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A Concise Synthesis of Substituted Thiourea Derivatives in Aqueous Medium

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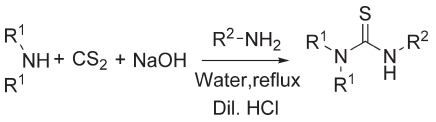

An efficient method for the synthesis of symmetrical and unsymmetrical substituted thiourea derivatives by means of simple condensation between available building blocks such as amines and carbon disulfide in aqueous medium is presented. This protocol works smoothly with aliphatic primary amines to afford various di- and trisubstituted thiourea derivatives. The present method is also useful in synthesizing various substituted 2-mercapto imidazole heterocycles. This method proceeds through a xanthate (amino dithiol deivative) intermediate, unlike isothiocyanate as in an earlier known method.

Introduction

Thioureas are the subject of significant interest because of their usefulness in medicinal chemistry due to their biological activity as fungicides, herbicides,[1] rodenticides,[2] and phenoloxidase enzymatic inhibitors.[3] Thiourea derivatives and their metal complexes exhibit analgesic, anti-inflammatory, antimicrobial, and anticancer activities. Thiourea derivatives are valuable building blocks for the synthesis of amides, guanidines, and varieties of heterocycles.[4] Recently, thiourea derivatives have found use in organocatalysis.[5] For these reasons, a number of procedures have been reported for the synthesis of thioureas. Among the numerous methods for the synthesis of thioureas,[2a,6] condensation of primary and secondary amine with isothiocyanate,[6a] thiophosgene[6b] or its derivatives[6c] constitutes the most widely accepted general methods. Further, the reaction of primary amines with carbon disulfide in the presence of mercury acetate and the reaction of unsubstituted thioureas with primary alkyl amines[7] are a few more methods to synthesize thioureas. Despite the toxicity of the reagents, the applications of these reagents remain inevitable because of the importance of thioureas in biological field.[8] Therefore, safer, nontoxic, and user-friendly procedures to synthesize thioureas are yet to be developed.

Results and Discussion

The development of environmentally benign synthetic procedures, particularly in aqueous medium, constitutes an

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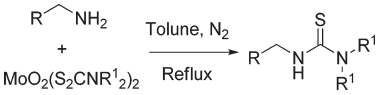
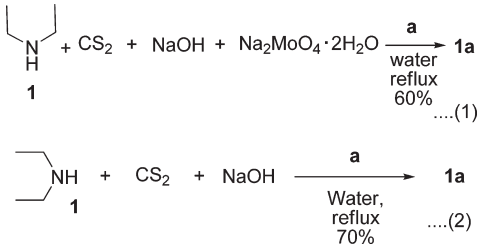
SCHEME 1. Synthesis of Di- and Tri-substituted Thiourea Using Molybdenum Xanthate[10]



important goal in organic synthesis.[9] In continuation of our research in developing green reaction conditions, we were interested in synthesizing these classes of compounds in environmentally benign reaction conditions, especially in aqueous medium. Recently, we have reported the synthesis of thiourea derivatives by reacting primary amines with molybdenum xanthate[10] (Scheme 1).

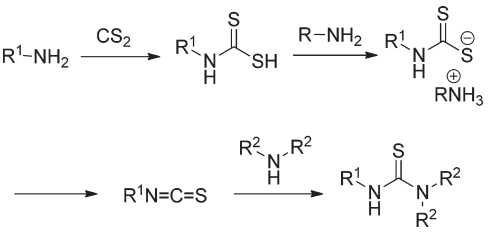
As molybdenum xanthate[11] is prepared in water, we initiated a reaction of primary amine with in situ generated molybdenum xanthate in aqueous medium. In this reaction, diethyl amine (**1**) was treated with carbon disulfide in the presence of sodium hydroxide as a base to form the corresponding xanthate, followed by the addition of sodium molybdate to produce molybdenum xanthate in water. Interestingly, when the above solution of molybdenum xanthate was reacted with *n*-hexyl amine (a) at reflux condition, the corresponding trisubstituted thiourea **1a** (1,1-diethyl-3-hexylthiourea) was obtained in good yield (eq 1). In order to test the necessity of molybdenum reagent, we performed a controlled reaction in the absence of molybdenum complex. This experiment using xanthate solution with *n*-hexyl amine resulted in the formation of the corresponding trisubstituted thiourea, ruling out the requirement of molybdenum reagent in the reaction (eq 2).



A review of the literature for the synthesis of thiourea[2a] reveals that isothiocyanate is a key intermediate in synthesizing thioureas. Therefore, the reaction of carbon disulfide with primary amines produces the corresponding isothiocyanate via thiocarbamic acid. The isothiocyanate thus produced reacts with another molecule of amine (primary or secondary) to produce the corresponding di- or trisubstituted thiourea derivative (Scheme 2).

It is trivial that it is not possible to synthesize isothiocyanates by the reaction of secondary amines with carbon disulfide. Therefore, through the reaction of secondary amine with carbon disulfide followed by the treatment with either primary or secondary amine it is not possible to synthesize thiourea, as there is no possibility to obtain isothiocyanate from secondary amine under the reaction condition employed.

SCHEME 2. Synthesis of Di- and Tri-substituted Thiourea



Additionally, it is documented that resin-bound *N*,*N*-disubstituted dithiocarbamates derived from secondary amines react with primary amines to produce a very small amount of thioureas[12] under forcing conditions. Apart from this, there is also a report on the synthesis of trisubstituted thiourea by the reaction of zinc dialkyldithiocarbamates with primary aliphatic amines.[13] However, zinc dialkylthiocarbamates[14] were prepared in two steps by using amines and carbon disulfide to generate the sodium dialkylthiocarbamates, which were further converted to the corresponding zinc dialkylthiocarbamates, whereas the present method provides an easy protocol of generating the sodium dialkylthiocarbamates (in situ) and further reacting with several amines. We believe that the present methodology provides a greater flexibility of using amines (dialkyl amines and primary amines) at our convenience and is superior to other methods.

After several experimental trials, it was optimized that dialkyl amine (1.4 mmol) and carbon disulfide (1.5 mmol) in aqueous NaOH (1.4 mmol) furnished the corresponding sodium salt of dialkyldithiocarbamates. This dialkylthiocarbamates solution, without isolation, was heated at reflux with primary amine (1 mmol). After the completion of the reaction (TLC), the reaction mixture was acidified using dilute HCl (pH = 2) to furnish the corresponding tri substituted thiourea in good to excellent yields.

A variety of di- and tri-substituted thiourea derivatives were synthesized by using this strategy (Table 1). Secondary amines such as diethyl amine (**1**), piperidine (**2**), and morpholine (**3**) were used to prepare the corresponding sodium dialkylthiocarbamates in water at ambient temperature. These in situ generated sodium dialkylthiocarbamates were heated at reflux with primary amines such as *n*-hexylamine (**a**), 2-phenylethyl amine (**b**), 1-phenylethyl amine (**c**), and 2-furfuryl amine (**d**) to furnish the corresponding trisubstituted thiourea in good to excellent yields.[15] As seen from the Table 1, under the optimized conditions, the *in situ* generated sodium thiocarbamate of diethyl amine (**1**) reacted with hexyamine (**a**) under the typical reaction conditions to produce the corresponding trisubstituted thiourea **1a** in excellent yield (90%, entry 1, Table 1). Similarly, 2-phenylethyl amine (**b**) and 1-phenylethyl amine (**c**) underwent

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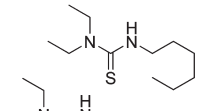
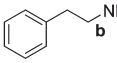
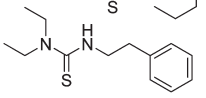
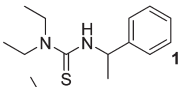
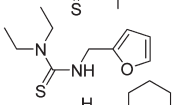
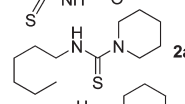
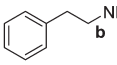
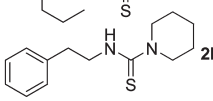
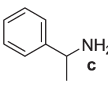
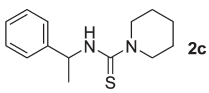
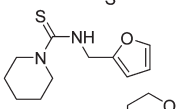
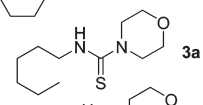
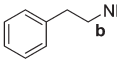
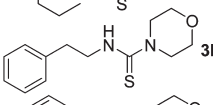
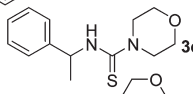
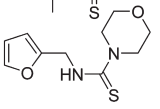
(15) Although the present methodology produces the corresponding trisubstituted thioureas as major products, trace amounts of symmetrical thioureas were also isolated and are indicated in Tables 1 and 2.

TABLE 1. Synthesis of Tri-substituted Thiourea from Preformed Dialkylxanthate in a One-Pot Reaction

Entry	2° Amine	1° Amine	Time(h)[a]	Product	Yield(%)[b,c]
1	 **1**	 **a**	7		**1a** 90(2)
2	**1**	 **b**	8		**1b** 84(9)
3	**1**	 **c**	10		**1c** 70(10)
4	**1**	 **d**	12		**1d** 40(4)
5	 **2**	 **a**	7		**2a** 84(4)
6	**2**	 **b**	9		**2b** 82(4)
7	**2**	 **c**	10		**2c** 93(trace)
8	**2**	 **d**	11		**2d** 61(11)
9	 **3**	 **a**	8		**3a** 70(24)
10	**3**	 **b**	9		**3b** 75(8)
11	**3**	 **c**	10		**3c** 62(9)
12	**3**	 **d**	10		**3d** 68(8)

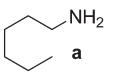
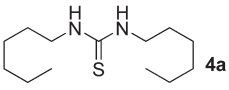
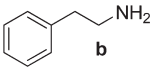
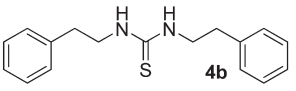
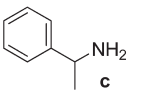
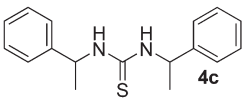
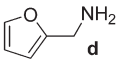
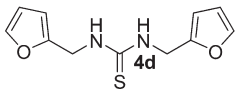
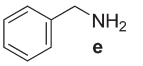
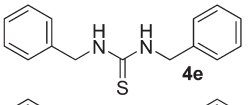
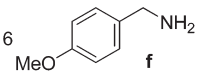
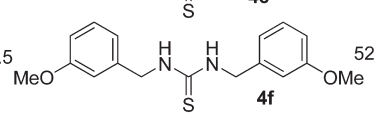
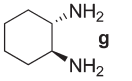
[a]Heated at 100 °C. [b]Isolated pure yields based on starting materials. [c]Yields in paranthesis are corresponding symmetrical disubstituted thiourea.

similar reaction with **1** to produce the corresponding thioureas **1b** and **1c**, respectively, in good yields (entries 2 and 3, Table 1). 2-Fufuryl amine (**d**) under the similar reaction with **1** produced the corresponding thiourea **1d** in moderate yield (40%, entry 4, Table 1).

Similarly, the sodium xanthate of piperidine reacted well with *n*-hexylamine (**a**), 2-phenyl ethylamine (**b**), 1-phenyl ethylamine (**c**), and 2-furfuryl amine (**d**) to furnish the corresponding trisubstituted thioureas **2a**, **2b**, **2c**, and **2d**, respectively, in good to excellent yields (entries 5−8, Table 1). As expected, sodium xanthate of morpholine prepared in situ reacted with *n*-hexylamine (**a**), 2-phenylethyl amine (**b**), 1-phenylethyl amine (**c**), and 2-furfuryl amine (**d**) to produce the corresponding substituted thiourea derivatives **3a**, **3b**, **3c**, and **3d** under the similar reaction conditions in water (entries 9−12, Table 1).

Interestingly, several disubstituted thioureas are prepared by the reaction of dialkyldithiocarbamate (in situ generated by the reaction of primary alkyl amine, CS_2, and NaOH) with another molecule of primary amine. As seen from

TABLE 2. Synthesis of Symmetrical Di-substituted Thiourea Derivatives

Entry	Substrates	Time (h)	Product	Yield(%)[a,b]
1	 **a**	3	 **4a**	90
2	 **b**	3	 **4b**	88
3	 **c**	3.5	 **4c**	90
4	 **d**	4	 **4d**	65
5	 **e**	4	 **4e**	62
6	 **f**	3.5	 **4f**	52
7	 **g**	4	**4g**	51

[a]Heated at 100 °C. [b]Isolated pure yields based on starting materials.

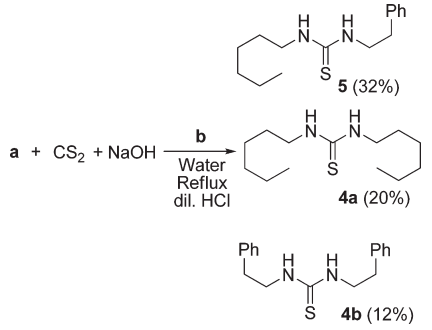
Table 2, *n*-hexylamine (**a**), 2-phenyl ethylamine (**b**), and 1-phenyl ethylamine (**c**) furnished the corresponding symmetrical disubstituted thiourea derivatives **4a** (90%), **4b** (88%), and **4c** (90%) under the reaction conditions employed in a short period of time (entries 1−3, Table 2). 2-Furfuryl amine (**d**) also afforded the corresponding symmetrical disubstituted thiourea **4d** in moderate yield (65%, entry 4, Table 2) in water at reflux conditions. Benzyl amine (**e**) and *p*-methoxybenzyl amine (**f**) produced the corresponding symmetrical thiourea derivatives **4e** (62%) and **4f** (52%) in moderate yields (entries 5 and 6, Table 2). *trans*-Cyclohexyl diamine (**g**) produced the cyclic thiourea (**4g**) in moderate yield under the reaction conditions employed (51%, entry 7, Table 2).

Our attempt to synthesize mixed disubstituted thiourea by using the present strategy has resulted in the formation of mixture of all possible thiourea derivatives. As seen from Scheme 3, the xanthate of *n*-hexylamine (**a**) generated in situ was reacted with 2-phenylethyl amine (**b**) at reflux temperature. As expected, mixed thiourea **5** obtained in only 32% yield along with corresponding symmetrical disubstituted thiourea derivatives **4a** (20%) and **4b** (12%) as shown in scheme 3.

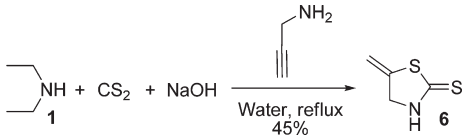
Quite interestingly, the reaction of sodium xanthate of **1** (which was generated by the reaction of **1** with CS_2 and NaOH in water) with propargyl amine at reflux condition produced the cyclic thiozolidine[9] derivative **6** in moderate yield (45%, Scheme 4).

Tentative Reaction Mechanism. The formation of thiourea by the present method could be explained by the involvement of dithiol derivative as presented in Scheme 5. It is important to note that the formation of isothiocyanate is not possible as shown in scheme 5. We believe that the present method

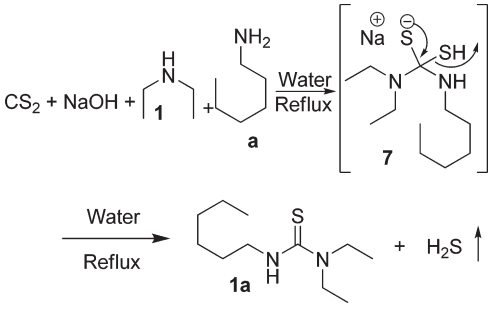
SCHEME 3. Synthesis of Mixed Di-substituted Thiourea



SCHEME 4. Synthesis of Cyclic Thiazolidine Derivatives



SCHEME 5. Possibility of Amino Dithiol (7) as an Intermediate

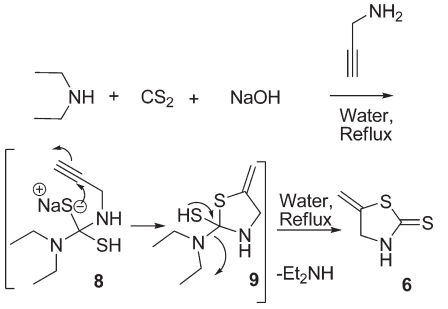


proceeds through amino dithiol derivative **7** as an intermediate. This intermediate **7**, by the expulsion of hydrogen sulfide gas, produces the corresponding substituted thiourea. The formation of hydrogen sulfide gas is confirmed by passing the gas generated during the reaction of sodium xanthate with hexylamine through the aqueous solutions of zinc chloride and cadmium acetate.[13b,16,17]

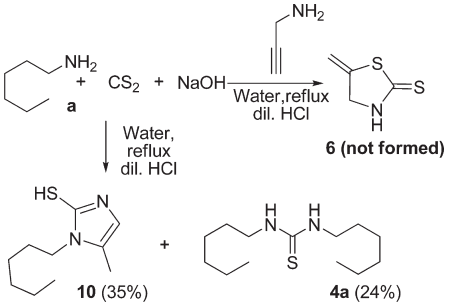
On the basis of the above results of formation of trisubstituted thiourea from the corresponding dialkyl xanthate as well as the formation of thiazolidine derivative (**6**, Scheme 4), we have proposed a plausible reaction mechanism for the formation of thiazolidine derivative as shown in scheme 6.

As seen from the scheme 6, the nucleophilic thio-anion (intermediate **8**) attacks the electrophilic alkyne to furnish the corresponding five-membered intermediate **9**. Later on, elimination of diethyl amine results in the formation of thiazolidine compound **6**. In this reaction, it was envisaged

SCHEME 6. Proposed Reaction Mechanism



SCHEME 7. Synthesis of Imidazole Derivatives



that by installing a poor leaving group in the intermediate **9**, for example, a primary amine group instead of dialkylamine, it may be possible to obtain either a substituted heterocyclic compound or the desired thiourea derivative. If this mechanism is operating, the reaction of primary aliphatic amine, CS_2, NaOH, and propargyl amine should not produce the thiozolidine derivative **6**. Therefore, we have decided to use an aliphatic primary amine in place of the dialkyl amine to prepare the corresponding xanthate. Accordingly, *n*-hexylamine (**a**) was converted into the corresponding xanthate by using carbon disulfide. As anticipated, the reaction of this xanthate with propargyl amine at reflux conditions in water did not produce **6** but resulted in the formation of imidazole derivative **10** as the major product in low yield (35%) along with formation of symmetrical dihexyl thiourea (**4a**) in minor amounts (24%, Scheme 7). This reaction clearly supports the mechanism presented in Scheme 6.

Further, we believe the present method (Scheme 5) proceeds through amino dithiol derivative **7** as an intermediate. This intermediate **7**, by the expulsion of hydrogen sulfide gas, produces the corresponding substituted thiourea as shown in Scheme 5. The formation of the imidazole derivative (Scheme 7) very clearly supports the mechanism presented in Scheme 5. Therefore the formation of various imidazole derivatives in the above reaction conditions may be explained by the tentative reaction mechanism shown in Scheme 8.

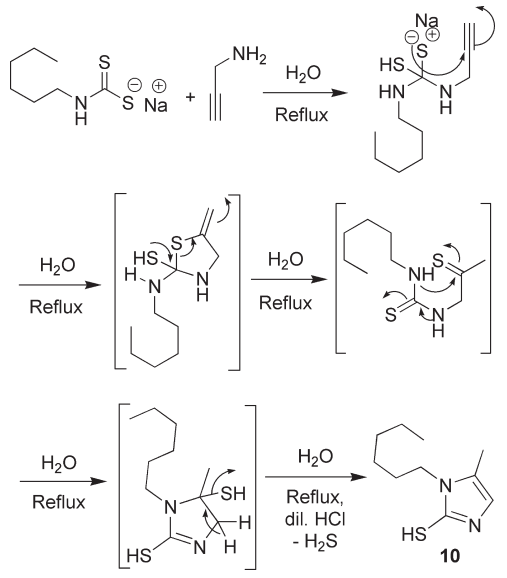
Conclusion

We have developed an effective and convenient method for the synthesis of di and tri substituted thiourea derivatives under aqueous reaction conditions in very good yields. Present method describes the involvement of amino dithiol moiety as an intermediate. Though this methodology is not successful with secondary amines and aryl amines to synthesize the corresponding thiourea derivatives, it works

(16) The generation of H_2S gas during the reaction was confirmed by passing the gas generated during the reaction of the sodium salt of diethyl xanthate and hexylamine in water through aqueous solutions of zinc chloride and cadmium acetate, which has resulted in the formation of white and yellow precipitates, respectively, indicating the formation of the corresponding sulfides. Additionally, the H_2S gas evolved during the reaction is identified by its characteristic odor and by exposure of filter paper moistened with lead acetate solution.

(17) In *Vogel's Qualitative Inorganic Analysis*, 7th ed.; Svehla, G., Ed.; Longman Publishers: Singapore, 1996.

SCHEME 8. Proposed Mechanism for the Formation of Imidazole Derivative



smoothly with aliphatic primary amines to afford various di and tri substituted thiourea derivatives. Unlike earlier, present method is not successful in synthesizing amino acid derivativatized thioureas, indicating that molybdenum xanthate is a useful reagent in synthesizing such class of chiral thiourea derivatives. The present method also allows the synthesis of substituted 2-marcaptoimidazole compounds in moderate yields.

Experimental Section

General Experimental Procedure. To a well-stirred solution of dialkylamine (1.4 mmol) in water was added sodium hydroxide (1.4 mmol) followed by carbon disulfide (1.5 mmol) at room temperature, and stirring was continued for 1 h. To this pale yellow colored suspension was added a primary amine (1.0 mmol), and the mixture was heated to 100 °C until the completion of reaction (monitored by TLC). The mixture was cooled, acidified with dilute hydrochloric acid, and extracted into CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over sodium sulfate, and the solvent was removed completely. The residue was purified by column chromatography on silica gel to obtain thiourea derivative.

1,1-Diethyl-3-hexylthiourea (1a).[13] Prepared as described in general procedure. R_f (10% EtOAc/hexane) 0.20; pale brown viscous liquid; yield 90%; IR (neat, cm^{-1}) 1532, 3309; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6.6 Hz), 1.23 (t, 6H, J = 7.2 Hz), 1.30−1.40 (m, 6H), 1.58 1.66 (m, 2H), 3.61−3.69 (m, 6H), 5.36 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6, 13.9, 22.5, 26.6, 29.3, 31.4, 44.9, 46.1, 180.0; HRESI-MS (m/z) calcd for $C_{11}H_{24}N_2S$ (M + Na) 239.1558, found (M + Na) 239.1559.

1,1-Diethyl-3-(2-phenylethyl)thiourea (1b).[18] Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.25; colorless solid; yield 84%; mp 67−69 °C; IR (neat, cm^{-1}) 1530, 3318; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, 6H, J = 7.2 Hz), 2.96 (t, 2H, J = 6.6 Hz), 3.55 (q, 4H, J = 7.2 Hz), 3.85−3.96 (m, 2H), 5.28 (br, 1H), 7.21−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4, 35.1, 44.9, 46.6, 126.6, 128.7, 128.8, 138.9, 180.1; HRESI-MS (m/z) calcd for $C_{13}H_{20}N_2S$ (M + Na) 259.1245, found (M + Na) 259.1244.

(18) Vassilev, G. N. *Dokl. Bulg. Akad. Nauk*. **1995**, *48*, 51–54.

1,1-Diethyl-3-(furan-2-ylmethyl)thiourea (1d). Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.25; yellow liquid; yield 40%; IR (neat, cm^{-1}) 1531, 3309; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, J = 7.2 Hz), 3.69 (q, 4H, J = 7.2 Hz), 4.87 (d, 6H, J = 4.8 Hz), 5.60 (br, 1H), 6.29−6.30 (m, 1H), 6.30−6.35 (m, 1H), 7.37−7.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.6, 42.9, 45.2, 107.8, 110.4, 142.2, 151.2, 180.1; HRESI-MS (m/z) calcd for $C_{10}H_{16}N_2OS$ (M + H) 213.1061, found (M + H) 213.1063.

***N*-Hexylpiperidine-1-carbothioamide (2a).** Prepared as described in general procedure. R_f (10% EtOAc/hexane) 0.15; brown viscous liquid; yield 84%; IR (neat, cm^{-1}) 1537, 3294; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 5.8 Hz), 1.24−1.35 (m, 6H), 1.55−1.65 (m, 8H), 3.60−3.66 (m, 2H), 3.78−3.80 (m, 4H), 5.74 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 22.3, 24.0, 25.2, 26.3, 29.1, 31.2, 46.0, 48.5, 180.6; HRESI-MS (m/z) calcd for $C_{12}H_{24}N_2S$ (M + Na) 251.1558, found (M + Na) 251.1558.

***N*-(2-Phenylethyl)piperidine-1-carbothioamide (2b).**[19] Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.25; colorless solid; yield 82%; mp 90−94 °C; IR (neat, cm^{-1}) 1533, 3303; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53−1.69 (m, 6H), 2.95 (t, 2H, J = 7.0 Hz), 3.68 (t, 4H, J = 5.4 Hz), 3.90−3.96 (m, 2H), 5.48 (br, 1H), 7.20−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2, 25.3, 35.2, 46.8, 48.6, 126.5, 128.6, 128.8, 138.9, 180.9; HRESI-MS (m/z) calcd for $C_{14}H_{20}N_2S$ (M + Na) 271.1245, found (M + Na) 271.1241.

***N*-(2-Phenylethyl)morpholine-4-carbothioamide (3b).** Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.10; colorless solid; yield 75%; mp 75−78 °C; IR (KBr, cm^{-1}) 1534, 3315; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.95 (t, 2H, J = 6.8 Hz), 3.62−3.70 (m, 8H), 3.86−3.94 (m, 2H), 5.92 (br, 1H), 7.16−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.8, 46.7, 47.1, 65.8, 126.3, 128.4, 128.5, 138.6, 182.0; HRESI-MS (m/z) calcd for $C_{13}H_{18}N_2OS$ (M + Na) 273.1038, found (M + Na) 273.1039.

***N*-(Furan-2-ylmethyl)morpholine-4-carbothioamide (3d).** Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.10; brown solid; yield 68%; mp 86−89 °C; IR (neat, cm^{-1}) 1538, 3271; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.70−3.80 (m, 8H), 4.87 (d, 2H, J = 3.2 Hz), 5.83 (br, 1H), 6.30−6.36 (m, 2H), 7.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.9, 47.4, 66.0, 108.3, 110.5, 142.3, 150.6, 182.3; HRESI-MS (m/z) calcd for $C_{10}H_{14}N_2O_2S$ (M + Na) 249.0674, found (M + Na) 249.0675.

1,3-Dihexylthiourea (4a).[20] Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.30; colorless solid; yield 90%; mp 35−39 °C; IR (neat, cm^{-1}) 1555, 3260; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 6H, J = 6.6 Hz), 1.25−1.40 (m, 12H), 1.55−1.64 (m, 4H), 3.42 (br, 4H), 6.25 (br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 22.3, 26.4, 28.8, 31.3, 44.3, 181.2; HRESI-MS (m/z) calcd for $C_{13}H_{28}N_2S$ (M + Na) 267.1871, found (M + Na) 267.1872.

1,3-Bis(furan-2-ylmethyl)thiourea (4d).[21] Prepared as described in general procedure. R_f (25% EtOAc/hexane) 0.20; pale brown solid; yield 65%; mp 68−73 °C; IR (neat, cm^{-1}) 1548, 3271; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.62 (d, 4H, J = 3.6 Hz), 6.24−6.26 (m, 2H), 6.30−6.32 (m, 2H), 6.58 (br, 2H), 7.32−7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.4, 108.1, 110.5, 142.3, 150.1, 182.0; HRESI-MS (m/z) calcd for $C_{11}H_{12}N_2O_2S$ (M + Na) 259.0517, found (M + Na) 259.0515.

1,3-Bis(phenylmethyl)thiourea (4e).[22] Prepared as described in general procedure. R_f (25% EtOAc/hexane) 0.20; cream solid;

(19) (a) Cho, J. K; White, P. D.; Klute, W.; Dean, T. W.; Bradley, M. *Chem. Commun*. **2004**, 502–503. (b) Mohanta, P. K.; Dhar, S.; Samal, S. K.; Ila, H.; Junjappa, H. *Tetrahedron* **2000**, *56*, 629–637. (c) Tisler, M. *Croat. Chem. Acta* **1957**, *29*, 409–411.

(20) Sambrook, M. R.; Beer, P. D.; Wisner, J. A.; Paul, R. L.; Cowley, A. R.; Szemes, F.; Drew, M. G. B. *J. Am. Chem. Soc*. **2005**, *127*, 2292–2302.

(21) McKay, A. F.; Garmaise, D. L.; Baker, H. A.; Hawkins, L. R.; Falta, V.; Gaudry, R.; Paris, G. Y. *J. Med. Chem*. **1963**, *6*, 587–595.

(22) Hisaki, I.; Sasaki, S.; Hirose, K.; Tobe, Y. *Eur. J. Org. Chem*. **2007**, 607–615.

yield 62%; mp 135−139 °C; IR (neat, cm^{-1}) 1552, 3253; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.60 (s, 2H), 6.20 (br, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.6, 127.5, 127.9, 128.9, 136.7, 182.0; HRESI-MS (*m*/*z*) calcd for $C_{15}H_{16}N_2S$ (M + Na) 279.0932, found (M + Na) 279.0930.

1,3-Bis(4-methoxyphenylmethyl)thiourea (4f).[23] Prepared as described in general procedure. R_f (25% EtOAc/hexane) 0.20; cream solid; yield 52%; mp 145−146 °C; IR (KBr, cm^{-1}) 1551, 3305; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 4.52 (s, 2H), 6.10 (br, 1H), 6.83 (d, 2H, J = 8.8 Hz), 7.15 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.1, 55.3, 114.3, 128.6, 128.9, 159.3, 181.6; HRESI-MS (*m*/*z*) calcd for $C_{17}H_{20}N_2O_2S$ (M + Na) 339.1143, found (M + Na) 339.1139.

(3a*S*,7a*S*)-Octahydro-2*H*-benzimidazole-2-thione (4g).[24] Prepared as described in general procedure. R_f (30% EtOAc/hexane) 0.20; colorless solid; yield 51%; mp 180−190 °C; IR (neat, cm^{-1}) 1513, 3223; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28−1.38 (m, 2H), 1.43−1.55 (m, 2H), 1.77−1.87 (m, 2H), 2.05−2.08 (m, 2H), 3.25−3.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 28.9, 64.7, 187.2; calcd for $C_7H_{12}N_2S$ (M + H) 157.0799, found (M + H) 157.0797.

1-Hexyl-3-(2-phenylethyl)thiourea (5). Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.25; colorless solid; yield 32%; mp 60−62 °C; IR (neat, cm^{-1}) 1552, 3258; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J = 6.8 Hz), 1.20−1.35 (m, 6H), 1.45−1.52 (m, 2H), 2.92 (t, 2H, J = 6.8 Hz), 3.21 (br, 2H), 3.76 (br, 2H), 5.45−6.05 (m, 2H), 7.19−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 22.4, 26.5, 28.7, 31.3, 35.2, 43.9, 45.6, 126.7, 128.7, 128.73, 138.4, 181.4; HRESI-MS (*m*/*z*) calcd for $C_{15}H_{24}N_2S$ (M + H) 265.1738, found (M + H) 265.1734; GC-MS calcd for $C_{15}H_{24}N_2S$: 264, found 264 (M^+).

1-Hexyl-5-methyl-1*H*-imidazole-2-thiol (10). Prepared as described in general procedure. R_f (20% EtOAc/hexane) 0.10; cream solid; yield 35%; mp 72−75 °C; IR (neat, cm^{-1}) 1624, 3090, 3132; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6.2 Hz), 1.26−1.45 (m, 6H), 1.68−1.77 (m, 2H), 2.17 (s, 3H), 3.97 (t, 2H, J = 7.8 Hz), 6.47 (s, 1H), 11.78 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.2, 13.8, 22.4, 26.3, 28.5, 31.2, 44.3, 110.9, 126.2, 159.0; HRESI-MS (*m*/*z*) calcd for $C_{10}H_{18}N_2S$ (M + Na) 221.1088, found (M + Na) 221.1089.

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Supporting Information Available: Experimental procedures and characterization data including ^1H and ^{13}C NMR spectra for thiourea derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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