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ORIGINAL PAPER

# Synthesis of carbamothioate derivatives via a copper catalyzed thiocarboxamidation of aryl iodides

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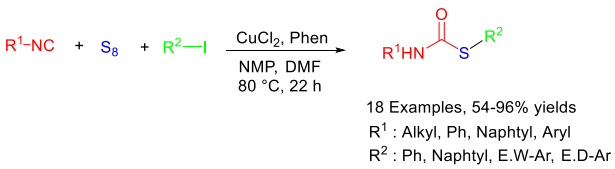
## Abstract

A catalytic route to carbamothioate derivatives through a reaction involving isocyanides, elemental sulfur, and aryl iodides has been developed. The reaction scope has been examined using a range of isocyanides and aryl iodides. The reactions involve two consecutive C–S bond formations. Control experiment revealed that the reaction proceeds through an iminium species.

### Graphic abstract




**Keywords** Cross-coupling reaction · Carbamothioate · Isocyanide · Copper catalysis · Aryl iodide

## Introduction

Metal catalyzed cross-coupling reactions play a significant role in syntheses of C–C and C–heteroatom bonds [1–3]. Of the cross-coupling reactions, the methods for C–S bond formations are prominence due to the importance of C–S bond in pharmaceutical agents and materials science [4–6]. Since the pioneering work of Migita in cross-coupling reaction of aryl halides and thiols with $Pd(PPh_3)_4$ [7, 8], many reports have been developed to circumvent the problems of the transformation such as lack the efficiency and tolerance of functional groups [9, 10].

The first mechanistic study in carbon–sulfur bond formation advanced by Hartwig's group [11]. Subsequently, a great number of reports by Buchwald, Venkataraman, and Li have been developed [12–16]. Particularly, Buchwald described an interesting protocol to form C–S bond which tolerated an exceptional level of functional-groups [17]. Wang's laboratory developed a versatile method for the synthesis of sulfone skeletons using cross-coupling strategy [18]. Consecutive cross-coupling/C–H functionalization has been utilized to form a wide range of 2-(phenylthio)phenols [19]. Jiang has developed tandem C–S bond formation/condensation of 2-haloanilides with metal sulfides to access benzothiazoles skeletons [20].

In this context, Zheng's report on-palladium catalyzed cross-coupling of thiophenols and aryl triflates serves as a useful procedure for the synthesis of aryl sulfide skeletons [21]. Sulfide salts have been also used as sulfur source for synthesis of C–S bond [22]. Copper-catalyzed thioetherification of aryl halides with thiourea provides a complementary route to produce aryl sulfide derivatives [23]. Based on previous reports, the reaction of isocyanides with elemental afforded isothiocyanate derivatives via a nitrile sulfide intermediate [24, 25].

The carbamothioate motif is important skeleton, which exhibited a broad range of activities such as antiviral, bactericidal, anesthetic, and pesticidal [26–28]. There are many reports in literature featuring synthesis of this important class of organosulfur compounds with reactions involving isocyanides are among the most documented methods

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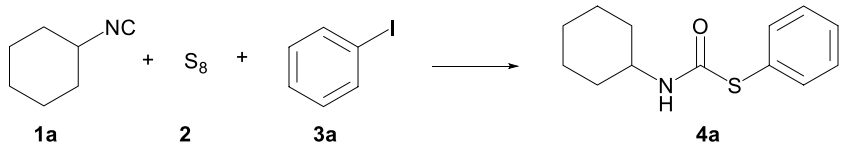
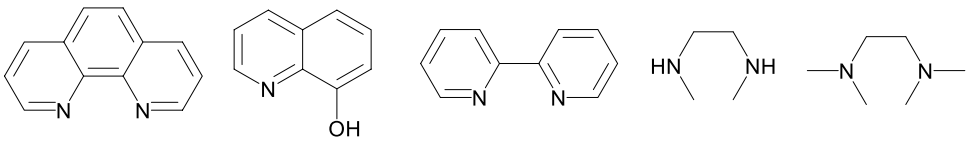
**Table 1** Optimization of the reaction conditions




**1a** **2** **3a** **4a**




**L1** **L2** **L3** **L4** **L5**

| Entry | Catalyst | Ligand | Solvent | Yield/% |
|---|---|---|---|---|
| 1 | CuI | **L1** | DMF | 44 |
| 2 | CuOTf | **L1** | DMF | 34 |
| 3 | CuOAc | **L1** | DMF | 53 |
| 4 | $Cu_2O$ | **L1** | DMF | 21 |
| 5 | CuBr | **L1** | DMF | 17 |
| 6 | CuCl | **L1** | DMF | 29 |
| 7 | $CuCl_2{\cdot}2H_2O$ | **L1** | DMF | 86 |
| 8 | $Cu(OAc)_2{\cdot}H_2O$ | **L1** | DMF | 78 |
| 9 | – | **L1** | DMF | N.R |
| 10 | $CuCl_2{\cdot}2H_2O$ | **L1** | MeCN | 53 |
| 11 | $CuCl_2{\cdot}2H_2O$ | **L1** | Toluene | Trace |
| 12 | $CuCl_2{\cdot}2H_2O$ | **L1** | THF | Trace |
| 13 | $CuCl_2{\cdot}2H_2O$ | **L1** | Dioxane | 34 |
| 14 | $CuCl_2{\cdot}2H_2O$ | **L1** | DMSO | 79 |
| 15 | $CuCl_2{\cdot}2H_2O$ | **L2** | DMF | 34 |
| 16 | $CuCl_2{\cdot}2H_2O$ | **L3** | DMF | 51 |
| 17 | $CuCl_2{\cdot}2H_2O$ | **L4** | DMF | 69 |
| 18 | $CuCl_2{\cdot}2H_2O$ | **L5** | DMF | 35 |
| 19 | $CuCl_2{\cdot}2H_2O$ | – | DMF | 17 |
| 20 | $CuCl_2{\cdot}2H_2O$ | **L1** | DMF | 57[a] |
| 21 | $CuCl_2{\cdot}2H_2O$ | **L1** | DMF | 71[b] |
| 22 | $CuCl_2{\cdot}2H_2O$ | **L1** | DMF | 48[c] |

Reaction conditions for all entries except stated otherwise: **1a** (1.2 mmol), **2a** (0.2 equiv.), **3a** (1.0 mmol), copper salt (0.1 mmol), ligand (0.1 mmol), NMP (1.5 mmol), 3.0 $cm^3$ solvent, 80 °C for 22 h

[a]0.05 mmol of $CuCl_2{\cdot}2H_2O$ was used

[b]18 h

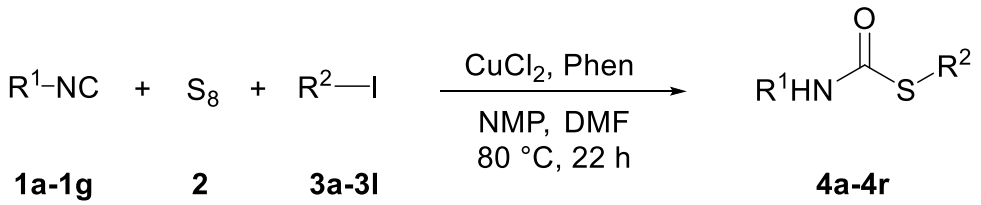
[c]NMP (1.0 mmol)

[29–32]. Previous method in cross-coupling reactions [33–35] encouraged us to evaluate the reactivity of isocyanides, elemental sulfur, and aryl iodides in preparation of carbamothioate skeletons through C-S cross-coupling reaction.

## Results and discussion

The reaction was initially conducted with cyclohexyl isocyanide (**1a**), elemental sulfur (**2**), and iodobenzene (**3a**) as substrates, CuI as the catalyst, and 1,10-phenanthroline (Phen) as the ligand in MeCN at 80 °C. $^1$H NMR spectra

**Table 2** Reaction scope with isocyanides and aryl iodides



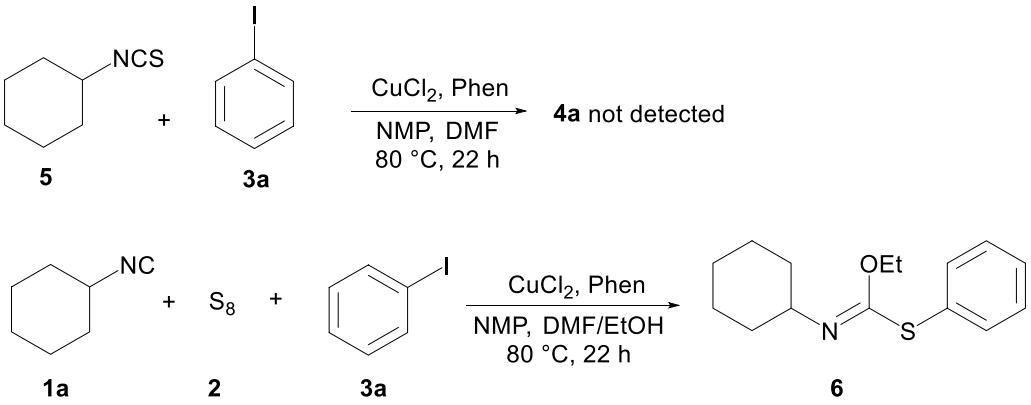

| Entry | Isocyanide, $R^1$ | | Aryl iodide, $R^2$ | | **4**, Yield/% |
|---|---|---|---|---|---|
| 1 | **1a** | Cyclohexyl | **3a** | Phenyl | **4a**, 86 |
| 2 | **1a** | Cyclohexyl | **3b** | *o*-Tolyl | **4b**, 54 |
| 3 | **1a** | Cyclohexyl | **3c** | *m*-Tolyl | **4c**, 81 |
| 4 | **1a** | Cyclohexyl | **3d** | *p*-Tolyl | **4d**, 83 |
| 5 | **1a** | Cyclohexyl | **3e** | 1-Naphthyl | **4e**, 71 |
| 6 | **1a** | Cyclohexyl | **3f** | 4-MeO-$C_6H_4$ | **4f**, 57 |
| 7 | **1a** | Cyclohexyl | **3g** | 4-Br-$C_6H_4$ | **4g**, 81 |
| 8 | **1a** | Cyclohexyl | **3h** | 4-$NO_2$-$C_6H_4$ | **4h**, 93 |
| 9 | **1a** | Cyclohexyl | **3i** | 4-$CH_3OCO$-$C_6H_4$ | **4i**, 89 |
| 10 | **1a** | Cyclohexyl | **3j** | 3-$CF_3$-$C_6H_4$ | **4j**, 96 |
| 11 | **1a** | Cyclohexyl | **3k** | 4-CN-$C_6H_4$ | **4k**, 61 |
| 12 | **1a** | Cyclohexyl | **3l** | 2-Thienyl | **4l**, 75 |
| 13 | **1b** | 1,1,3,3-Tetramethylbutyl | **3a** | Phenyl | **4m**, 81 |
| 14 | **1c** | *tert*-Butyl | **3a** | Phenyl | **4n**, 80 |
| 15 | **1d** | Benzyl | **3a** | Phenyl | **4o**, 83 |
| 16 | **1e** | Phenyl | **3a** | Phenyl | **4p**, 72 |
| 17 | **1f** | 2,6-Dimethylphenyl | **3a** | Phenyl | **4q**, 51 |
| 18 | **1g** | 2-Naphthyl | **3a** | Phenyl | **4r**, 74 |

Reaction conditions: **1** (1.2 mmol), **2** (0.2 equiv.), **3** (1.0 mmol), $CuCl_2$ (0.1 mmol), Phen (0.1 mmol), NMP (1.5 mmol), 3.0 $cm^3$ DMF, 80 °C for 22 h

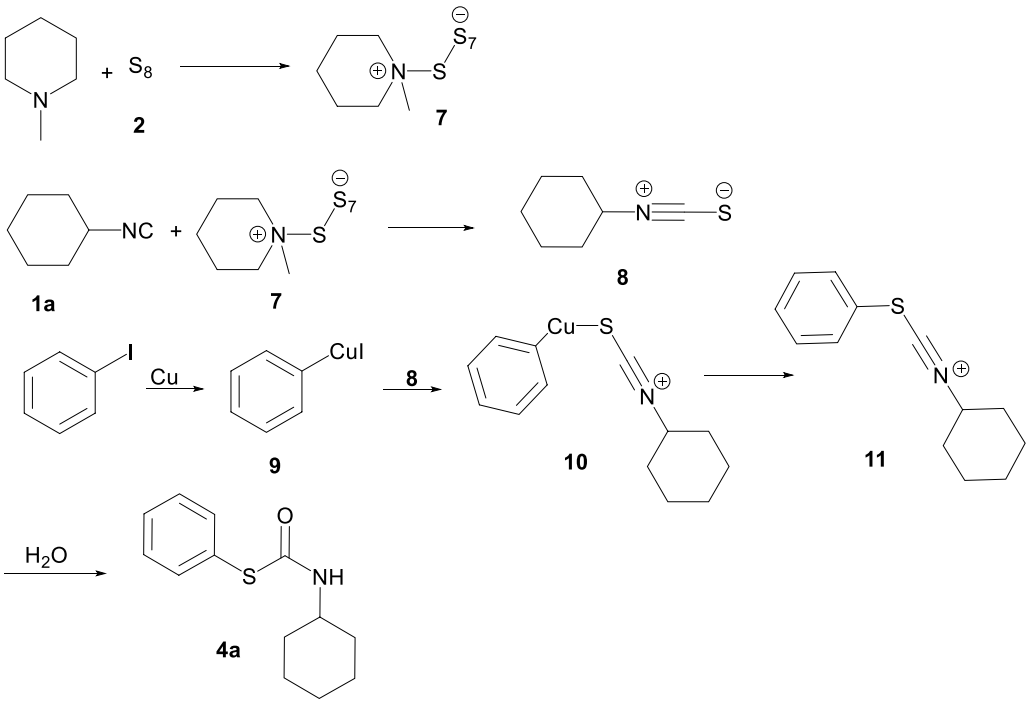
of the crude reaction mixture indicated that the reaction is not productive even at elevated temperatures and for a prolonged time (not shown in Table 1). A literature surveying revealed that *N*-methylpiperidine (NMP) effectively reacts with cyclooctasulfur, affording an active electrophile sulfur source. Accordingly, the use of NMP as the additive led to a promising 44% yield of the desired product together with isothiocyanate cyclohexane in 21% yield (Table 1, entry 1). Whit this result, a range of catalysts have been examined to further improve the reaction yield. The copper screen indicated that the choice of copper salt has great impact on the reaction outcome (Table 1, entries 1–8). $CuCl_2$ represented the optimum choice of catalyst for the reaction (Table 1, entry 7). Meanwhile, $Cu(OAc)_2$ also provided a good yield (Table 1, entry 8). As expected, the targeted product did not obtain without the copper catalyst (Table 1, entry 9). To further develop the reaction conditions, the reaction was conducted in various solvents (Table 1, entries 10–14). Polar solvents were more productive in this transformation. A ligand screen proved the essential presence of L1 for success of the transformation (Table 1, entries 15–19). Additionally, the reaction also shows a great dependence on the amount of the catalyst (Table 1, entry 20). It is also noted that the reduction of the reaction time and additive amount resulted in inferior yields (Table 1, entries 21, 22).

The generality of this transformation was then evaluated with different aryl iodides and isocyanides and the results are shown in Table 2. Iodobenzene (**3a**) reacted efficiently and gave the desired product **4a** in good yield (entry 1). As expected, steric hindrance of aryl synthon affected the reaction yield; as 1-iodo-2-methylbenzene (**3b**) resulted in diminished yield (entry 2). 3- and 4-methyl substituted iodobenzenes **3c**, **3d** also afforded the corresponding product in good yields (entries 3, 4). 1-Iodonaphthalene (**3e**) was also tolerated however, the yield was slightly lower (entry 5). The presence of electron-donating group like methoxy adversely affected the yield presumably duo to the interfering of methoxy group in coordination of copper catalyst and the lower electrophilicity of the substrate (entry 6). The

**Scheme 1**




**Scheme 2**




chemoselectivity of the proposed reaction was also examined using 1-bromo-4-iodobenzene (**3g**) and only the product derived from cross-coupling at 4-position is detected in crude reaction mixture analysis (entry 7). Gratefully, the chemoselectivity in cross-coupling reaction gives further advantage to the current work from a synthetic point of view. Electron-deficient aryl iodides **3h**–**3k** were also subjected to the proposed cross-coupling reaction and the corresponding carbamothioate products were achieved in good yields however, the presence of CN- group on aryl ring resulted in lower yield (entries 8–11). Heteroaromatic substrate **3l** afforded the desired product in reasonable yield (entry 12). To further develop the scope of the proposed transformation a range of alkyl and aryl isocyanides were also examined. The study indicated that alkyl isocyanides were more efficient than those of aryl isocyanides (entries 13–18).

To get insight on the reaction pathway, the reaction was conducted with isothiocyanate cyclohexane **5**. This experiment revealed that the reaction did not proceed through isothiocyanate intermediate (Scheme 1). Additionally, the reaction was conducted in DMF:EtOH (1:1, 4.0 $cm^3$) providing corresponding imidothioate **6** in 71% yield. This study clearly indicated that the reaction proceeds through active nitrilium species **11** (see Scheme 2).

Based on our experimental results and previous reports [24, 25], the possible reaction pathway is depicted in

Scheme 2. Initially, ring opening activation of elemental sulfur with NMP afforded active species **7** which further reacted with isocyanide **1a** to give intermediate **8**. In parallel reaction, iodobenzene oxidatively added to copper catalyst to form active intermediate **9**. Ligand exchange of intermediate **9** with species **8** gives intermediate **10** which further transferred to C–S coupling intermediate **11** via a reductive elimination sequence. Finally, **11** is hydrolyzed during the aqueous work-up to afford the targeted product **4a** (Scheme 2).

## Conclusion

In conclusion, we have developed a catalytic system for direct thiocarboxamidation of aryl iodides using commercially available substrates. A decent range of aryl iodides and isocyanides were tolerated, providing the corresponding products in reasonable yields.

## Experimental

All reagents, catalysts, and solvents were obtained from commercial sources (Aldrich, Acros, Merck, Fluka). Solvents were stored over activated molecular sieves 3 Å or 4 Å before the use. All reactions were carried out in Schlenk tube (25 $cm^3$). M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. $^1H$ and $^{13}C$ NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp; $\delta$ in ppm, $J$ in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer. Elemental analyses (C, H, N) were performed with a Heraeus Rapid analyzer. Column chromatography was performed using Silica gel 60 (particle size 63–200 µm). The reactions were monitored by thin layer chromatography (silica gel 60, Merck, item number 116835) using UV light (254 nm) to visualize the progress of the reactions.

### General procedure for compounds 4

A Schlenk tube (25 $cm^3$) was charged with Cu salt (0.1 mmol), NMP (1.5 mmol), isocyanide (1.2 mmol), Phen (0.1 mmol), elemental sulfur (0.2 equiv.), aryl iodide (1.0 mmol), and 3.0 $cm^3$ DMF. The mixture was stirred for 30 min at ambient conditions and then warmed up to 80 °C. The reaction mixture was then stirred for 22 h at 80 °C. After consuming the starting material (TLC monitoring), the resulting slurry was quenched with 5 $cm^3$ sat.aq $NH_4Cl$ and extracted with $CH_2Cl_2$ ($3\times10$ $cm^3$). The organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was subjected to flash chromatography (silica gel, hexane:EtOAc) to give the pure targeted product **4**.

***S*-Phenyl cyclohexylcarbamothioate (4a, $C_{13}H_{17}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.24) affording 0.20 g (86%) of **4a**. IR (KBr): $\bar{\nu}$ = 3311, 3036, 2959, 1653, 1461, 1243, 1067 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.23–1.99 (10H, m, 5 $CH_2$), 3.87–3.93 (1H, m, CH), 6.73 (1H, d, $^3J$ = 5.8 Hz, NH), 7.25 (1H, t, $^3J$ = 7.3 Hz, CH), 7.31 (2H, t, $^3J$ = 7.3 Hz, 2 CH), 7.41 (2H, t, $^3J$ = 7.3 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 25.3 (2 $CH_2$), 26.6 ($CH_2$), 34.9 (2 $CH_2$), 56.1 (CH), 126.1 (CH), 128.7 (2 CH), 130.1 (2 CH), 137.2 (C), 170.4 (C) ppm; EI-MS (70 eV): $m/z$ (%) = 235 ($M^+$, 2), 152 (13), 126 (34), 83 (81), 77 (100).

***S*-(*o*-Tolyl) cyclohexylcarbamothioate (4b, $C_{14}H_{19}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.23) affording 0.15 g (54%) **4b**. IR (KBr): $\bar{\nu}$ = 3327, 3043, 2968, 1651, 1412, 1304, 1087 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.27–1.96 (10H, m, 5 $CH_2$), 2.38 (3H, s, Me), 3.78–3.83 (1H, m, CH), 6.89 (1H, d, $^3J$ = 5.5 Hz, NH), 7.21 (1H, t, $^3J$ = 7.8 Hz, CH), 7.35 (1H, d, $^3J$ = 7.8 Hz, CH), 7.44 (1H, t, $^3J$ = 7.8 Hz, CH), 7.56 (1H, d, $^3J$ = 7.7 Hz, CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 23.9 (Me), 26.0 (2 $CH_2$), 28.5 ($CH_2$), 36.1 (2 $CH_2$), 60.3 (CH), 126.1 (CH), 126.8 (CH), 128.3 (CH), 132.6 (CH), 135.1 (C), 144.7 (C), 171.2 (C) ppm; EI-MS (70 eV): $m/z$ (%) = 249 ($M^+$, 1), 166 (26), 151 (47), 126 (67), 121 (78), 83 (100).

***S*-(*p*-Tolyl) cyclohexylcarbamothioate (4c, $C_{14}H_{19}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 4/1, $R_f$: 0.19) affording 0.20 g (81%) **4c**. IR (KBr): $\bar{\nu}$ = 3316, 3030, 2973, 1647, 1472, 1311, 1158 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.30–2.06 (10H, m, 5 $CH_2$), 2.41 (3H, s, Me), 3.75–3.80 (1H, m, CH), 6.72 (1H, d, $^3J$ = 5.7 Hz, NH), 6.85 (2H, d, $^3J$ = 7.5 Hz, 2 CH), 6.97 (2H, d, $^3J$ = 7.5 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 23.5 (Me), 26.3 (2 $CH_2$), 29.2 ($CH_2$), 36.4 (2 $CH_2$), 59.7 (CH), 128.7 (2 CH), 130.6 (2 CH), 133.5 (C), 139.2 (C), 171.5 (C) ppm; EI-MS (70 eV): $m/z$ (%) = 249 ($M^+$, 1), 166 (19), 151 (43), 121 (55), 98 (63), 83 (100).

***S*-(*m*-Tolyl) cyclohexylcarbamothioate (4d, $C_{14}H_{19}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.29) affording 0.21 g (83%) **4d**. IR (KBr): $\bar{\nu}$ = 3322, 3019, 2958, 1643, 1462, 1266, 1097 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.26–1.92 (10H, m, 5 $CH_2$), 2.45 (3H, s, Me), 3.71–3.77 (1H, m, CH), 6.72 (1H, d, $^3J$ = 5.5 Hz, NH), 6.91 (1H, d, $^3J$ = 7.9 Hz, CH), 7.13 (1H, s, CH), 7.19 (1H, t, $^3J$ = 7.9 Hz, CH), 7.33 (1H, d, $^3J$ = 7.8 Hz, CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 23.7 (Me), 26.1 (2 $CH_2$), 27.9 ($CH_2$), 35.1 (2 $CH_2$), 58.1 (CH), 127.1 (CH), 127.9 (CH), 129.8 (CH), 134.3 (CH),

137.1 (C), 141.4 (C), 172.3 (C) ppm; EI-MS (70 eV): *m/z* (%) = 249 ($M^+$, 1), 166 (19), 151 (54), 126 (39), 123 (69), 83 (100).

***S*-(Naphthalen-1-yl) cyclohexylcarbamothioate (4e, $C_{17}H_{19}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 4/1, $R_f$: 0.16) affording 0.20 g (71%) **4e**. IR (KBr): $\bar{\nu}$ = 3317, 3031, 2971, 1647, 1456, 1311, 1201, 1068 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.19–1.87 (10H, m, 5 $CH_2$), 3.76–3.82 (1H, m, CH), 6.88 (1H, d, $^3J$ = 5.7 Hz, NH), 7.39–7.55 (4H, m, 4 CH), 7.84 (1H, d, $^3J$ = 7.6 Hz, CH), 8.03 (1H, d, $^3J$ = 7.8 Hz, CH), 8.26 (1H, d, $^3J$ = 7.4 Hz, CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 25.8 (2 $CH_2$), 28.3 ($CH_2$), 36.2 (2 $CH_2$), 59.3 (CH), 124.3 (CH), 125.2 (CH), 127.3 (CH), 127.8 (CH), 129.5 (CH), 129.8 (CH), 130.3 (C), 131.7 (CH), 134.5 (C), 136.1 (C), 170.8 (C) ppm; EI-MS (70 eV): *m/z* (%) = 285 ($M^+$, 1), 202 (13), 187 (32), 159 (41), 127 (72), 83 (100).

***S*-(4-Methoxyphenyl) cyclohexylcarbamothioate (4f, $C_{14}H_{19}NO_2S$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.14) affording 0.15 g (57%) **4f**. IR (KBr): $\bar{\nu}$ = 3314, 3042, 2981, 1640, 1311, 1232, 1066 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.24–1.84 (10H, m, 5 $CH_2$), 3.76 (3H, s, OMe), 3.87–3.92 (1H, m, CH), 6.89 (1H, d, $^3J$ = 5.6 Hz, NH), 7.12 (2H, d, $^3J$ = 7.8 Hz, 2 CH), 7.55 (2H, d, $^3J$ = 7.8 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 24.1 (2 $CH_2$), 28.4 ($CH_2$), 36.2 (2 $CH_2$), 56.1 (OMe), 60.3 (CH), 114.3 (2 CH), 129.9 (C), 131.2 (2 CH), 159.1 (C), 171.2 (C) ppm; EI-MS (70 eV): *m/z* (%) = 265 ($M^+$, 1), 182 (13), 167 (25), 139 (78), 126 (52), 107 (100), 83 (89).

***S*-(4-Bromophenyl) cyclohexylcarbamothioate (4g, $C_{13}H_{16}BrNOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 4/1, $R_f$: 0.29) affording 0.25 g (81%) **4g**. IR (KBr): $\bar{\nu}$ = 3328, 3017, 2981, 1651, 1478, 1244, 1063 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.34–1.95 (10H, m, 5 $CH_2$), 3.93–3.97 (1H, m, CH), 6.77 (1H, d, $^3J$ = 5.5 Hz, NH), 7.32 (2H, d, $^3J$ = 7.3 Hz, 2 CH), 7.82 (2H, d, $^3J$ = 7.3 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 25.7 (2 $CH_2$), 29.6 ($CH_2$), 35.4 (2 $CH_2$), 58.7 (CH), 122.1 (C), 130.5 (2 CH), 132.8 (2 CH), 136.2 (C), 170.2 (C) ppm; EI-MS (70 eV): *m/z* (%) = 313 ($M^+$ + 2, 3), 313 ($M^+$, 3), 217 (26), 215 (26), 189 (43),187 (43), 126 (62), 98 (81), 83 (100).

***S*-(4-Nitrophenyl) cyclohexylcarbamothioate (4h, $C_{13}H_{16}N_2O_3S$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 1/1, $R_f$: 0.18) affording 0.26 g (93%) **4h**. IR (KBr): $\bar{\nu}$ = 3341, 3018, 2953, 1654, 1518, 1473, 1344, 1219, 1054 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.33–1.96 (10H, m, 5 $CH_2$), 3.86–3.91 (1H, m, CH), 7.08 (1H, d, $^3J$ = 5.8 Hz, NH), 7.71 (2H, d, $^3J$ = 7.4 Hz, 2 CH), 8.11 (2H, d, $^3J$ = 7.4 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 24.7 (2 $CH_2$), 30.1 ($CH_2$), 35.7 (2 $CH_2$), 60.7 (CH), 126.4 (2 CH), 134.1 (2 CH), 139.7 (C), 148.3 (C), 172.4 (C) ppm; EI-MS (70 eV): *m/z* (%) = 280 ($M^+$, 1), 197 (11), 182 (34), 154 (26), 126 (89), 83 (100).

**Methyl 4-[(cyclohexylcarbamoyl)thio]benzoate (4i, $C_{15}H_{19}NO_3S$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.34) affording 0.26 g (89%) **4i**. IR (KBr): $\bar{\nu}$ = 3327, 3032, 2961, 1737, 1644, 1272, 1068 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.29–1.95 (10H, m, 5 $CH_2$), 3.81 (3H, s, OMe), 3.90–3.95 (1H, m, CH), 6.72 (1H, d, $^3J$ = 5.4 Hz, NH), 7.37 (2H, d, $^3J$ = 7.6 Hz, 2 CH), 7.90 (2H, d, $^3J$ = 7.6 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 24.8 (2 $CH_2$), 29.6 ($CH_2$), 35.3 (2 $CH_2$), 54.12 (OMe), 59.5 (CH), 128.2 (C), 130.5 (2 CH), 132.7 (2 CH), 141.4 (C), 167.4 (C), 170.8 (C) ppm; EI-MS (70 eV): *m/z* (%) = 293 ($M^+$, 1), 262 (11), 210 (31), 195 (48), 126 (78), 83 (100).

***S*-[3-(Trifluoromethyl)phenyl] cyclohexylcarbamothioate (4j, $C_{14}H_{16}F_3NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 2/1, $R_f$: 0.29) affording 0.28 g (93%) **4j**. IR (KBr): $\bar{\nu}$ = 3332, 3044, 2985, 1652, 1467, 1248, 1076 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.18–1.92 (10H, m, 5 $CH_2$), 3.96–4.03 (1H, m, CH), 7.02 (1H, d, $^3J$ = 5.4 Hz, NH), 7.18 (1H, d, $^3J$ = 7.5 Hz, CH), 7.31 (1H, t, $^3J$ = 7.6 Hz, CH), 7.40 (1H, d, $^3J$ = 7.6 Hz, CH), 7.53 (1H, s, CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 23.8 (2 $CH_2$), 27.8 ($CH_2$), 36.7 (2 $CH_2$), 60.7 (CH), 124.2 (CH, q, $^3J$ = 4.1 Hz), 125.3 (CH, q, $^3J$ = 4.1 Hz), 128.2 ($CF_3$, q, $^1J$ = 268.5 Hz), 129.7 (CH), 129.5 (CH), 132.6 (C, q, $^2J$ = 34.8 Hz), 134.2 (CH), 137.6 (C), 173.8 (C) ppm; EI-MS (70 eV): *m/z* (%) = 303 ($M^+$, 4), 220 (9), 205 (31), 177 (74), 98 (66), 83 (100).

***S*-(4-Cyanophenyl) cyclohexylcarbamothioate (4k, $C_{14}H_{16}N_2OS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 2/1, $R_f$: 0.31) affording 0.16 g (61%) **4k**. IR (KBr): $\bar{\nu}$ = 3322, 3045, 2976, 2241, 1649, 1463, 1266, 1061 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.21–1.88 (10H, m, 5 $CH_2$), 3.84–3.91 (1H, m, CH), 6.92 (1H, d, $^3J$ = 5.7 Hz, NH), 7.41 (2H, d, $^3J$ = 7.8 Hz, 2 CH), 7.67 (2H, d, $^3J$ = 7.8 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 24.3 (2 $CH_2$), 30.1 ($CH_2$), 36.1 (2 $CH_2$), 60.1 (CH), 116.3 (C), 128.9 (2 CH), 134.1 (2 CH), 139.2 (C), 142.7 (C), 170.5 (C) ppm; EI-MS (70 eV): *m/z* (%) = 260 ($M^+$, 1), 177 (34), 162 (16), 134 (31), 128 (89), 83 (100).

***S*-(Thiophen-2-yl) cyclohexylcarbamothioate (4l, $C_{11}H_{15}NOS_2$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 4/1, $R_f$: 0.16) affording 0.18 g (75%) **4l**. IR (KBr): $\bar{\nu}$ = 3316, 3044, 2980, 1647, 1454, 1311, 1198, 1046 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.29–1.93 (10H, m, 5 $CH_2$), 3.88–3.93 (1H, m, CH), 6.71 (1H, d, $^3J$ = 5.5 Hz, NH), 6.93 (1H, t, $^3J$ = 7.0 Hz, CH), 7.19 (1H, d, $^3J$ = 7.0 Hz, CH), 7.54 (1H, d, $^3J$ = 7.0 Hz, CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 25.3 (2 $CH_2$), 28.2 ($CH_2$), 35.1 (2 $CH_2$), 57.9 (CH), 124.6 (C), 125.1 (CH), 128.3 (CH), 129.7 (CH), 169.6 (C) ppm; EI-MS (70 eV): *m/z* (%) = 241 ($M^+$, 1), 158 (43), 143 (24), 126 (67), 115 (86), 83 (100).

***S*-Phenyl (2,4,4-trimethyl-2-pentyl)carbamothioate (4m, $C_{15}H_{23}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 4/1, $R_f$: 0.35) affording 0.21 g (81%) **4m**. IR (KBr): $\bar{\nu}$ = 3331, 3035, 2973, 1651, 1471, 1411, 1265, 1143, 1062 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.09 (9H, s, 3 Me), 1.45 (2H, s, $CH_2$), 1.54 (6H, s, 2 Me), 6.80 (1H, d, $^3J$ = 5.4 Hz, NH), 7.29 (1H, t, $^3J$ = 7.7 Hz, CH), 7.33 (2H, t, $^3J$ = 7.7 Hz, 2 CH), 7.46 (2H, t, $^3J$ = 7.7 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 28.9 (2 Me), 32.6 (3 Me), 34.1 (C), 48.2 (C), 55.7 ($CH_2$), 126.4 (CH), 128.9 (2 CH), 130.4 (2 CH), 136.4 (C), 169.2 (C) ppm; EI-MS (70 eV): *m/z* (%) = 265 ($M^+$, 2), 208 (16), 156 (55), 152 (34), 113 (78), 109 (19), 57 (100).

***S*-Phenyl *tert*-butylcarbamothioate (4n, $C_{11}H_{15}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.32) affording 0.17 g (80%) **4n**. IR (KBr): $\bar{\nu}$ = 3327, 3043, 2952, 1651, 1473, 1311, 1199, 1075 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.49 (9H, s, 3 Me), 6.72 (1H, d, $^3J$ = 5.6 Hz, NH), 7.26 (1H, t, $^3J$ = 7.4 Hz, CH), 7.32 (2H, t, $^3J$ = 7.4 Hz, 2 CH), 7.43 (2H, t, $^3J$ = 7.4 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 32.9 (3 Me), 60.3 (C), 126.9 (CH), 129.3 (2 CH), 129.8 (2 CH), 136.7 (C), 169.8 (C) ppm; EI-MS (70 eV): *m/z* (%) = 209 ($M^+$, 2), 152 (27), 109 (16), 100 (57), 77 (83), 57 (100).

***S*-Phenyl benzylcarbamothioate (4o, $C_{14}H_{13}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 5/1, $R_f$: 0.19) affording 0.20 g (83%) **4o**. (KBr): $\bar{\nu}$ = 3322, 3017, 2971, 1653, 1455, 1276, 1083 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 4.44 (2H, d, $^3J$ = 5.7 Hz, $CH_2$), 6.83 (1H, t, $^3J$ = 5.7 Hz, NH), 7.24–7.41 (10H, m, 10 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 49.2 ($CH_2$), 124.7 (CH), 126.3 (CH), 127.3 (2 CH), 128.8 (2 CH), 130.1 (2 CH), 131.3 (2 CH), 136.2 (C), 139.4 (C), 171.1 (C) ppm; EI-MS (70 eV): *m/z* (%) = 243 ($M^+$, 1), 152 (16), 134 (61), 106 (33), 91 (100), 77 (68).

***S*-Phenyl phenylcarbamothioate (4p, $C_{13}H_{11}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.18) affording 0.16 g (72%) **4p**. IR (KBr): $\bar{\nu}$ = 3341, 3045, 2971, 1655, 1411, 1314, 1182, 1061 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 7.11 (1H, t, $^3J$ = 7.8 Hz, CH), 7.23–7.34 (5H, m, 5 CH), 7.43 (2H, d, $^3J$ = 7.4 Hz, 2 CH), 7.66 (2H, d, $^3J$ = 7.8 Hz, 2 CH), 8.19 (1H, br s, NH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 119.8 (2 CH), 126.2 (CH), 127.1 (CH), 128.1 (2 CH), 129.7 (2 CH), 130.7 (2 CH), 136.1 (C), 138.2 (C), 168.3 (C) ppm; EI-MS (70 eV): *m/z* (%) = 229 ($M^+$, 1), 152 (54), 120 (76), 109 (43), 77 (100), 54 (42).

***S*-Phenyl (2,6-dimethylphenyl)carbamothioate (4q, $C_{15}H_{15}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 5/1, $R_f$: 0.21) affording 0.13 g (51%) **4q**. IR (KBr): $\bar{\nu}$ = 3341, 3046, 2966, 1652, 1478, 1317, 1178, 1072 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 2.29 (6H, s, 2 Me), 6.98 (1H, t, $^3J$ = 7.3 Hz, CH), 7.13 (2H, d, $^3J$ = 7.3 Hz, 2 CH), 7.25–7.34 (3H, m, 3 CH), 7.44 (2H, d, $^3J$ = 7.6 Hz, 2 CH), 8.02 (1H, br s, NH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 20.1 (2 Me), 125.2 (CH), 126.7 (CH), 127.6 (2 CH), 128.7 (2 CH), 129.4 (2 CH), 132.5 (2 C), 136.3 (C), 137.1 (C), 167.1 (C) ppm; EI-MS (70 eV): *m/z* (%) = 257 ($M^+$, 1), 152 (19), 148 (67), 109 (43), 105 (100), 77 (76).

***S*-Phenyl naphthalen-2-ylcarbamothioate (4r, $C_{17}H_{13}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 3/1, $R_f$: 0.30) affording 0.21 g (74%) **4r**. IR (KBr): $\bar{\nu}$ = 3340, 3051, 2963, 1651, 1478, 1287, 1167, 1076 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 6.98 (1H, t, $^3J$ = 7.3 Hz, CH), 7.08 (1H, s, CH), 7.27–7.44 (8H, m, 8 CH), 7.59 (1H, d, $^3J$ = 7.4 Hz, CH), 7.73 (1H, d, $^3J$ = 7.2 Hz, CH), 7.82 (1H, d, $^3J$ = 7.4 Hz, CH), 8.11 (1H, br s, NH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 118.2 (CH), 120.2 (CH), 122.5 (CH), 125.1 (CH), 125.5 (C), 125.7 (CH), 126.2 (CH), 126.7 (CH), 128.9 (CH), 129.2 (2 CH), 130.5 (2 CH), 134.1 (C), 136.2 (C), 137.8 (C), 167.5 (C) ppm; EI-MS (70 eV): *m/z* (%) = 279 ($M^+$, 2), 170 (74), 142 (51), 137 (40), 127 (83), 77 (100).

***O*-Ethyl *S*-phenyl cyclohexylcarbonimidothioate (6, $C_{15}H_{21}NOS$)** The crude product was purified by column chromatography ($SiO_2$, hexane/EtOAc 6/1, $R_f$: 0.32) affording 0.20 g (71%) of **6**. IR (KBr): $\bar{\nu}$ = 3052, 2981, 1606, 1452, 1311, 1182 $cm^{-1}$; $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta$ = 1.20 (3H, t, $^3J$ = 5.8 Hz, $CH_3$), 1.32–1.87 (10H, m, 5 $CH_2$), 3.76 (2H, q, $^3J$ = 5.8 Hz, $CH_2$), 4.03–4.09 (1H, m, CH), 7.26 (2H, d, $^3J$ = 7.8 Hz, 2 CH), 7.31 (1H, t, $^3J$ = 7.8 Hz, CH), 7.43 (2H, t, $^3J$ = 7.8 Hz, 2 CH) ppm; $^{13}C$ NMR (125.7 MHz, $CDCl_3$): $\delta$ = 17.9 ($CH_3$), 27.3 (2 $CH_2$), 29.1 ($CH_2$), 35.2 (2 $CH_2$), 60.8 (CH), 64.2 ($CH_2$), 126.7 (CH), 130.2 (2 CH),

131.6 (2 CH), 134.9 (C), 155.2 (C) ppm; EI-MS (70 eV): $m/z$ (%) = 235 ($M^+$, 2), 152 (13), 126 (34), 83 (81), 77 (100).

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