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1-(Alkyl/Arylthiocarbamoyl)benzotriazoles as Stable Isothiocyanate Equivalents: Synthesis of Di- and Trisubstituted Thioureas

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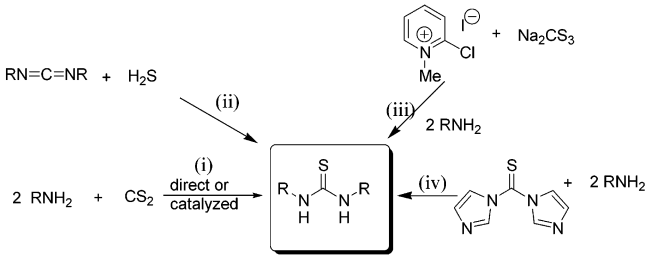
1-(Alkyl/arylthiocarbamoyl)benzotriazoles **4a**−**i** were synthesized in yields of 91−99% from bis-(benzotriazolyl)methanethione (**3**). Reagents **4a**−**g** were then used as isothiocyanate equivalents for the efficient synthesis of 10 secondary and 14 tertiary thioureas in high-yielding, convenient processes.

Introduction

Thioureas are of importance in medicinal chemistry[1] due to their biological activity,[2] e.g., against bacteria and microbial infection,[3] as fungicides, herbicides, and rodenticides,[4,5] as phenoloxidase enzymatic inhibitors,[6] and in connection with biomimetic models.[1,7] Thioureas are valuable building blocks for the synthesis of five- and six-membered heterocycles.[8] Amines are often derivatized as stable thioureas.[9]

Treatment of 2 equiv of a primary or secondary amine with thiophosgene is the easiest method of making symmetrical thioureas;[10] the unpleasant nature of thiophosgene can be avoided by using thiophosgene equivalents such as 1,1′-thiocarbonyldiimidazole.[11] Reaction of isothiocyanates with primary or secondary amines is a common method of making unsymmetrical thioureas[12,13] but suffers from side reactions such as urethane formation (in alcoholic medium where the reaction is often carried out) or exchange between the amine and the isothiocyanate.[14] Many isothiocyanates are tedious to prepare and display poor long-term stability. Hence, numerous alternative methods have been developed for the synthesis of both symmetrical and unsymmetrical thioureas avoiding the use of isothiocyanates. Thus, symmetrical thioureas are formed as shown in Scheme 1 by (i) either the direct[15] or catalyzed[16] reaction of carbon disulfide and amines; (ii) the reaction of carbodiimides with hydrogen sulfide;[17] (iii) the reaction of 2-chloropyridinium salts with sodium trithiocarbonate and amines;[18] or (iv) the reaction of 1,1′-thiocarbonyldiimidazole[11] with amines.

SCHEME 1



Methods for the preparation of unsymmetrical thioureas (Scheme 2) include (i) the use of 1-(methyldithiocarbonyl)imidazole as a thiocarbonyl transfer reagent;[19] (ii) the activation of a dithiocarbamate with a 2-halothiazolium salt and subsequent reaction with an amine;[20] (iii)

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(16) (a)Yamazaki, N.; Higashi, F.; Iguchi, T. *Tetrahedron Lett*. **1974**, 1191. (b) Ballabeni, M.; Ballini, R.; Bigi, F.; Maggi, R.; Parrini, M.; Predieri, G.; Sartori, G. *J. Org. Chem*. **1999**, *64*, 1029.
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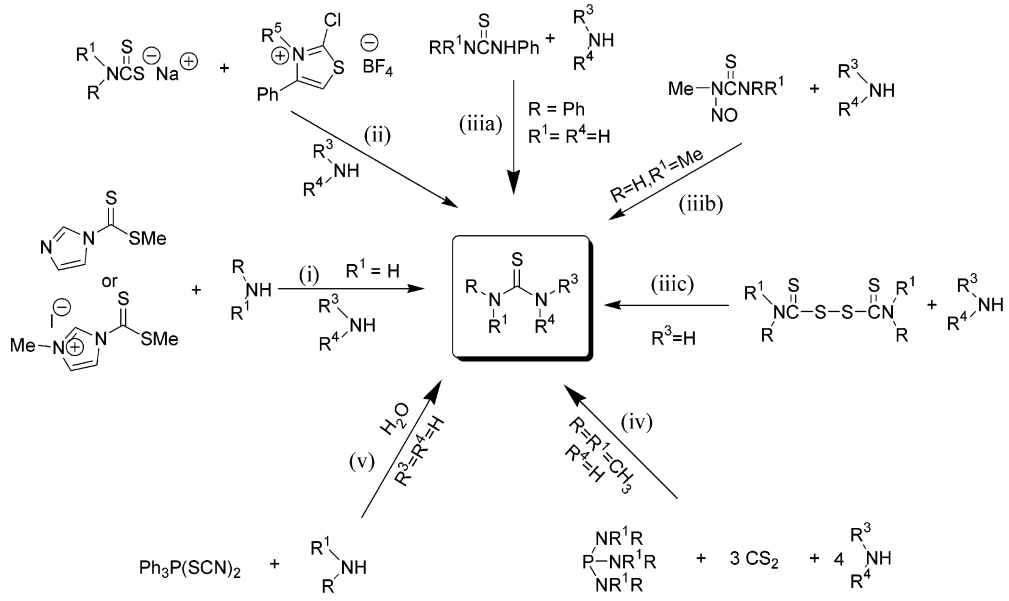
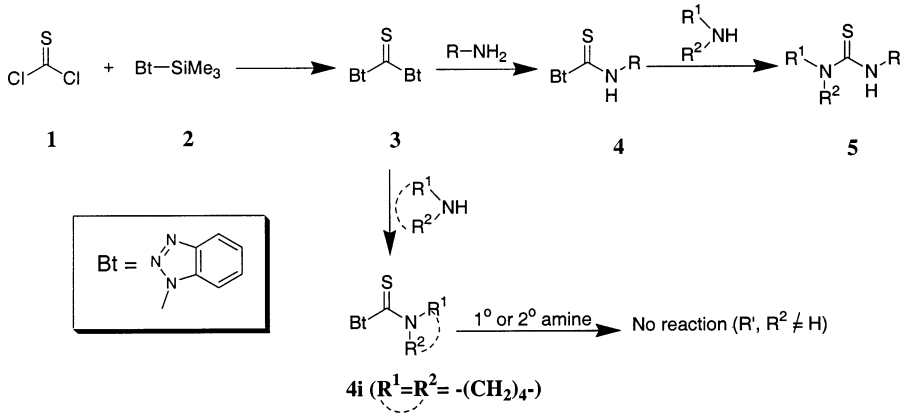
SCHEME 2 [a]



[a] R, R^1, R^2, R^3, R^4 = alkyl or aryl, unless specified.

SCHEME 3 [a]



[a] See Table 2 for designations of R, R^1, and R^2.

direct displacement, by amines, from 1,3-diphenylthiourea (iiia),[21] nitrosothiourea (iiib),[22] or thiuram disulfide (iiic);[23] or (iv) the reaction of carbon disulfide with primary amines in the presence of a triaryl phosphite or a hexaalkyl phosphorustriamide.[24] 1,1-Disubstituted thioureas are formed by the reaction of secondary amines with triphenylphosphine-thiocyanogen (v).[25] Although these additional methods are of great utility in the synthesis of many thioureas, a synthetic equivalent to isothiocyanate or a protected form of it that is stable, readily available, and easy to handle would be of considerable benefit. In this paper, we describe the preparation and utility of 1-(alkyl/arylthiocarbamoyl)benzotriazoles, which, in keeping with other classes of acylbenzotriazoles,[26] are highly effective thioacylating agents behaving as masked isothiocyanates.

Results and Discussion

Preparation of (Alky/Arylthiocarbamoyl)benzotriazoles 4. Bis(benzotriazolyl)methanethione (**3**) is easily prepared from 1-trimethylsilybenzotriazole and thiophosgene in quantitative yield (Scheme 3).[27] The literature shows only one reaction of this compound with an amine,

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(25) (a)Tamura, Y.; Adachi, M.; Kawasaki, T.; Kita, Y. *Tetrahedron Lett*. **1978**, 1753. (b) Tamura, Y.; Kawasaki, T.; Adachi, M.; Kita, Y. *Chem. Pharm. Bull*. **1979**, *27*, 1636.
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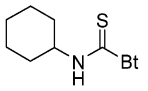
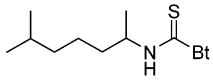
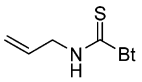
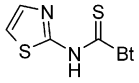
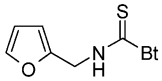
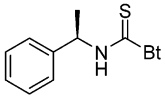
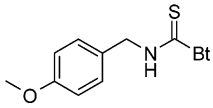
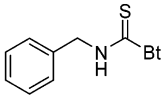
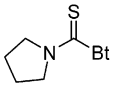
TABLE 1. Thiocarbamoybenzotriazoles 4 Prepared

Entry	1°Amine	Thiocarbamoyl benzotriazoles 4	Yield (%)
a	Cyclohexylamine		95
b	1,5-Dimethylhexylamine		99
c	Allylamine		93
d	2-Thiazolylamine		91
e	2-Furfurylamine		99
f	α-(*R*)-Methylbenzylamine		99
g	*p*-Methoxybenzylamine		97
h	Benzylamine		97
i	Pyrrolidine		99

with aniline to give diphenylthiourea.[27] As part of our ongoing research on the synthesis and utility of benzotriazole-functionalized reagents,[28] we considered the possibility of using **3** as a thiophosgene equivalent in the synthesis of unsymmetrical thioureas. Thus, the reactivity of **3** with various primary amines was investigated first. Treatment of **3** with cyclohexylamine in methylene chloride at 20 °C followed by a 5% Na_2CO_3 wash and recrystallization afforded benzotriazole-1-carbothioic acid cyclohexylamide (**4a**) in 95% yield (Scheme 3, Table 1). Significantly, **4a** was stored at room temperature for weeks without decomposition. Similarly, compounds **4b**−**h** from other primary amines were also prepared in nearly quantitative yields (Table 1). As will be shown, reagents **4a**−**h** are masked isothiocyanates and are useful alternatives for isothiocyanates in the preparation of secondary and tertiary thioureas.

See Table 2 for the designations of R, R^1, and R^2

Preparation of Di- and Trisubstituted Thioureas. Thiocarbamoylbenzotriazoles **4a**−**g** were reacted with a second primary amine to generate the corresponding disubstituted thioureas. Thus, when benzotriazole-1-carbothioic acid cyclohexylamide (**4a**) was treated with 2-amino-(4-methyl)pyridine, thiourea **5a** was isolated in 90% yield (Scheme 3, Table 2). The reaction was carried out in methylene chloride, and the byproduct, benzotriazole, was removed by 5% sodium carbonate wash. Similar reactions of **4a**−**g** with other primary amines afforded the corresponding secondary thioureas **5b**−**n** in 57−100% yields (Table 2).

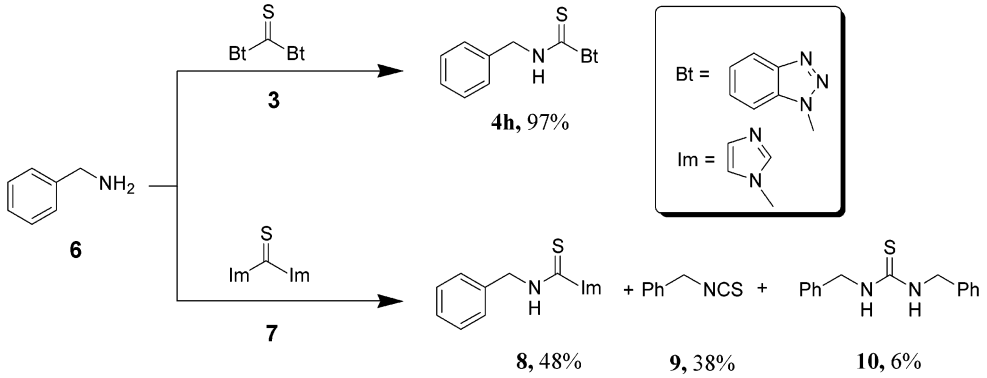
TABLE 2. Di- and Trisubstituted Thioureas 5 Prepared

5	R	R^1	R^2	yield (%)
a	cyclohexyl	2-(4-methyl)pyridyl	H	90
b	1,5-dimethylhexyl	4-$MeOC_6H_4CH_2$	H	99
c	4-$MeOC_6H_4CH_2$	1-methylbutyl	H	93
d	α-(*R*)-methylbenzyl	$EtO(CH_2)_2$	H	99
e	furfuryl	4-$CO_2EtC_6H_4$	H	57
f	2-thiazolyl	phenethyl	H	95
g	allyl	phenethyl	H	97
h	cyclohexyl	phenyl	methyl	91
i	allyl	phenethyl	methyl	92
j	1,5-dimethylhexyl	phenyl	methyl	61
k	4-$MeOC_6H_4CH_2$	$-(CH_2)_5-$		95
l	α-(*R*)-methylbenzyl	$-(CH_2)_2-O-(CH_2)_2-$		92
m	furfuryl	$-(CH_2)_5-$		94
n	2-thiazolyl	3-methylpiperidinyl		87

(N,N)-Disubstituted Thiocarbamoylbenzotriazoles. Reaction of secondary amines with bis(benzotriazolyl)methanethione (**3**) also proceeded smoothly. Thus,

(28) (a) Katritzky, A. R. *J. Heterocyl. Chem.* **1999**, *36*, 1501. (b) Katritzky, A. R.; Denisko, O. V. *Pure Appl. Chem.* **2000**, *72*, 1597. (c) Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155.

SCHEME 4



the thiocarbamoylbenzotriazole **4i** was prepared in 99% yield from pyrrolidine and **3**. The reaction of **4i** with a second secondary amine was attempted with the expected formation of the corresponding tetrasubstituted thiourea. However, in this case, substitution of the second benzotriazole group did not proceed even with a primary amine under forcing conditions (refluxing DMF) and unreacted reagent **4i** was recovered.

We believe that reactions of **4a**−**g** with primary amines proceed with the intermediate formation of isothiocyanates, which add the amine to form the thiourea. This is supported by the observation that **4i** failed to give thiourea by the reaction with a second amine. (Evidently, electronic assistance from a nitrogen lone pair is insufficient to energetically favor benzotriazole group displacement.) Moreover, on reaction with **3**, aromatic amines (*p*-anisidine, *p*-ethoxycarbonylaniline) gave the corresponding isothiocyanates instead of the expected thiocarbamoyl reagents. This result could be advantageous since such isothiocyanate formation was observed only in those cases where the isothiocyanate is stabilized as in aromatic isothiocyanates. In cases where the isothiocyanate has a low stability (e.g., alkyl isothiocyanates), the reaction stops at the thiocarbamoylbenzotriazole-formation stage, which is in fact a protected isothiocyanate. Thus, reagents **4a**−**h** can potentially replace unstable isothiocyanates.

Reagent **3** also has advantages over its close counterpart, 1,1-thiocarbonyldiimidazole (**7**), which is hygroscopic and relatively unstable[29] even though **7** has been extensively used as a thiocarbonyl transfer reagent.[11,30] Bis(benzotriazolyl)methanethione **3** is stable at room temperature for months without any loss in reactivity. On reaction with primary amines (e.g., benzylamine), 1,1′-thiocarbamoyldiimidazole (**7**) reportedly produced a mixture of the corresponding thiocarbamoylimidazole **8**, isothiocyanate **9**, and the bisthiourea **10** in yields of 48, 38, and 6%, respectively (Scheme 4).[31] In contrast, **3** afforded the thiocarbamoylbenzotriazole **4h** (Table 1) as the sole product in 97% yield from benzylamine. The bis-substitution product was never detected in the reactions of **3** with 1 equiv of a primary amine unlike the case of thiophosgene, where the reaction mixture is often contaminated by the bis-substitution product.[4]

One-Pot Synthesis of Unsymmetrical Thioureas. In a further demonstration of the utility of intermediate thiocarbamoylbenzotriazoles in the preparation of unsymmetrical thioureas, we have utilized **3** in a one-pot reaction with a primary and a secondary amine in a sequential fashion. Thus, when **3** was treated with aniline in methylene chloride followed by the addition of pyrrolidine, the corresponding trisubstituted thiourea **17** was isolated in 93% yield. A distinct advantage is that the purification requires only a mild base (5% Na_2CO_3) wash to remove the eliminated benzotriazole. Other trisubstituted thioureas **12**−**16** and **20** were also prepared in good to excellent yields by reacting, sequentially, the appropriate primary and secondary amine, respectively, with **3** (Table 3). Sequential use of two different primary amines in the one-pot reaction also afforded disubstituted thioureas **11**, **18**, and **19** in 89−97% yields (Table 3).

Conclusion

In conclusion, we have demonstrated the utility of 1-(alkyl/arylthiocarbamoyl)benzotriazoles (**4**) as masked isothiocyanates and bis(benzotriazolyl)methanethione (**3**) as a thiophosgene equivalent. Reactions of **4** with amines are faster, high-yielding, and less laborious in isolation and purification procedures than those with isothiocyanates. Di- and trisubstituted thioureas can be prepared from **4** in either one-pot or two-step procedures. Compared to thiocarbamoyl chloride and isothiocyanates, thiocarbamoylbenzotriazoles (in most cases) and bis-(benzotriazolyl)methanethione are stable crystalline solids that can be stored for extended periods.

Experimental Section

Melting points were determined on a hot-stage apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer in chloroform-*d* or DMSO-d_6 solution with tetramethylsilane as an internal reference for ^{1}H and solvent as an internal reference for ^{13}C. Column chromatography was performed on silica gel (230−425 mesh).

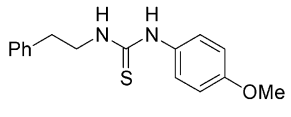
General Procedure for the Preparation of Reagents 4a−**i.** Bisbenzotriazol-1-yl methanethione[27] (0.56 g, 2 mmol) was dissolved in methylene chloride at room temperature. The appropriate primary amine (2 mmol) was added dropwise, and the reaction mixture was stirred for 18 h. Solvent was removed

(29) Ref 31 reports that 1,1′-thiocarbonyldiimidazole had decomposed 80% upon exposure to the atmosphere at room temperature for 1 day, and complete decomposition occurred after 2 days.

(30) (a)Harpp, D. N.; MacDonald, J. G. *Tetrahedron Lett.* **1983**, *24*, 4927. (b) Harpp, D. N.; MacDonald, J. G.; Larsen, C. *Can. J. Chem.* **1985**, *63*, 951.

(31) Kim, S.; Yang Yi, K. Y. *J. Org. Chem.* **1986**, *51*, 2613.

TABLE 3. Thioureas Prepared Using 1 in One-Pot Reactions with Primary and Secondary Amines



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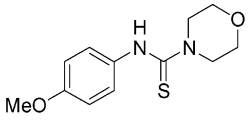
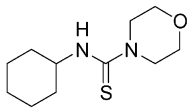
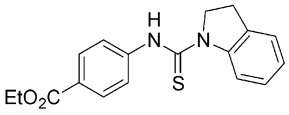


12 (99%)



13 (91%)



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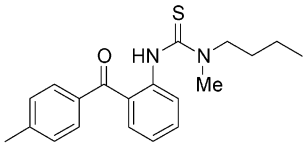
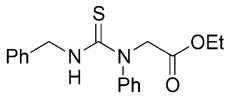
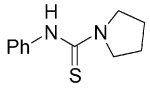


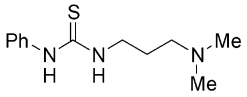
15 (76%)



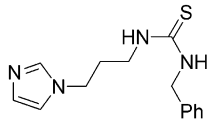
16 (52%)



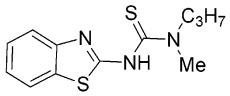
17 (93%)



18 (97%)



19 (89%)



20 (68%)

under vacuum, and the residue was redissolved in EtOAc and washed with 5% aqueous sodium carbonate, water, and brine before drying over anhydrous sodium sulfate. Solvent was removed under vacuum and 1-thiocarbamoylbenzotriazole was recrystallized from ethyl acetate.

Benzotriazole-1-carbothioic Acid Cyclohexylamide (4a): white cubes (from EtOAc/hexanes), 95%, mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.55 (m, 5H), 1.69−1.85 (m, 3H), 2.04−2.23 (m, 2H), 4.45−4.48 (m, 1H), 7.47−7.50 (m, 1H), 7.63−7.66 (m, 1H), 8.08 (dd, 1H, J = 8.1, 0.6 Hz), 8.92−9.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.4, 31.7, 53.7, 116.2, 120.2, 125.6, 130.2, 132.5, 147.1, 173.1. Anal. Calcd for $C_{13}H_{16}N_4S$: C, 59.97; H, 6.19; N, 21.52. Found: C, 59.83; H, 6.17; N, 21.50.

Benzotriazole-1-carbothioic Acid (1,5-Dimethylhexyl)-amide (4b): yellow oil, 99%; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, 6H, J = 6.6 Hz), 1.20−1.28 (m, 2H), 1.39−1.81 (m, 8H), 4.66−4.71 (m, 1H), 7.45−7.50 (m, 1H), 7.62−7.67 (m, 1H), 8.09 (d, 1H, J = 8.2 Hz), 8.90−8.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 22.5, 23.7, 27.8, 36.2, 38.6, 51.0, 116.2, 120.2, 125.6, 130.2, 132.5, 147.1, 173.4. Anal. Calcd for $C_{15}H_{22}N_4S$: C, 62.03; H, 7.64; N, 19.29. Found: C, 62.48; H, 7.70; N, 19.52.

Benzotriazole-1-carbothioic Acid Allylamide (4c): yellow needles (from EtOAc/hexanes), 93%, mp 56−57 °C; ^{1}H NMR ($CDCl_3$) δ 4.50 (t, 2H, J = 5.7 Hz), 5.32−5.45 (m, 2H), 5.97−6.10 (m, 1H), 7.49 (t, 1H, J = 8.1 Hz), 7.66 (t, 1H, J = 7.5 Hz), 8.11 (d, 1H, J = 8.1 Hz), 8.91 (d, 1H, J = 8.7 Hz), 9.16 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 47.2, 116.0, 118.8, 120.2, 125.7, 130.4, 131.3, 147.1, 155.4, 174.5. Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.67. Found: C, 55.21; H, 4.51; N, 25.86.

Benzotriazole-1-carbothioic Acid Thiazol-2-ylamide (4d): yellow powder, 91%, mp 160−161 °C; ^{1}H NMR (DMSO-d_6) δ 7.45−7.58 (m, 3H), 7.73 (t, 1H, J = 7.3 Hz), 7.96 (d, 1H, J = 4.4 Hz), 8.18 (d, 1H, J = 8.2 Hz), 8.88 (d, 1H, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 112.2, 116.3, 119.4, 125.1, 125.9, 129.0, 130.6, 130.9, 146.0, 170.3. Anal. Calcd for $C_{10}H_7N_5S_2$: C, 45.96; H, 2.70; N, 26.80. Found: C, 45.48; H, 2.66; N, 26.26.

Benzotriazole-1-carbothioic Acid (Furan-2-ylmethyl)-amide (4e): brown needles (from EtOAc/hexanes), 99%, mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 5.03 (d, 2H, J = 5.4 Hz), 6.37−6.45 (m, 2H), 7.43−7.50 (m, 2H), 7.61−7.67 (m, 1H), 8.09 (d, 1H, J = 8.1 Hz), 8.90 (d, 1H, J = 8.4 Hz), 9.32 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 41.8, 109.3, 110.6, 115.9, 120.3, 125.7, 130.4, 132.4, 143.0, 147.0, 148.5, 174.2. Anal. Calcd for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 56.04; H, 3.85; N, 21.81.

Benzotriazole-1-carbothioic Acid [(*R*)-1-Phenylethyl]-amide (4f): yellow oil, 99%; ^{1}H NMR ($CDCl_3$) δ 1.77 (d, 3H, J = 7.2 Hz), 5.74−5.84 (m, 1H), 7.30−7.50 (m, 6H), 7.61−7.66 (m, 1H), 8.09 (d, 1H, J = 8.2 Hz), 8.90 (d, 1H, J = 8.5 Hz), 9.32 (d, 1H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 54.1, 116.1, 120.2, 125.7, 126.5, 128.0, 128.9, 130.3, 132.5, 141.1, 147.1, 173.4. Anal. Calcd for $C_{15}H_{14}N_4S$: C, 63.80; H, 5.00; N, 19.84. Found: C, 64.06; H, 4.93; N, 20.29.

Benzotriazole-1-carbothioic Acid 4-Methoxybenzyl-amide (4g): white needles, 97%, mp 82−83 °C; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.95 (d, 2H, J = 5.4 Hz), 6.91 (dd, 2H, J = 6.6, 2.1 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.44−7.50 (m, 1H), 7.62−7.69 (m, 1H), 8.07 (d, 1H, J = 8.1 Hz), 8.92 (d, 1H, J = 8.4 Hz), 9.25 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.6, 55.3, 114.3, 116.0, 120.2, 125.6, 127.5, 129.7, 130.3, 132.4, 147.0, 159.6, 174.1. Anal. Calcd for $C_{15}H_{14}N_4OS$: C, 60.38; H, 4.73; N, 18.78. Found: C, 60.48; H, 4.49; N, 19.56.

Benzotriazole-1-carbothioic Acid Benzylamide (4h): white needles (from EtOAc/hexanes), 97%, mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 5.04 (d, 2H, J = 4.2 Hz), 7.33−7.52 (m, 6H), 7.66 (t, 1H, J = 7.2 Hz), 8.10 (d, 1H, J = 8.4 Hz), 8.94 (d, 1H, J = 8.7 Hz), 9.32 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 49.0, 116.0, 120.3, 125.7, 128.2, 128.3, 129.0, 130.4, 132.4, 135.5, 147.1, 174.4. Anal. Calcd for $C_{14}H_{12}N_4S$: C, 62.66; H, 4.51; N, 20.88. Found: C, 62.79; H, 4.44; N, 20.82.

Benzotriazol-1-ylpyrrolidin-1-ylmethanethione (4i): white needles (from EtOAc/hexanes), 99%, mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 2.02−2.09 (m, 2H), 2.11−2.18 (m, 2H), 3.98 (t, 1H, J = 6.9 Hz), 4.11 (t, 2H, J = 6.9 Hz), 7.46−7.52 (m,

1H), 7.62−7.67 (m, 1H), 8.13 (dd, 1H, J = 8.1, 0.9 Hz), 8.30 (dd, 1H, J = 8.4, 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.4, 54.3, 54.6, 114.5, 119.8, 125.1, 128.8, 133.0, 145.8, 172.0. Anal. Calcd for $C_{11}H_{12}N_4S$: C, 56.87; H, 5.21; N, 24.12. Found: C, 56.64; H, 5.02; N, 23.89.

General Procedure for the Preparation of Thioureas 5a−n. The appropriate thiocarbamoylbenzotriazole (1 mmol) was dissolved in methylene chloride at room temperature. The corresponding amine (1 mmol) was added followed by triethylamine (0.3 mL, 2 mmol), and the reaction mixture was stirred for 24 h. Solvent was removed under vacuum, and the residue was redissolved in EtOAc, washed with 5% aqueous sodium carbonate, 1 M HCl, water, and brine before drying over anhydrous sodium sulfate. Solvent was removed under vacuum, and the thioureas **5a−n** were purified by recrystallization (in the case of solids) or column chromatography (in the case of oils) on silica gel (200−400 mesh, EtOAc/hexanes).

1-Cyclohexyl-3-(4-methylpyridin-2-yl)thiourea (5a): plates (from EtOAc/hexanes), 90%, mp 167−168 °C; ^{1}H NMR ($CDCl_3$) δ 1.33−1.54 (m, 4H), 1.59−1.82 (m, 4H), 1.83−2.07−2.10 (m, 2H) 2.32 (s, 3H), 4.33−4.37 (m, 1H), 6.61 (s, 1H), 6.76 (d, 1H, J = 5.4 Hz), 8.01 (d, 1H, J = 5.1 Hz) 8.71 (br s, 1H), 11.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.3, 25.6, 32.0, 53.8, 112.1, 119.1, 145.2, 150.0, 153.6, 177.8. Anal. Calcd for $C_{13}H_{19}N_3S$: C, 62.61; H, 7.68; N, 16.85. Found: C, 62.62; H, 7.83; N, 16.79.

1-(1,5-Dimethylhexyl)-3-(4-methoxybenzyl)thiourea (5b): orange needles (from EtOAc/hexanes), 100%, mp 57−62 °C; ^{1}H NMR ($CDCl_3$) δ 0.84 (m, 6H, J = 6.6 Hz), 1.07−1.55 (m, 10H), 3.80 (s, 3H), 4.04 (br s, 1H), 4.55 (br s, 2H), 5.56 (br s, 1H), 5.94 (br s, 1H), 6.87−6.90 (m, 2H), 7.25 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5, 22.5, 23.5, 27.8, 36.9, 38.7, 47.8, 50.4, 55.2, 114.3, 128.9, 159.3, 180.7. Anal. Calcd for $C_{17}H_{28}N_2OS$: C, 66.19; H, 9.15; N, 9.08. Found: C, 66.41; H, 9.19; N, 9.33.

1-(4-Methoxybenzyl)-3-(1-methylbutyl)thiourea (5c): yellow oil, 93%; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz), 1.15 (d, 3H, J = 6.6 Hz), 1.20−1.50 (m, 5H), 3.81 (s, 3H), 4.05 (br s, 1H), 4.55 (br s, 2H), 5.56 (s, 1H), 5.94 (s, 1H), 6.89 (d, 2H, J = 8.7 Hz), 7.25 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9,19.0, 20.6, 38.9, 47.9, 50.2, 55.3, 114.3, 125.9, 128.9, 159.3, 180.7. Anal. Calcd for $C_{14}H_{22}N_2OS$: C, 63.12; H, 8.32; N, 10.52. Found: C, 63.50; H, 8.70; N, 11.41.

1-(2-Ethoxyethyl)-3-[(*R*)-1-phenylethyl]thiourea (5d): yellow oil, 99%; $[\alpha]_D^{25}$ +0.1° (*c* 0.04, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 6.9 Hz), 1.53 (d, 3H, J = 6.6 Hz), 3.32−3.60 (m, 7H), 5.02 (br s, 1H), 6.11 (br s, 1H), 7.21−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 22.9, 44.7, 53.8, 66.3, 69.0, 125.8, 127.4, 128.6, 142.4, 181.3. Anal. Calcd for $C_{13}H_{20}N_2OS$: C, 61.87; H, 7.99; N, 11.10. Found: C, 61.65; H, 8.22; N, 11.10.

4-(3-Furan-2-ylmethylthioureido)benzoic Acid Ethyl Ester (5e): green needles (from EtOAc/hexanes), 57%, mp 115−116 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 7.2 Hz), 4.36 (q, 2H, J = 7.2 Hz), 4.86 (d, 2H, J = 5.1 Hz), 6.31−6.34 (m, 2H), 6.55 (br s, 1H), 7.28 (d, 2H, J = 8.4 Hz), 7.35−7.36 (m, 1H), 8.06 (d, 2H, J = 8.4 Hz), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 42.4, 61.2, 108.5, 110.5, 123.0, 128.1, 131.5, 140.4, 142.6, 149.7, 165.6, 180.1. Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.06; H, 5.25; N, 9.34.

1-Phenethyl-3-thiazol-2-ylthiourea (5f): orange needles (from EtOAc/hexanes), 95%, mp 162−164 °C (lit.[32] mp 169.5−170.5 °C); ^{1}H NMR ($CDCl_3$) δ 3.03 (t, 2H, J = 7.2 Hz), 3.99 (q, 2H, J = 7.2 Hz), 6.80 (d, 1H, J = 3.6 Hz), 7.20−7.35 (m, 6H), 10.50 (br s, 1H), 10.83 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.8, 47.0, 111.1, 126.6, 128.6, 128.9, 137.6, 138.5, 161.6, 177.6. Anal. Calcd for $C_{12}H_{13}N_3S_2$: C, 54.72; H, 4.97; N, 15.95. Found: C, 54.99; H, 4.80; N, 15.93.

1-Allyl-3-phenethylthiourea (5g): yellow oil, 97%; ^{1}H NMR ($CDCl_3$) δ 2.91 (t, 2H, J = 6.9 Hz); 3.76−3.78 (d, 2H, J = 5.1 Hz); 3.92 (s, 2H); 5.09−5.17 (m, 2H); 5.71−5.80 (m, 1H); 5.99 (br s, 1H); 6.24 (br s, 1H); 7.19−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 35.0, 45.7, 46.5, 117.6, 126.7, 128.7, 132.9, 138.3, 182.0. Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.62; H, 7.41; N, 13.10.

3-Cyclohexyl-1-methyl-1-phenylthiourea (5h): yellow oil, 91%; ^{1}H NMR ($CDCl_3$) δ 0.93−1.12 (m, 3H), 1.29−1.41 (m, 2H), 1.54 (d, 3H, J = 10.2 Hz), 1.94 (d, 2H, J = 9.9 Hz), 3.66 (s, 3H), 4.21−4.31 (m, 1H), 5.19 (d, 1H, J = 7.2 Hz), 7.21−7.23 (m, 2H), 7.37−7.42 (m, 1H) 7.47−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.5, 25.4, 32.5, 43.0, 53.8, 127.0, 128.3, 130.5, 142.9, 180.6. Anal. Calcd for $C_{14}H_{20}N_2S$: C, 67.70; H, 8.12; N, 11.28. Found: C, 67.59; H, 8.22; N, 11.32.

3-Allyl-1-methyl-1-phenethylthiourea (5i): yellow oil, 92%; ^{1}H NMR ($CDCl_3$) δ 2.98 (t, 2H, J = 7.5 Hz), 3.05 (s, 3H), 4.00 (t, 2H, J = 7.2 Hz), 4.27 (t, 2H, J = 5.4 Hz), 5.14−5.22 (m, 2H), 5.23 (br s, 1H), 5.83−5.94 (m, 1H), 7.21−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 33.8, 38.0, 48.5, 55.8, 116.8, 126.5, 128.6, 128.8, 134.2, 138.7, 181.6. Anal. Calcd for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95. Found: C, 66.31; H, 7.79; N, 12.37.

3-(1,5-Dimethylhexyl)-1-methyl-1-phenylthiourea (5j): orange oil, 61%; ^{1}H NMR ($CDCl_3$) δ 0.82−0.85 (dd, 6H, J = 6.6, 1.5 Hz), 1.07−1.52 (m, 10H), 3.66 (s, 3H), 4.40−4.51 (m, 1H), 5.06 (d, 1H, J = 8.1 Hz), 7.21 (d, 2H, J = 7.2 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.47−7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.3, 22.4, 23.5, 27.7, 36.6, 38.6, 43.1, 51.4, 127.1, 128.4, 130.5, 142.9, 181.0. Anal. Calcd for $C_{16}H_{26}N_2S$: C, 69.01; H, 9.41; N, 10.06. Found: C, 69.33; H, 9.61; N, 10.29.

Piperidine-1-carbothioic Acid 4-Methoxybenzylamide (5k): yellow oil, 95%; ^{1}H NMR ($CDCl_3$) δ 1.65−1.68 (m, 6H), 3.81−3.81 (m, 7H), 4.82 (d, 2H, J = 4.5 Hz), 5.64 (br s, 1H), 6.91 (d, 2H, J = 8.4 Hz), 7.31 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.1, 25.3, 48.8, 49.8, 55.2, 114.0, 129.4, 130.1, 159.0, 180.9. Anal. Calcd for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.62; N, 10.60. Found: C, 63.09; H, 7.50; N, 11.31.

Morpholine-4-carbothioic Acid [(*R*)-1-Phenylethyl]-amide (5l): white needles (from EtOAc/hexanes), 92%, mp 117−119 °C; $[\alpha]_D^{25}$ −3.5° (*c* 0.04, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.61 (d, 3H, J = 6.6 Hz), 3.72−3.84 (m, 8H), 5.66 (br s, 1H), 5.77−5.87 (m, 1H), 7.26−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.4, 47.4, 54.6, 66.1, 126.4, 127.5, 128.7, 142.9, 181.9. Anal. Calcd for $C_{13}H_{18}N_2OS$: C, 62.36; H, 7.25; N, 11.19. Found: C, 62.05; H, 7.25; N, 11.62.

Piperidine-1-carbothioic Acid (Furan-2-ylmethyl)-amide (5m): white needles (from EtOAc/hexanes), 94%, mp 104−107 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (br s, 6H), 3.78−3.80 (m, 4H), 4.87 (d, 2H, J = 4.8 Hz), 5.64 (br s, 1H), 6.30−6.34 (m, 2H) 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.2, 25.4, 43.1, 48.8, 108.0, 110.5, 142.2, 151.1, 181.0. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 58.35; H, 7.31; N, 12.28.

3-Methylpiperidine-1-carbothioic Acid Thiazol-2-yl-amide (5n): orange oil, 87%; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, J = 6.6 Hz), 1.10−1.26 (m, 1H), 1.45−1.85 (m, 4H), 2.66 (t, 1H, J = 11.1 Hz), 2.89−3.03 (m, 1H), 4.84 (t, 2H, J = 14.1 Hz) 6.62 (d, 1H, J = 4.2 Hz), 7.16 (d, 1H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ 18.9, 25.1, 31.3, 33.0, 48.6, 55.2, 109.9, 127.6, 167.8, 180.6. Anal. Calcd for $C_{10}H_{15}N_3S_2$: C, 49.76; H, 6.26; N, 17.41. Found: C, 49.99; H, 6.28; N, 17.11.

General Procedure for the One-Pot Preparation of Thioureas 11−20. To 0.56 g of bis-benzotriazol-1-yl-methanethione (2 mmol) in 30 mL of THF was added the appropriate primary amine (2 mmol), and the mixture was stirred for 36 h. Then, triethylamine (0.6 mL, 4 mmol) and the second primary amine or a secondary amine (2 mmol) were added, and the mixture was stirred for an additional 36 h. Solvent was evaporated, and the remaining oil was dissolved in ethyl acetate and washed with 1 M HCl, 10% aqueous solution sodium carbonate, water, and brine. The organic layer was

(32) Bell, F. W.; Cantrell, A. S.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Teransky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929.

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dried over anhydrous sodium sulfate, concentrated, and purified by recrystallization or column chromatography (10% EtOAc/hexanes).

1-(4-Methoxyphenyl)-3-phenethylthiourea (11): gray needles (from EtOAc/hexanes), 94%, mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 2.89 (t, 2H, J = 6.9 Hz), 3.81 (s, 3H), 3.86 (q, 2H, J = 6.9 Hz), 5.75 (br s, 1H), 6.82−6.86 (m, 2H), 6.95 (d, 2H, J = 8.7 Hz), 7.10−7.13 (m, 2H), 7.21−7.29 (m, 3H), 7.51 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.8, 46.1, 55.4, 115.1, 126.5, 127.6, 128.1, 128.6, 128.7, 138.4, 158.8, 180.9. Anal. Calcd for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.33; N, 9.78. Found: C, 67.29; H, 6.38; N, 9.96.

Morpholine-1-carbothioic Acid 4-Methoxyphenylamide (12): colorless microcrystals (from ethanol), 99%, mp 155−156 °C (lit.[33] 158−159 °C); ^{1}H NMR ($CDCl_3$) δ 3.65−3.73 (m, 4H), 3.75−3.85 (m, 7H), 6.85 (d, 2H, J = 8.7 Hz), 7.09 (d, 2H, J = 8.7 Hz), 7.28 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 49.0, 55.4, 66.1, 114.2, 126.0, 132.6, 157.5, 183.8.

Morpholine-1-carbothioic Acid Cyclohexylamide (13): colorless prisms (from ethanol), 91%, mp 127−130 °C; ^{1}H NMR ($CDCl_3$) δ 1.10−1.23 (m, 3H), 1.36−1.49 (m, 2H), 1.63−1.75 (m, 3H), 2.09−2.18 (m, 2H), 3.75 (d, 8H, J = 3.6 Hz), 4.32−4.42 (m, 1H), 5.35 (d, 1H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.5, 33.0, 47.2, 54.3, 66.0, 181.4. Anal. Calcd for $C_{11}H_{20}N_2OS$: C, 57.86; H, 8.83; N, 12.27. Found: C, 58.15; H, 8.98; N, 12.35.

4-[(2,3-Dihydroindole-1-carbothioyl)amino]benzoic Acid Ethyl Ester (14): gray needles (from EtOAc/hexanes), 87%, mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3H, J = 7.2 Hz), 3.12 (t, 2H, J = 8.1 Hz), 4.35 (q, 2H, J = 7.2 Hz), 4.45 (t, 2H, J = 8.1 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.17 (t, 1H, J = 7.8 Hz), 7.29 (d, 1H, J = 7.5 Hz), 7.43−7.50 (m, 3H), 7.83 (br s, 1H), 8.00 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4, 27.3, 55.0, 60.9, 114.9, 121.7, 124.4, 126.3, 126.6, 127.5, 130.6, 134.7, 141.5, 143.1, 166.1, 177.7. Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.53; H, 5.61; N, 8.60.

1-Butyl-1-methyl-3-[2-(4-methylbenzoyl)phenyl] Thiourea (15): yellow oil, 76%; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, J = 7.2 Hz), 1.38−1.46 (m, 2H), 1.67−1.77 (m, 2H), 2.44 (s, 3H), 3.38 (s, 3H), 3.87 (br s, 2H), 7.05−7.11 (m, 1H), 7.28 (d, 2H, J = 8.1 Hz), 7.49−7.56 (m, 2H), 7.67 (d, 2H, J = 8.1 Hz), 8.72 (d, 1H, J = 8.4 Hz), 10.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.1, 21.7, 29.2, 53.7, 122.1, 125.0, 125.9, 129.0, 130.5, 132.4, 132.6, 135.5, 142.2, 143.6, 179.6, 199.1. Anal. Calcd for $C_{20}H_{24}N_2OS$: C, 70.55; H, 7.10; N, 8.23. Found: C, 70.19; H, 7.18; N, 8.64.

(3-Benzyl-1-phenylthioureido)acetic Acid Ethyl Ester (16): red oil, 52%; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.82 (d, 2H, J = 5.4 Hz), 4.89 (s, 2H), 5.76 (br s, 1H), 7.17−7.48 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.1, 49.9, 56.4, 61.2, 127.2, 127.4, 127.9, 128.6, 129.1, 130.6, 137.7, 141.4, 169.3, 182.9. Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 66.19; H, 6.20; N, 8.62.

Pyrrolidine-1-carbothioic Acid Phenylamide (17): colorless prisms (from ethanol), 93%, mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.95−2.01 (m, 4H), 3.67 (t, 4H, J = 6.6 Hz), 6.90 (br s, 1H), 7.12−7.16 (m, 1H), 7.24−7.37 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.4, 50.3, 125.1, 125.3, 128.5, 139.7, 179.1. Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.26; H, 7.05; N, 13.63.

1-(3-Dimethylaminopropyl)-3-phenyl thiourea (18): Yellow needles (from EtOAc/hexanes), 97%, mp 99−100 °C; ^{1}H NMR ($CDCl_3$) δ 1.65−1.72 (m, 2H), 1.88 (s, 6H), 2.38 (t, 2H, J = 5.7 Hz), 3.74 (br s, 2H), 7.23−7.29 (m, 3H), 7.39 (t, 2H, J = 7.8 Hz), 8.00 (br s, 1H), 8.82 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.2, 44.5, 47.0, 59.0, 115.0, 125.6, 126.6, 129.2, 129.5, 136.8, 180.3. Anal. Calcd for $C_{12}H_{19}N_3S$: C, 60.72; H, 8.07; N, 17.70. Found: C, 60.40; H, 8.01; N, 17.72.

1-Benzyl-3-(3-imidazol-1-ylpropyl)thiourea (19): colorless oil, 89%; ^{1}H NMR ($CDCl_3$) δ 1.96−2.06 (m, 2H), 3.48 (q, 2H, J = 5.7 Hz), 3.89 (t, 2H, J = 6.6 Hz), 4.65 (d, 2H, J = 3.6 Hz), 6.86 (s, 2H), 7.19 (s, 1H), 7.26−7.33 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 30.3, 41.2, 44.3, 48.0, 119.1, 127.4, 127.5, 128.6, 128.7, 136.8, 137.5, 183.0. Anal. Calcd for $C_{14}H_{18}N_4S$: C, 61.28; H, 6.61; N, 20.42. Found: C, 60.93; H, 6.79; N, 20.02.

1-Benzothiazolyl-3-methyl-3-(butyl)thiourea (20): yellow powder (from EtOAc/hexanes), 68%, mp 114−116 °C; ^{1}H NMR (DMSO-d_6) δ 0.92 (t, 3H, J = 7.2 Hz), 1.22 (d, 3H, J = 6.6 Hz), 1.32−1.43 (m, 2H), 1.48−1.67 (m, 2H), 4.30−4.39 (m, 1H), 7.28 (t, 1H, J = 7.8 Hz), 7.41 (t, 1H, J = 6.9 Hz), 7.64 (d, 1H, J = 7.8 Hz), 7.90 (d, 1H, J = 7.8 Hz), 9.84 (br s, 1H), 11.74 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.8, 18.6, 19.7, 37.6, 49.8, 119.1, 121.7, 123.6, 126.2, 129.6, 161.5, 178.1. Anal. Calcd for $C_{13}H_{17}N_3S_2$: C, 55.88; H, 6.13; N, 15.04. Found: C, 55.20; H, 5.99; N, 15.04.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **4b**, **4f**, **4g**, **5c**, **5i**, **5k**, **5m**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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