Three-Component Reaction between Isocyanides, Aliphatic Amines and Elemental Sulfur: Preparation of Thioureas under Mild Conditions with Complete Atom Economy

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Abstract: The reaction of isocyanides with aliphatic amines in the presence of elemental sulfur was found to proceed efficiently at, or near, room temperature to produce thioureas in excellent yields and with complete atom economy.

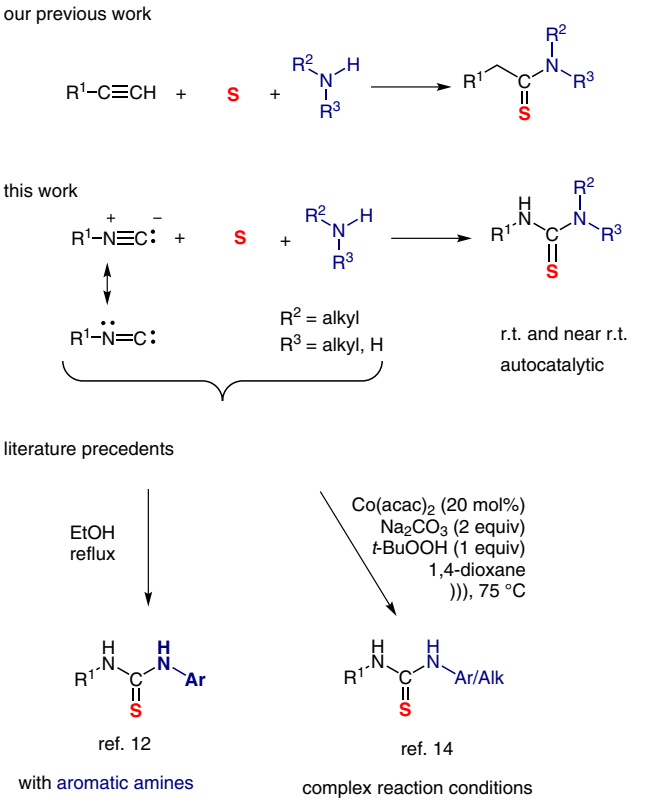
Key words: multicomponent reactions, elemental sulfur, isocyanides, thioureas, atom economy, sulfur–amine interaction

The thiourea group constitutes an important motif found in various biologically active compounds.[1] Additionally, thioureas are key intermediates in the preparation of nitrogen- and/or sulfur-containing compounds, including heterocycles.[2] Recently, thiourea derivatives have emerged as one of the most efficient and popular classes of organocatalysts.[3]

Consequently, a number of methods[4] are commonly employed for the formation of this linkage, including the addition of amines to isothiocyanates,[5] thiophosgene,[6] carbon disulfide[7] and other thioacylating reagents.[8]

Reactions involving elemental sulfur as a reaction component are highly interesting from practical, cost-effective and synthetic convenience points of view. First, elemental sulfur is a readily available and inexpensive reagent, even in high degrees of purity.[9] Second, being a nontoxic, free-flowing and stable solid under normal conditions, sulfur is easy to handle. Finally, although elemental sulfur itself is only weakly reactive, its reactivity towards other functional groups can be enhanced profoundly in the presence of catalysts or activators of both Lewis acidic or basic natures. Among these activators, aliphatic amines are remarkable candidates due to their strong interaction with elemental sulfur[10] as well as their presence in reaction mixtures as reaction components.

From this analysis, we were particularly interested in a multicomponent combination using elemental sulfur and aliphatic amines for the construction of thioureas with respect to the concept of atom economy. The present study was inspired partially by our recent investigation on the autocatalyzed three-component reaction between alkynes, aliphatic amines and elemental sulfur leading to the corresponding thioamides.[11] We hypothesized that isocyanides, which are described by two resonance structures, one with a triple bond between the nitrogen and the carbon (Scheme 1), would react with amines and elemental sulfur in a similar manner. Indeed, such an approach has been described for anilines in refluxing ethanol;[12] at this temperature, isothiocyanates are formed in situ from isocyanides and elemental sulfur even without external activation,[13] and subsequently react with the anilines to provide the corresponding *N*-arylthioureas (Scheme 1). Very recently, a set of catalytic conditions [$Co(acac)_2$ (20 mol%), 1,4-dioxane, 75 °C, ultrasonic activation[14]] for such transformations has been described (Scheme 1).[15] Although, in principle, no external oxidizing agent is required for this transformation, *tert*-butyl hydroperoxide (1 equiv) was used in the presence of sodium carbonate (2 equiv). Finally, isocyanides can be transformed into thioureas by a two-step sequence via isothiocyanates (by the reaction with sulfur catalyzed by selenium).[16]



Scheme 1 Thioureas from isocyanides, sulfur and amines

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Herein, we report the first example of the autocatalytic three-component reaction between isocyanides, aliphatic amines and elemental sulfur at, or near, room temperature. The notable features of this reaction are its simplicity, generality for aliphatic amines, atom efficiency and mild reaction conditions.

In accordance with our hypothesis, we commenced this study with the reaction of cyclohexyl isocyanide (**1**, R = Cy), 2-phenethylamine [**2**; $R^1 = (CH_2)_2Ph$, $R^2 = H$] and elemental sulfur, S_8. To our delight, the reaction proceeded smoothly and slightly exothermically at room temperature to provide the desired thiourea quantitatively.

The substrate scope of the reaction was then investigated. A variety of N,N′-disubstituted and N,N,N′-trisubstituted thioureas were synthesized by using this method (Scheme 2).

The mild reaction conditions allowed the thionation and amination of isocyanides to be carried out in the presence of a range of functional groups, including aromatic chloro (**3ab**, **3ac**, **3cb**), hydroxy (**3al**), anilino (**3am**), double bond (**3an**) and ester (**3dh**) groups. Primary (**2a–g**, **2l–p**) and secondary (**2h–k**) amines were competent substrates at ambient temperature. Notably, even for the substrates bearing sterically demanding groups (isocyanide **1c**, amines **2e–k**), good reactivities were still observed although a gentle heating (40–50 °C) may be necessary to accelerate the reactions. Ethyl isocyanoacetate (**1d**) was shown to be extremely reactive; its reaction with *N*-benzylmethylamine (**2h**) was achieved in less than 30 minutes of mixing at room temperature, giving thiourea **3dh** in 93% yield (Scheme 2).

To investigate the mechanism of the thionation and amination of isocyanides, several experiments were performed. First, cyclohexyl isocyanide (**1a**, R = Cy) was stirred separately with amine **2a** ($R^1 = CH_2C_6H_4$-4-Me, $R^2 = H$) and with sulfur. In both cases, isocyanide **1a** was

Biographical Sketches

Dr. **Ali Al-Mourabit** (left) was born in 1958 at Beni Chiker, Nador, Morroco and received his education in organic chemistry and natural substances in France. He obtained his Ph.D in 1989 from Paris XI University under the supervision of Dr. P. Potier at the Institut de Chimie des Substances Naturelles. After an Alexander von Humboldt postdoctoral fellowship in Germany in organic synthesis, he began his academic career as a researcher (Chargé de Recherche) at the CNRS-ICSN (Gif-sur-Yvette, France). At present, he is head of the marine natural products chemistry group and the coordinator of Natural Substances and Medicinal Chemistry at the ICSN. He founded the BioChiMar network that is under his leadership since 2009. His current research interests include bioactive natural products isolation, biomimetic synthesis, medicinal chemistry and green chemistry.

Ludmila Ermolenko (middle) graduated MS in chemistry from the Lomonosov University (Moscow, Russia) in 1975. She received her PhD degree from the École Normale Supérieur de Cachan (France) under the supervision of J. Delaire on the photocatalyzed aerobic oxidation of alkanes in the presence of decatungstates. In 1997, she was appointed at CNRS as a postdoctoral fellow and then as a research engineer. She worked successively on new methodologies for the stereoselective synthesis of L-hexoses and 2-deoxy-2-amino hexoses and the synthesis of inhibitors of AGEs involved in the complications of diabetes (Pierre Potier's group). In 2007, she joined the group of Dr. A. Al-Mourabit at the ICSN. Her current research interests involve synthetic methodology, biomimetic synthesis of marine metabolites, and mechanistic studies of the secondary metabolite formation.

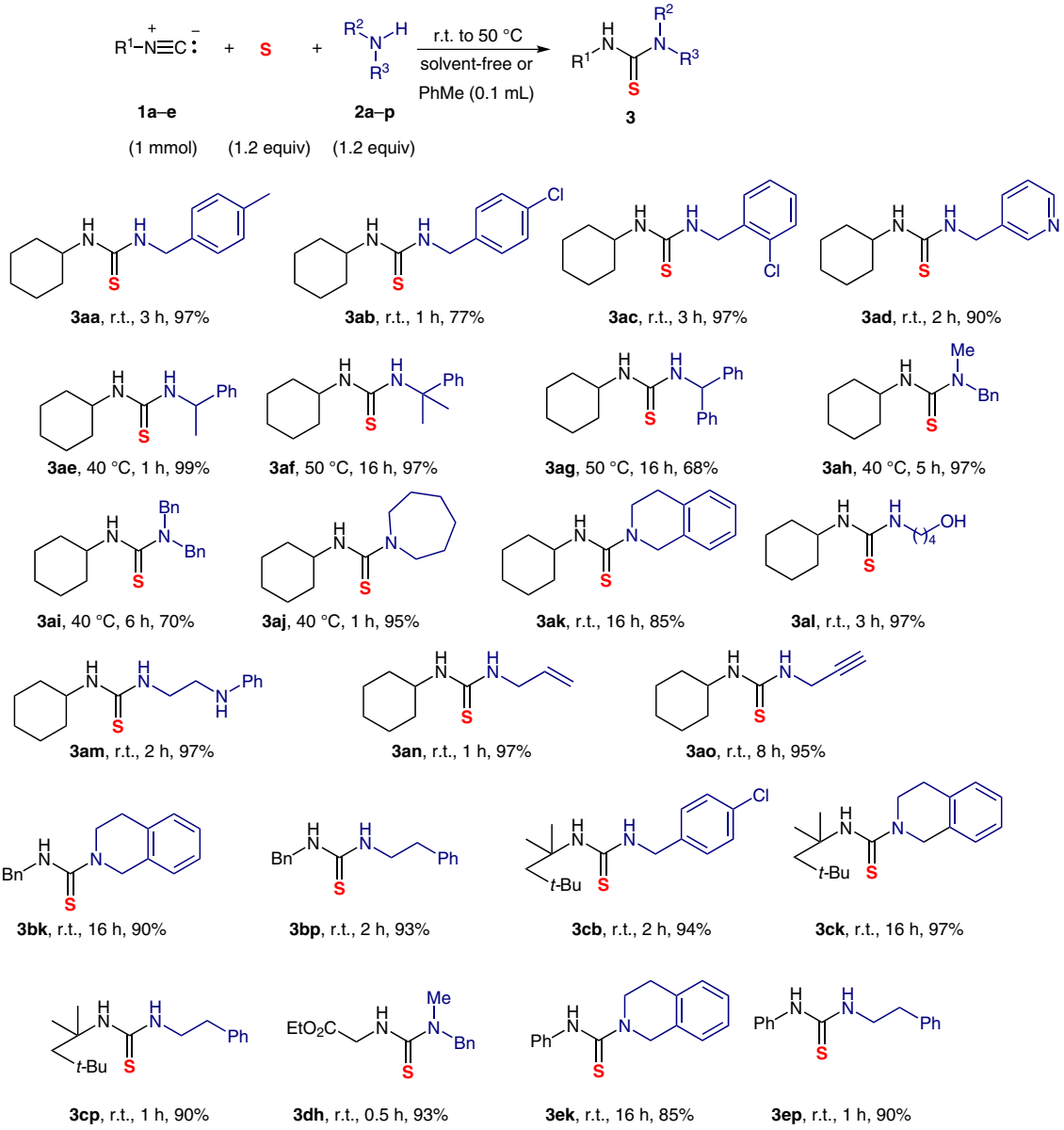
Thanh Binh Nguyen (right) was born in Hanoi, Vietnam in 1982. He obtained his BS degree from University of Natural Sciences, Hochiminh city in 2004. He subsequently received his MS (2005, Pr. J. Mortier) and PhD (2008, Dr. G. Dujardin) from University of Maine, Le Mans, France. From 2009 to 2011, he was a postdoctoral fellow at the Institut de Chimie des Substances Naturelles (ICSN) with Dr. F. Guéritte and Dr. Qian Wang Zhu. He then joined the group of Dr. A. Al-Mourabit - Centre National de la Recherche Scientifique as a researcher (Chargé de Recherche) at the same Institute in October 2011. His current research interests include medicinal chemistry, synthesis of marine natural products, new methods for carbon–nitrogen bond formation involving elemental sulfur, iron/sulfur catalysis and green chemistry.

shown to be inert towards amine **2a** and elemental sulfur without the addition of a catalyst at the usual reaction temperature.[12,17] Consequently, the formation of thiourea by the present method could be initiated with the activation of elemental sulfur by the aliphatic amine,[9] as presented in Scheme 3. Aliphatic amine **2** reacts with cyclic S_8 to yield a zwitterionic ammonium polysulfide chain **4**. The chain length of this zwitterion **4** can vary in a wide range depending on the temperature and concentration, as well as the sulfur-to-amine ratio. The zwitterion form **4** can be in equilibrium with its neutral form **4′**. Having a negatively charged sulfur terminus which is very nucleophilic due to both the anionic and alpha effects of the polysulfane chain, the zwitterion form **4** can attack the carbenoid carbon atom of the isocyanide **1** to yield the thiourea **3** in a concerted fashion with concomitant extrusion of the cyclic polysulfane with one less sulfur atom. Alternatively, this step can occur in a stepwise manner to give isothiocyanate which is trapped by free amine in the reaction medium, leading to thiourea **3**.

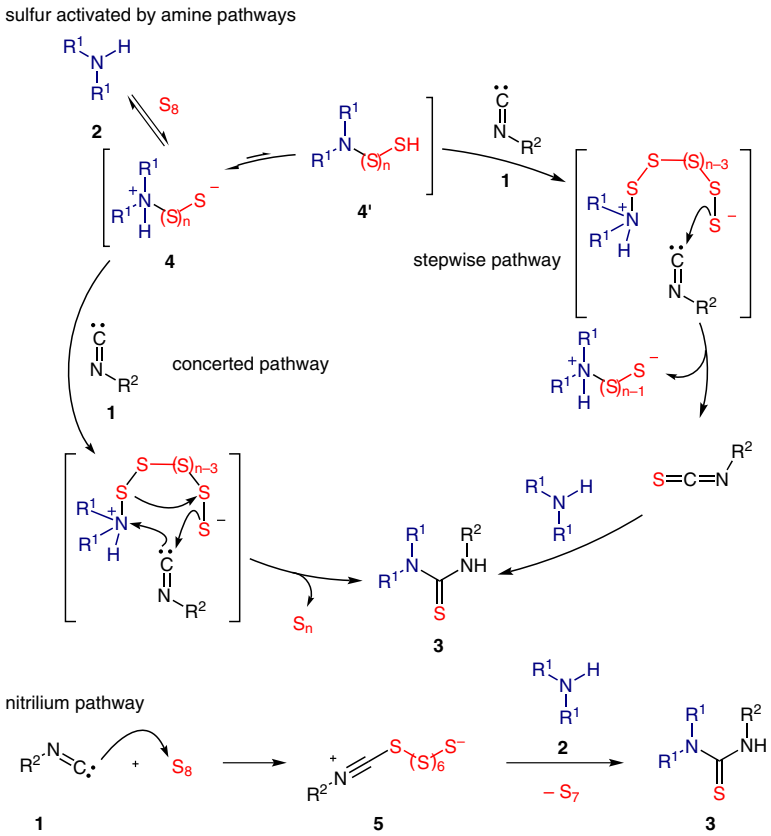
An alternative nitrilium pathway would be initiated by a nucleophilic addition of the isocyanide **1** to elemental sulfur leading to nitrilium **5**. Trapping of intermediate **5** by amine **2** and subsequent transformation leads to thiourea **3**.[18]

To demonstrate the synthetic utility of our method, we applied the present reaction conditions to both *m*- and *p*-aminobenzylamine (Scheme 4). The reactions proceeded smoothly at room temperature and selectively afforded the aminobenzyl-substituted thioureas in excellent yields.

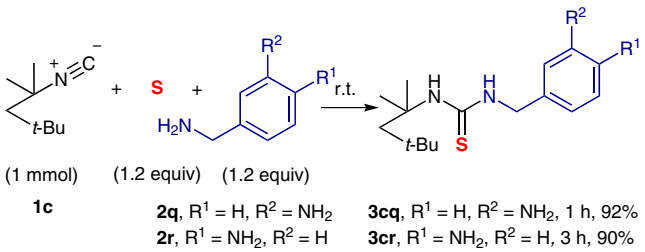
In summary, we have developed the first thionation and amination of isocyanides using elemental sulfur and aliphatic amines at room temperature. This reaction provides



Scheme 2 Thioureas from isocyanides, sulfur and amines



Scheme 3 Proposed mechanism



Scheme 4 Chemoselective formation of thioureas from aminobenzylamines **2q** and **2r**

an efficient and convenient multicomponent approach to unsymmetrical thioureas in a total atom-economical manner. Considering the mild reaction conditions and high functional group tolerance of the present reaction, as well as the widely known applications of thiourea moieties in medicinal chemistry and asymmetric synthesis, this method could be very useful for the direct transformation of available isocyanide natural products[19] or building blocks[15] into a wide range of thioureas for structure–activity relationship studies.

Commercially available starting materials were purchased from Sigma-Aldrich and used without further purification. ^{1}H and ^{13}C NMR spectra were acquired using a Bruker (300 MHz) spectrometer. $CDCl_3$ was used as the solvent. Chemical shifts are reported in ppm with internal reference to residual $CHCl_3$ at 7.24 ppm. Coupling constants are reported in Hz. Reaction progress was monitored by TLC on precoated silica gel (Kieselgel 60 F254) plates. The spots were visualized under UV light (254 nm) or with vanillin stain (green spots). Flash column chromatography was conducted using silica gel (230–400 mesh) with different mixtures of solvents as the mobile phase (CH_2Cl_2–MeOH or EtOAc–heptane).

Thioureas 3 from Isocyanides 1, Sulfur and Amines 2; General Procedure

A 10-mL test tube equipped with a magnetic stir bar was charged with an isocyanide **1** (1 mmol, 1 equiv), elemental sulfur (38.4 mg, 1.2 mmol, 1.2 equiv) and an amine **2** (1.2 mmol, 1.2 equiv). The resulting mixture was stirred for the indicated time at the indicated temperature (see Schemes 2 and 4). Toluene (0.1 mL) can be added if necessary to facilitate the stirring. The crude mixture (oily or solid) was purified by silica gel column chromatography (eluent: appropriate mixtures of heptane–EtOAc, heptane–CH_2Cl_2 or CH_2Cl_2–MeOH).

1-Cyclohexyl-3-(4-methylbenzyl)thiourea (3aa)

Eluent: heptane–EtOAc, 3:1.

Yield: 254 mg (97%); white solid; mp 108 °C.

IR (neat): 3228, 3048, 2929, 2853, 1539, 1515, 1447, 1340, 1254, 1230, 1059, 811 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (dd, *J* = 15.3, 7.8 Hz, 4 H), 6.35 (br s, 1 H), 5.95 (br s, 1 H), 4.55 (br s, 2 H), 3.87 (br s, 1 H), 2.32 (s, 3 H), 1.93 (m, 2 H), 1.61 (m, 3 H), 1.33 (m, 2 H), 1.13 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.4, 137.7, 129.4, 127.6, 53.4, 48.2, 32.8, 25.5, 24.7, 21.4.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}N_2S$: 263.1582; found: 263.1578.

1-(4-Chlorobenzyl)-3-cyclohexylthiourea (3ab)[20]
Eluent: heptane–EtOAc, 3:1.

Yield: 218 mg (77%); white solid; mp 115 °C.

IR (neat): 3238, 3050, 2930, 2853, 1539, 1488, 1449, 1318, 1235, 1061, 1012, 813, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 4 H), 6.42 (s, 1 H), 6.05 (s, 1 H), 4.62 (s, 2 H), 3.83 (s, 1 H), 1.93 (m, 2 H), 1.65 (m, 3 H), 1.30 (m, 2 H), 1.18 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8, 135.8, 133.8, 129.3, 53.3, 47.8, 32.8, 25.5, 24.6.

1-(2-Chlorobenzyl)-3-cyclohexylthiourea (3ac)
Eluent: heptane–EtOAc, 3:1.

Yield: 274 mg (97%); pale yellow solid; mp 140 °C.

IR (neat): 3203, 3060, 2930, 2854, 1550, 1489, 1410, 1371, 1317, 1236, 1086, 1012, 933, 826, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (m, 2 H), 7.27 (m, 2 H), 6.34 (s, 1 H), 5.93 (s, 1 H), 4.78 (s, 2 H), 3.81 (s, 1 H), 1.99 (m, 2 H), 1.68 (m, 3 H), 1.35 (m, 2 H), 1.17 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.6, 134.7, 133.3, 130.1, 129.6, 129.2, 127.2, 53.2, 46.0, 32.7, 25.4, 24.9.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{20}ClN_2S$: 283.1036; found: 283.1044.

1-Cyclohexyl-3-(pyridin-3-ylmethyl)thiourea (3ad)[21]
The product was obtained by washing the solid, crude mixture with toluene.

Yield: 224 mg (90%); pale yellow solid; mp 215 °C.

IR (neat): 3295, 3210, 3062, 2930, 2854, 1555, 1489, 1410, 1372, 1344, 1317, 1237, 1087, 1062, 1012, 974, 934, 826, 797, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 4.5 Hz, 1 H), 7.84 (s, 1 H), 7.62 (t, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.14 (t, *J* = 8.1 Hz, 1 H), 4.63 (s, 2 H), 3.90 (m, 1 H), 1.86 (m, 2 H), 1.52 (m, 2 H), 1.51 (m, 1 H), 1.17 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.4, 156.5, 148.6, 137.2, 122.6, 53.1, 49.6, 32.5, 25.7, 24.3.

1-Cyclohexyl-3-(1-phenylethyl)thiourea (3ae)
Eluent: heptane–EtOAc, 3:1.

Yield: 259 mg (99%); white solid; mp 130 °C.

IR (neat): 3375, 3218, 2925, 2853, 1542, 1513, 1494, 1446, 1256, 1228, 760, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 6.43 (m, 1 H), 5.52 (s, 1 H), 4.83 (s, 1 H), 3.99 (s, 1 H), 1.93 (s, 1 H), 1.67 (m, 1 H), 1.50 (m, 5 H), 1.27 (s, 3 H), 1.09 (m, 2 H), 0.87 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 142.0, 129.3, 127.9, 125.8, 54.0, 53.2, 32.6, 32.2, 25.3, 24.3, 24.1, 23.6.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}N_2S$: 263.1582; found: 263.1591.

1-Cyclohexyl-3-(2-phenylpropan-2-yl)thiourea (3af)
Eluent: heptane–EtOAc, 3:1.

Yield: 268 mg (97%); white solid; mp 128 °C.

IR (neat): 3372, 3218, 2928, 2850, 1539, 1515, 1447, 1254, 1227, 757, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (m, 5 H), 6.53 (s, 1 H), 4.95 (s, 1 H), 4.03 (s, 1 H), 1.65 (s, 8 H), 1.37 (m, 1 H), 1.22 (m, 4 H), 1.00 (m, 1 H), 0.76 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.7, 144.0, 129.6, 128.5, 125.6, 57.5, 53.7, 32.0, 29.9, 25.3, 23.7.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2S$: 277.1738; found: 277.1725.

1-Benzhydryl-3-cyclohexylthiourea (3ag)
Eluent: heptane–EtOAc, 3:1.

Yield: 221 mg (68%); white solid; mp 193 °C.

IR (neat): 3375, 3211, 2922, 2850, 1540, 1511, 1448, 1254, 1225, 760, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 10 H), 6.39 (m, 1 H), 5.91 (s, 1 H), 5.51 (s, 1 H), 4.08 (s, 1 H), 1.86 (s, 2 H), 1.50 (m, 3 H), 1.34 (m, 2 H), 1.05 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 140.1, 129.4, 128.9, 127.5, 62.6, 53.6, 32.4, 25.3, 24.4.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2S$: 325.1738; found: 325.1720.

1-Benzyl-3-cyclohexyl-1-methylthiourea (3ah)
Eluent: heptane–EtOAc, 3:1.

Yield: 254 mg (97%); white solid; mp 90 °C.

IR (neat): 3279, 3055, 2932, 2855, 1538, 1488, 1452, 1409, 1370, 1317, 1236, 1086, 1062, 1012, 826, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.13 (m, 5 H), 5.31 (d, *J* = 7.5 Hz, 1 H), 5.03 (s, 2 H), 4.34 (m, 1 H), 3.15 (s, 3 H), 2.06 (m, 2 H), 1.64 (m, 3 H), 1.41 (m, 2 H), 1.15 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.2, 136.6, 129.0, 127.8, 127.2, 56.7, 54.4, 37.8, 33.4, 25.8, 25.0.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}N_2S$: 263.1582; found: 263.1567.

1,1-Dibenzyl-3-cyclohexylthiourea (3ai)
Eluent: heptane–EtOAc, 4:1.

Yield: 237 mg (70%); white solid; mp 113 °C.

IR (neat): 3375, 3215, 2922, 2850, 1542, 1511, 1448, 1257, 1229, 1088, 759, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 10 H), 5.38 (m, 1 H), 4.99 (s, 4 H), 4.33 (s, 1 H), 1.94 (s, 2 H), 1.49 (m, 3 H), 1.36 (m, 2 H), 1.00 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.6, 136.0, 128.9, 127.9, 127.1, 54.3, 54.1, 32.5, 25.4, 24.4.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{27}N_2S$: 339.1895; found: 339.1882.

***N*-Cyclohexylazepane-1-carbothioamide (3aj)**
Eluent: heptane–EtOAc, 3:1.

Yield: 228 mg (95%); white solid; mp 110 °C.

IR (neat): 3292, 3206, 3061, 2929, 2855, 1553, 1551, 1539, 1410, 1369, 1344, 1317, 1238, 1087, 1013, 974, 797, 693, 658 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.21 (d, *J* = 7.1 Hz, 1 H), 4.33 (m, 1 H), 3.76 (s, 4 H), 2.07 (m, 2 H), 1.63 (m, 11 H), 1.40 (m, 2 H), 1.16 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.6, 54.0, 50.5, 33.3, 27.6, 26.8, 25.6, 25.0.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{25}N_2S$: 241.1738; found: 241.1753.

***N*-Cyclohexyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (3ak)**
Eluent: heptane–EtOAc, 3:1.

Yield: 233 mg (85%); white solid; mp 126 °C.

IR (neat): 3362, 3256, 2949, 1733, 1535, 1491, 1455, 1340, 1218, 1193, 1092, 1019, 953, 742, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (m, 4 H), 5.34 (m, 1 H), 4.92 (s, 2 H), 4.43 (s, 1 H), 3.96 (t, *J* = 6.0 Hz, 2 H), 2.97 (t, *J* = 6.0 Hz, 2 H), 2.15 (s, 2 H), 1.72 (m, 3 H), 1.45 (m, 2 H), 1.22 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 135.4, 133.0, 127.8, 127.2, 126.8, 126.6, 54.2, 49.3, 45.5, 33.4, 29.1, 25.6, 25.2.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}N_2S$: 275.1582; found: 275.1566.

1-Cyclohexyl-3-(4-hydroxybutyl)thiourea (3al)
Eluent: CH_2Cl_2–MeOH, 93:7.

Yield: 223 mg (97%); pale yellow solid; mp 106 °C.

IR (neat): 3411, 3283, 3209, 3061, 2929, 2854, 1552, 1489, 1410, 1369, 1349, 1318, 1238, 1087, 1013, 798, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (s, 1 H), 6.37 (s, 1 H), 3.89 (s, 1 H), 3.61 (m, 2 H), 3.44 (s, 3 H), 1.94 (m, 2 H), 1.62 (m, 7 H), 1.22 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.7, 61.8, 53.0, 44.1, 32.9, 29.6, 25.8, 25.5, 24.9.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{23}N_2OS$: 231.1531; found: 231.1545.

1-Cyclohexyl-3-[2-(phenylamino)ethyl]thiourea (3am)
Eluent: heptane–EtOAc, 1:1.

Yield: 269 mg (97%); white solid; mp 102 °C.

IR (neat): 3295, 3211, 3061, 2928, 2855, 1555, 1488, 1343, 1315, 1254, 1236, 1086, 1061, 796 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.6 Hz, 2 H), 6.74 (t, *J* = 7.6 Hz, 1 H), 6.65 (br s, 1 H), 6.63 (d, *J* = 7.1 Hz, 2 H), 6.39 (m, 1 H), 4.21 (s, 1 H), 3.69 (s, 3 H), 3.29 (m, 2 H), 1.91 (m, 2 H), 1.63 (m, 3 H), 1.31 (m, 2 H), 1.08 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.7, 147.7, 129.9, 118.2, 113.1, 53.0, 44.0, 32.7, 25.4, 24.7.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}N_3S$: 278.1691; found: 278.1677.

1-Allyl-3-cyclohexylthiourea (3an)[22]
Eluent: heptane–EtOAc, 3:1.

Yield: 192 mg (97%); white solid; mp 82 °C.

IR (neat): 3379, 3218, 2922, 2846, 1537, 1513, 1445, 1256, 1225, 758, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 6.06 (s, 1 H), 5.88 (m, 1 H), 5.05–5.25 (m, 2 H), 4.07 (m, 3 H), 1.99 (m, 2 H), 1.66 (m, 3 H), 1.38, 1.18 (2 × m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.4, 133.7, 117.4, 53.2, 47.1, 33.2, 25.7, 24.9.

1-Cyclohexyl-3-prop-2-ynylthiourea (3ao)
Reaction was performed in toluene (0.2 mL). Eluent: heptane–CH_2Cl_2, 1:1 to 0:1.

Yield: 274 mg (95%; ~90% purity); amorphous solid.

IR (neat): 3256, 3056, 2119, 1628, 1613, 1537, 1449, 1364, 1340, 1220, 1152, 1063, 890 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.09 (br s, 1 H), 6.01 (br s, 1 H),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8, 79.0, 72.9, 53.3, 34.3, 32.9, 25.5, 24.8.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{17}N_2S$: 197.1112; found: 197.1102.

***N*-Benzyl-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (3bk)**[23]
Eluent: heptane–EtOAc, 3:1.

Yield: 254 mg (90%); white solid; mp 134 °C.

IR (neat): 3253, 3062, 2918, 1540, 1493, 1458, 1421, 1380, 1337, 1294, 1251, 1197, 1184, 1108, 1061, 746, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (m, 5 H), 7.23 (m, 4 H), 5.73 (m, 1 H), 4.97 (s, 4 H), 4.01 (t, *J* = 6.0 Hz, 2 H), 2.98 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.6, 138.2, 135.3, 132.9, 128.7, 128.2, 127.9, 127.8, 127.3, 126.8, 126.5, 50.5, 49.8, 45.8, 29.0.

1-Benzyl-3-phenethylthiourea (3bp)[24]
Eluent: heptane–EtOAc, 3:1.

Yield: 251 mg (93%); white solid; mp 127 °C.

IR (neat): 3365, 3256, 2952, 1537, 1491, 1382, 1343, 1292, 1215, 1195, 1185, 773, 749, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (m, 8 H), 7.13 (m, 2 H), 6.34 (m, 1 H), 5.92 (s, 1 H), 4.52 (s, 2 H), 3.74 (m, 2 H), 2.88 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9, 138.3, 136.7, 128.9, 128.8, 128.7, 128.0, 127.5, 126.8, 48.2, 45.8, 35.1.

1-(4-Chlorobenzyl)-3-(2,4,4-trimethylpentan-2-yl)thiourea (3cb)
Eluent: heptane–EtOAc, 3:1.

Yield: 294 mg (94%); white solid; mp 111 °C.

IR (neat): 3259, 2949, 1535, 1493, 1380, 1341, 1242, 1194, 1182, 1107, 1062, 743, 703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (m, 4 H), 6.11 (s, 1 H), 6.02 (s, 1 H), 4.74 (d, *J* = 5.4 Hz, 2 H), 1.71 (s, 2 H), 1.41 (s, 6 H), 0.99 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.2, 136.1, 133.5, 129.0, 128.9, 57.2, 52.3, 49.0, 31.7, 31.5, 30.7.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{26}ClN_2S$: 313.1505; found: 313.1523.

***N*-(2,4,4-Trimethylpentan-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carbothioamide (3ck)**
Eluent: heptane–EtOAc, 3:1.

Yield: 295 mg (97%); white solid; mp 90 °C.

IR (neat): 3249, 2925, 1537, 1494, 1376, 1339, 1315, 1196, 1186, 1060, 745, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 4 H), 5.44 (s, 1 H), 4.91 (s, 2 H), 3.94 (t, *J* = 6.0 Hz, 2 H), 2.96 (t, *J* = 6.0 Hz, 2 H), 2.11 (s, 2 H), 1.68 (s, 6 H), 1.05 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 135.4, 133.5, 127.8, 127.2, 126.7, 126.5, 58.4, 51.5, 48.9, 45.3, 31.8, 31.1, 30.1, 29.2.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{29}N_2S$: 305.2051; found: 305.2068.

1-Phenethyl-3-(2,4,4-trimethylpentan-2-yl)thiourea (3cp)
Eluent: heptane–EtOAc, 3:1.

Yield: 263 mg (90%); amorphous solid.

IR (neat): 3379, 3215, 2928, 2849, 1539, 1505, 1446, 1356, 1254, 1230, 888, 765, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32, 7.23 (2 × m, 5 H), 6.01 (s, 1 H), 5.57 (s, 1 H), 3.87 (m, 2 H), 2.94 (t, *J* = 6.7 Hz, 2 H), 1.45 (s, 2 H), 1.26 (s, 6 H), 0.92 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9, 138.4, 128.9, 128.6, 127.0, 56.5, 52.1, 46.7, 35.0, 31.6, 31.2, 30.2.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{29}N_2S$: 293.2051; found: 293.2065.

Ethyl 2-(3-Benzyl-3-methylthioureido)acetate (3dh)
Eluent: heptane–EtOAc, 2:1.

Yield: 248 mg (93%); white solid; mp 70 °C.

IR (neat): 3365, 3263, 2952, 1535, 1490, 1429, 1377, 1341, 1290, 1194, 1184, 747, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 5 H), 6.05 (s, 1 H), 5.01 (s, 2 H), 4.37 (d, *J* = 4.5 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.10 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.3, 170.3, 136.4, 128.8, 127.8, 127.4, 61.7, 57.1, 47.9, 37.5, 14.3.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_2S$: 267.1167; found: 267.1179.

_N_-Phenyl-3,4-dihydroisoquinoline-2(1_H_)-carbothioamide (3ek)
Eluent: heptane–EtOAc, 3:1.

Yield: 228 mg (85%); pale yellow solid; mp 143 °C.

IR (neat): 3372, 3191, 1593, 1539, 1491, 1450, 1351, 1314, 1246, 1176, 1160, 1109, 1065, 997 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.12 (m, 10 H), 4.94 (s, 2 H), 4.02 (t, *J* = 6.0 Hz, 2 H), 2.98 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.2, 139.9, 134.9, 132.8, 128.9, 128.1, 127.2, 126.7, 126.5, 125.6, 124.7, 51.0, 47.1, 28.8.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2S$: 269.1112; found: 269.1129.

1-Phenethyl-3-phenylthiourea (3ep)[24]
Eluent: heptane–EtOAc, 3:1.

Yield: 231 mg (90%); pale yellow solid; mp 106 °C (Lit.[23] 106 °C).

IR (neat): 3375, 3188, 1591, 1537, 1491, 1450, 1351, 1316, 1248, 1176, 1160, 1108, 1069, 999 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (br s, 1 H), 7.41–7.21 (m, 6 H), 7.17–7.14 (m, 2 H), 7.03–7.01 (m, 2 H), 6.03 (br s, 1 H), 3.91 (t, *J* = 6.8 Hz, 2 H), 2.93 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.1, 138.5, 136.1, 130.0, 128.8, 128.7, 127.0, 126.6, 125.0, 46.2, 34.8.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2S$: 257.1112; found: 257.1098.

1-(3-Aminobenzyl)-3-(2,4,4-trimethylpentan-2-yl)thiourea (3cq)
Eluent: heptane–EtOAc, 1:1.

Yield: 270 mg (92%); pale yellow solid; mp 125 °C.

IR (neat): 3255, 2945, 1535, 1496, 1451, 1376, 1341, 1193, 1151, 1110, 745, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (m, 1 H), 6.64 (m, 3 H), 6.02 (s, 2 H), 4.59 (s, 2 H), 3.61 (s, 2 H), 1.74 (s, 2 H), 1.42 (s, 6 H), 0.99 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9, 147.1, 138.6, 129.9, 117.8, 114.7, 114.3, 57.0, 51.9, 49.6, 31.7, 31.4, 30.3.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{28}N_3S$: 294.2004; found: 294.2015.

1-(4-Aminobenzyl)-3-(2,4,4-trimethylpentan-2-yl)thiourea (3cr)
Eluent: heptane–EtOAc, 1:1.

Yield: 264 mg (90%); yellow solid; mp 90 °C.

IR (neat): 3256, 2915, 1539, 1491, 1379, 1336, 1249, 1196, 1181, 1107, 1063, 745, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 6.4 Hz, 2 H), 6.60 (d, *J* = 6.4 Hz, 2 H), 6.00, 5.94 (2 × s, 2 H), 4.49 (s, 2 H), 3.76 (s, 2 H), 1.69 (s, 2 H), 1.36 (s, 6 H), 0.95 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.5, 146.4, 129.0, 115.4, 56.8, 51.8, 49.2, 31.6, 31.4, 30.3.

HRMS-ESI$^+$: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{28}N_3S$: 294.2004; found: 294.1995.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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