*-Thiocarbamates include (1) reacting toxic phosgene/triphosgene or carbonyldiimidazole with an amine and thiophenol (Scheme 1(a)),[14,15] (2) visible-light/rose bengal reactions (Scheme 1(b)),[7,16] and (3) molecular iodine–catalyzed reactions of thiosulfonates (prepared from thiols or sulfonyl chlorides) with isocyanides (Scheme 1(c)).[17] However, these methods have shortcomings such as poor atom economy, harsh reaction conditions, and the use of difficult-to-obtain precursors as well as unstable, toxic, and/or hazardous chemical reagents.[7] Thus, it is necessary to develop an efficient and general route for the construction and enrichment of *S*-Thiocarbamate compounds.

Sulfonyl chlorides are readily available and have been widely used in the fields of materials science as well as in organic and medicinal syntheses.[18–21] Nonetheless, there is no example of the direct generation of *S*-Thiocarbamates

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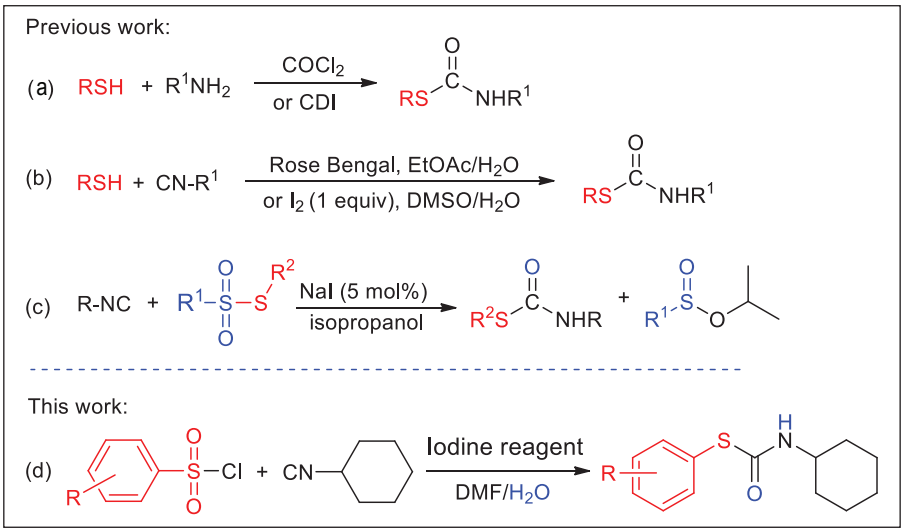
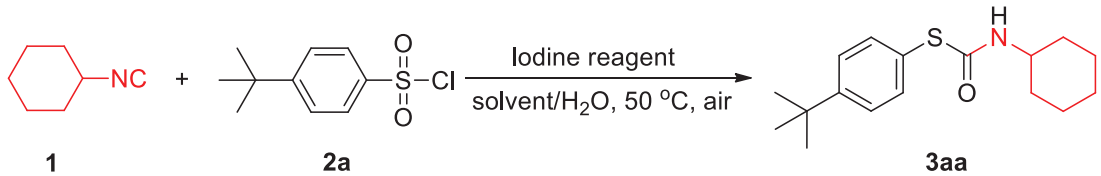


Scheme 1. Different synthetic routes for the synthesis of *S*-Thiocarbamates.
DMF: dimethylformamide; CDI: N,N'-Carbonyldiimidazole; DMSO: Dimethyl sulfoxide.

Table 1. Optimization of the reaction conditions[a].



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

Entry	Iodine reagent	Solvent	Temperature (°C)	Yield[b] (%)
1	KI (1.5)	DMF/H2O (50:1)	50	90
2	NaI (1.5)	DMF/H_2O (50:1)	50	67
3	TBAI (1.5)	DMF/H_2O (50:1)	50	52
4	NH_4I (1.5)	DMF/H_2O (50:1)	50	50
5	I_2 (1.5)	DMF/H_2O (50:1)	50	0
6	KI (1.5)	NMP/H_2O (50:1)	50	65
7	KI (1.5)	CH_3CN/H_2O (50:1)	50	68
8	KI (1.5)	THF/H_2O (50:1)	50	62
9	KI (1.5)	EtOH/H_2O (50:1)	50	42
10	KI (1.5)	DMSO/H_2O (50:1)	50	Trace
11	KI (1.5)	H_2O	50	60
12	KI (1.5)	DMF	50	Trace
13	KI (1.5)	DMF/H2O (50:1)	50	90
14	KI (2.0)	DMF/H_2O (50:1)	50	88
15	KI (1.0)	DMF/H_2O (50:1)	50	70
16	KI (0.5)	DMF/H_2O (50:1)	50	46
17	KI (0)	DMF/H_2O (50:1)	50	0
18	KI (1.5)	DMF/H_2O (50:1)	60	85
19	KI (1.5)	DMF/H_2O (50:1)	40	77

DMF: dimethylformamide; TBAI: tetrabutylammonium iodide; NMP: *N*-methyl-2-pyrrolidone; THF: tetrahydrofuran; DMSO: dimethyl sulfoxide.
[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.25 mmol), iodine reagent, solvent/H_2O (1.53 mL), 4 h.
[b]Isolated product yields after column chromatography.

from sulfonyl chlorides. On the contrary, methods based on metal iodide catalysis have gained significant attention in recent years because these processes are environmentally friendly and economical. In this paper, we report a simple and flexible synthetic route for the synthesis of various *S*-Thiocarbamates under mild reaction conditions using sulfonyl chlorides as the sulfur source (Scheme 1(d)).

Results and discussion

As a model reaction, the iodide-promoted reaction of cyclohexyl isocyanide (**1**) with 4-tert-butylbenzenesulfonyl chloride (**2a**) to give *S*-4-tert-butylphenyl cyclohexylcarbamothioate (**3aa**) (Table 1) was explored. The structure of product **3aa** was confirmed by X-ray crystallography as shown in

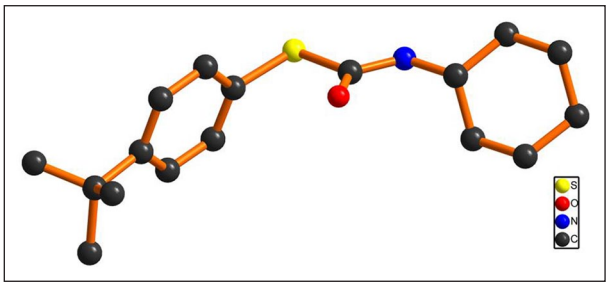


Figure 1. Ball-and-stick representation of the structure of **3aa**.

Figure 1. The results of screening and optimization of the reaction conditions are summarized in Table 1. By reacting **1** with **2a** at 50 °C for 4 h in the presence of KI (1.5 equiv.) in a dimethylformamide (DMF)/H_2O (50:1 V/V) volume ratio, the desired *S*-4-tert-butylphenyl cyclohexylcarbamothioate (**3aa**) was obtained in excellent yield (90%). As shown in Table 1 (entries 2–5), the use of other iodide sources as catalysts did not result in an increased yield of **3aa**. Therefore, KI was the reagent of choice for this reaction. We then screened a number of mixed solvents (solvent/water = 50:1, entries 6–11) and found that DMF/H_2O was the best. In the absence of water, the yield was insignificant (entry 12). Next, we optimized the amount of KI. The results showed that when the added KI exceeded 1.5 equiv. (entries 13 and 14), there was no further increase in the yield of **3aa**. When the amount of KI was 1 equiv., the yield of **3aa** was 70% (entry 15), and when the amount of KI is less than 1 equiv., there was a drastic decrease in the yield (entries 16 and 17). Finally, we optimized the reaction temperature and found that 50 °C was the best. A lower or higher temperature resulted in decreased product yields (entries 18 and 19).

Utilizing the optimized reaction conditions, we extended the reaction scope (Scheme 2). Various substituted benzenesulfonyl chlorides were examined. It was confirmed that the reaction has good applicability for various substituent groups, giving the corresponding thiocarbamate derivatives in excellent yields. When 10 mmol of cyclohexyl isocyanide (**1**) was reacted with 4-tert-butylbenzenesulfonyl chloride (**2a**) under the standard conditions, product **3aa** was obtained in 87% yield (Scheme 3). This result indicates that the synthetic method is suitable for the gram-scale production of *S*-thiocarbamates and has potential applications in drug synthesis.

Based on the report of Zhao and Zhou,[22] a possible reaction mechanism has been proposed (Scheme 4). First, KI reduces sulfonyl chloride **2** to produce intermediate ArSOCl **4** together with the generation of an iodine molecule, and the species ArSOCl **4** can continue to be reduced by KI to produce highly active ArSCl **5**.

The iodine can also reduce the sulfonyl and intermediate sulfinyl chlorides **2** and **4** into the sulfenyl chloride **5**. Disproportionation of the initially formed potassium hypoiodite then gives potassium iodate and iodine, that can carry out further reduction of the sulfonyl and sulfenyl chlorides, accounting for the requirement of less than two equivalents of KI. Addition of the isocyanide to the sulfenyl chloride **5** forms the intermediate **6**. Then the electron-deficient intermediate **6** then undergoes a nucleophilic substitution with water to form the product **3** after tautomerisation.

Conclusion

In summary, we have established a simple and convenient synthetic route for the preparation of *S*-Thiocarbamates. Using cheap and readily available sulfonyl chlorides as the sulfurizing reagents, *S*-Thiocarbamates with different substituents on the benzene ring can be constructed under mild reaction conditions. The protocol avoids the use of hazardous and unstable thiols. The reaction can be enlarged to gram scale, showing potential in industrial syntheses of *S*-thiocarbamates.

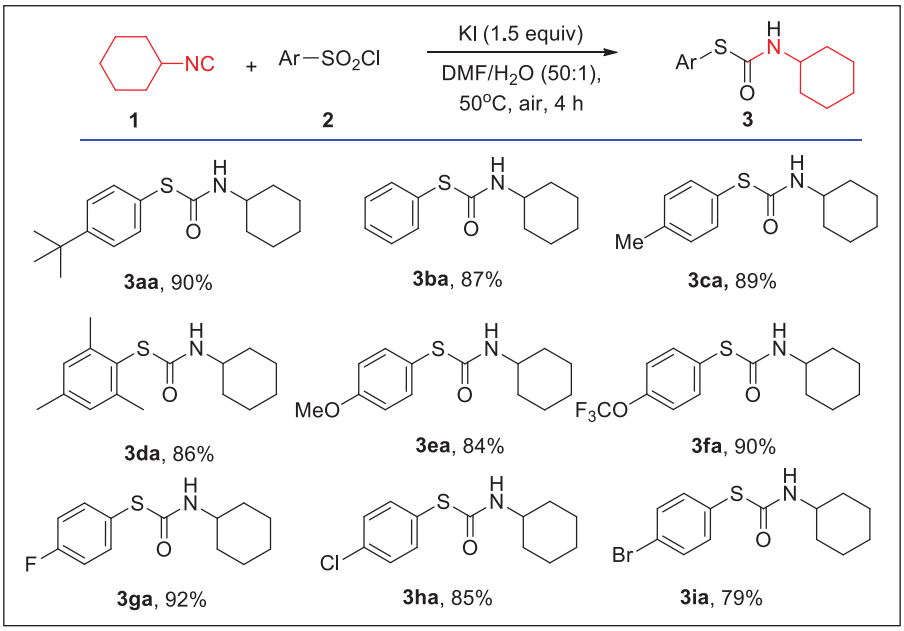
Experimental

All chemicals were commercially available and used without further purification. Analytical thin-layer chromatography (TLC) was performed on Merck Millipore silica gel 60 F254 plates. Column chromatography was carried out using 300–400 mesh silica gel (Qingdao Haiyang Chemical Co., Ltd).

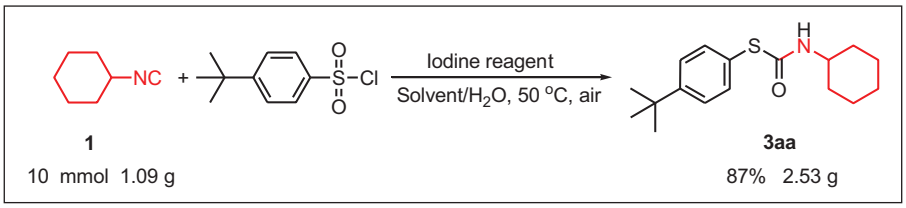
The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Mass spectrometric investigations were conducted with a Finnigan LCQ Advantage MAX mass spectrometer. Infrared (IR) spectra were recorded on a PerkinElmer spectrometer (Spectrum One). Melting points were measured with a Yanaco MP500 melting point apparatus and are uncorrected. Crystallographic determination of **3aa** was performed on a Bruker Apex-II charge-coupled device (CCD) diffractometer with monochromatic Mo Kα radiation (λ = 0.71073 Å) at 296(2) K. Crystal data for **3aa**: $C_{17}H_{25}NOS$, M_r = 291.44 g mol^{-1}, monoclinic space group $P2_1/c$, a = 10.7207(3) Å, b = 17.6682(5) Å, c = 10.1340(3) Å, β = 115.869(2)°, V = 1727.19(9) Å^3, T = 296(2) K, Z = 4, D_c = 1.121 g cm^{-3}, μ = 0.184 mm^{-1}, $F(000)$ = 632.0, R_{int} = 0.0726, 18,994 reflections, 3022 with $I > 2\sigma(I)$ for 214 parameters, Goodness-of-fit (GOF) on F^2 = 1.039, R_1 = 0.0635, wR_2 = 0.1331 ($I > 2\sigma(I)$) and R_1 = 0.1216, wR_2 = 0.1649 (all data). CCDC 1891207 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for the synthesis of 3

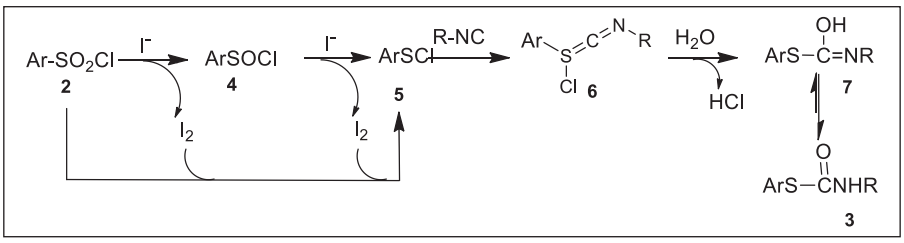
Cyclohexyl isocyanide **1** (0.1 mmol), sulfonyl chloride **2** (0.25 mmol), KI (0.15 mmol), and DMF/H_2O (50:1, 1.5 mL) were successively added to a round-bottom flask, and the mixture was then heated at 50 °C for 4 h. All the reactions were monitored by TLC. After completion, the reaction system was cooled to room temperature, saturated $Na_2S_2O_3$ solution (15 mL) was added, and the reaction mixture was extracted with EtOAc (10 mL × 3). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude product. The *S*-Thiocarbamates **3** were purified by column chromatography on silica gel.



Scheme 2. Substrate scope for the synthesis of **3**.
DMF: dimethylformamide.



Scheme 3. Gram-scale synthesis of **3aa**.



Scheme 4. A plausible reaction mechanism.

S-*4-tert-butylphenyl cyclohexylcarbamothioate* (**3aa**): White solid; yield 90%; m.p.: 108–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07–1.17 (m, 3H), 1.28–1.35 (m, 11H), 1.54–1.62 (m, 3H), 1.84–1.93 (m, 2H), 3.66–3.79 (m, 1H), 5.21 (br s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.52, 25.36, 31.22, 32.81, 34.82, 50.40, 125.34, 126.59, 135.18, 152.97, 165.43; IR (KBr) *v*: 1656 cm^{-1} (C=O); ESI-HRMS for $C_{17}H_{26}NOS$: 292.1730; found: 292.1726.

S-*phenyl cyclohexylcarbamothioate* (**3ba**): White solid; yield 87%; m.p.: 113–115 °C (lit.[23] 112–113 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06–1.16 (m, 3H), 1.28–1.36 (m, 2H), 1.54–1.63 (m, 3H), 1.87–1.90 (m, 2H), 3.72–3.74 (m, 1H), 5.19 (br s, 1H), 7.40–7.43 (m, 3H), 7.55–7.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.59, 25.36, 32.87, 50.50, 128.83, 129.44, 129.62, 135.46, 164.97; IR (KBr) *v*: 1656 cm^{-1} (C=O); ESI-HRMS for $C_{13}H_{18}NOS$: 236.1104; found: 236.1110.

S-*p-tolyl cyclohexylcarbamothioate* (**3ca**): White solid; yield 89%; m.p.: 130–132 °C (lit.[23] 130–132 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04–1.16 (m, 3H), 1.28–1.35 (m, 2H), 1.54–1.61 (m, 3H), 1.85–1.89 (m, 2H), 2.38 (s, 3H), 3.72–3.73 (m, 1H), 5.17 (br s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.39, 24.60, 25.36, 32.89, 50.40, 125.33, 130.33, 135.49, 140.05, 165.50; IR (KBr) *v*: 1647 cm^{-1} (C=O); ESI-HRMS for $C_{14}H_{20}NOS$: 250.1260; found: 250.1255.

S-*mesityl cyclohexylcarbamothioate* (**3da**): White solid; yield 86%; m.p.: 155–157 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96–1.11 (m, 3H), 1.26–1.33 (m, 2H), 1.52–1.57 (m, 3H), 1.78–1.84 (m, 2H), 2.30 (s, 3H), 2.43 (s, 6H), 3.69–3.71 (m, 1H), 5.07 (br s, 1H), 7.01 (s, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 21.23, 21.98, 24.54, 25.32, 32.89, 49.94, 124.82, 129.64, 140.46, 143.46, 165.04; IR (KBr) *v*: 1657 cm^{-1} (C=O); ESI-HRMS *m/z* $[M + H]^+$ calcd for $C_{16}H_{24}NOS$: 278.1573; found: 278.1578.

S-*4-methoxyphenyl cyclohexylcarbamothioate* (**3ea**): White solid; yield 84%; m.p.: 149–151 °C (lit.[7] 148–150 °C); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05–1.15 (m, 3H), 1.27–1.35 (m, 2H), 1.54–1.67 (m, 3H), 1.84–1.90 (m, 2H), 3.71–3.73 (m, 1H), 3.84 (s, 3H), 5.16 (br s, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.60, 25.36, 32.89, 50.36, 55.45, 115.09, 119.48, 137.27, 160.85, 165.96; IR (KBr) *v*: 1649 cm^{-1} (C=O); ESI-HRMS *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_2S$: 266.1209; found: 266.1215.

S-*4-(trifluoromethoxy)phenyl cyclohexylcarbamothioate* (**3fa**): White solid; yield 90%; m.p.: 134–136 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.09–1.21 (m, 3H), 1.29–1.34 (m, 2H), 1.57–1.69 (m, 3H), 189–1.96 (m, 2H), 3.69–3.77 (m, 1H), 5.26 (br s, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.67, 25.33, 32.95 50.92, 120.35 (q, *J* = 258 Hz), 121.45, 127.19, 136.84, 149.95, 163.92; IR (KBr) *v*: 1649 cm^{-1} (C=O); ESI-HRMS *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}F_3NOS$: 304.0977; found: 304.0980.

S-*4-fluorophenyl cyclohexylcarbamothioate* (**3ga**): White solid; yield 92%; m.p.: 146–148 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.08–1.22 (m, 3H), 1.30–1.36 (m, 2H), 1.58–1.69 (m, 3H), 1.90–1.94 (m, 2H), 3.70–3.78 (m, 1H), 5.21 (br s, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.50–7.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.66, 25.34, 32.95, 50.73, 116.54 (d, *J* = 22 Hz), 123.96, 137.57 (d, *J* = 8.6 Hz), 163.50 (d, *J* = 250 Hz), 164.63; IR (KBr) *v*: 1654 cm^{-1} (C=O); ESI-HRMS *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}FNOS$: 254.1009; found: 254.1005.

S-*4-chlorophenyl cyclohexylcarbamothioate* (**3ha**): White solid; yield 85%; m.p.: 141–143 °C (lit.[7] 140–142 °C); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.08–1.20 (m, 3H), 1.27–1.38 (m, 2H), 1.54–1.73 (m, 3H), 1.88–1.95 (m, 2H), 3.68–3.77 (m, 1H), 5.20 (br s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.68, 25.34, 32.96, 50.84, 127.14, 129.46, 135.82, 136.54, 164.06; IR (KBr) *v*: 1648 cm^{-1} (C=O); ESI-HRMS *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}ClNOS$: 270.0714; found: 270.0719.

S-*4-bromophenyl cyclohexylcarbamothioate* (**3ia**): White solid; yield 79%; m.p.: 142–144 °C (lit.[23] 141–143 °C); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05–1.22 (m, 3H), 1.27–1.38 (m, 2H), 1.55–1.71 (m, 3H), 1.88–1.95 (m, 2H), 3.68–3.78 (m, 1H), 5.20 (br s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.69, 25.34, 32.97, 50.86, 124.10, 127.77, 132.42, 136.75, 163.89; IR (KBr) *v*: 1653 cm^{-1} (C=O); ESI-HRMS *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}BrNOS$: 314.0209; found: 314.0215.

Declaration of conflicting interests

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