First Stable *O*-Amidinylhydroxylamines and Their Transformations into Sulfenamides by Intramolecular 1,5-O→S Amine Migration

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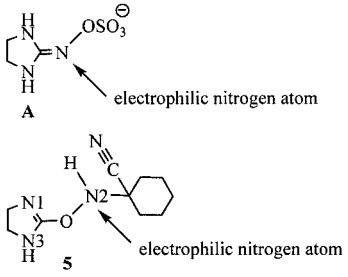
The reaction of 2-chloro-4,5-dihydroimidazole (**1**) with aliphatic hydroxylamines **2**–**4** gives *O*-amidinylhydroxylamines **5**–**7** in contrast to the analogous reaction of **1** with *N*-arylhydroxylamines in which *N*-substitution occurs. A number of thiocarbamoylsulfenamides **8**–**10** have been prepared by the reaction of **5**–**7** with carbon disulfide under basic and mild conditions. The key step in the 1,5-O→S amine migration involves the tandem nucleophilic addition-electrophilic amination reaction. The intermolecular version of this process using preformed triethylammonium dithiocarbamates gives the corresponding sulfenamides **14**–**16**. Functionalized ethylenediamines **17**–**19** are obtained by treatment of **8** and **9** with amines.

Introduction

Sulfenamides represent a diverse and important class of compounds, serving a variety of distinct functions in both synthetic and industrial chemistry.[1,2] Most of the sulfenamides described in the literature possess alkyl or aryl groups on the sulfur atom. However, the comparatively less common thiocarbamoylsulfenamides have been used in industry as rubber vulcanization accelerators[3] and have been developed as inhibitors of zinc enzyme carbonic anhydrase in medicinal chemistry.[4,5] In addition, thiocarbamoylsulfenamides have attracted increasing interest because of their use as nucleophilic reagents in the direct amination of nitroarenes.[6,7]

The S−N bond-forming reactions that lead to thiocarbamoylsulfenamides involve the reaction of CS_2, an amine and chloroamine in the presence of base,[8] the coupling of sodium or ammonium dithiocarbamates with either chloroamines[9−11] or amines in an oxidative environment[11,12] as well as an electrolytic cross-coupling reaction of bis(dialkylthiocarbamoyl) disulfides with amines.[13,14]

Recently, we reported[15] that 2-(hydroxylamino)-4,5-dihydroimidazolium *O*-sulfonate (**A**), which contains two endocyclic nucleophilic nitrogen atoms and an exocyclic electrophilic nitrogen atom (Figure 1), when treated with heterocumulenes such as carbon disulfide or isothiocyanates, undergoes tandem nucleophilic addition-electrophilic amination reactions to give a variety of S−N bond-containing heterocyclic compounds.



nucleophilic nitrogen atoms		electrophilic nitrogen atom
N1	**N3**	**N2**
–0.76	–0.71	–0.35
–0.80	–0.66	–0.55

Figure 1. Calculated[16] atomic charges and atomic charges derived from the electrostatic potential (underlined) of the nitrogen atoms of **5**

We have now successfully extended this strategy by using compounds of type **5** (Figure 1), which have a new *O*-amidinylhydroxylamine functionality as the core structure. We

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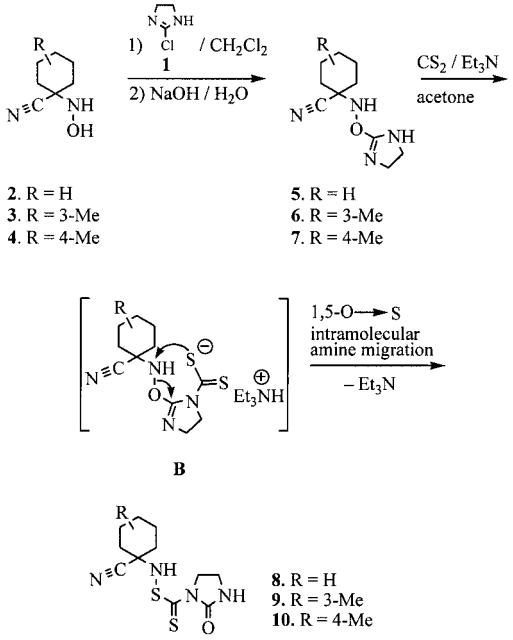
anticipated that these compounds would have the built-in potential to undergo tandem nucleophilic addition-electrophilic amination reactions to give novel thiocarbamoylsulfenamides that incorporate the 2-oxoimidazolidine moiety.

Results and Discussion

When 2-chloro-4,5-dihydroimidazole (**1**) was allowed to react with *N*-cyclohexylhydroxylamines **2**−**4** (ambident nucleophiles) in a ratio of 1.5:1, we found that *O*-heteroalkylation of the latter occurred to afford *O*-amidinylhydroxylamines **5**−**7** in 19−22% isolated yields (Scheme 1). This contrasted with our previous finding that *N*-arylhydroxylamines upon treatment with **1** underwent *N*-heteroalkylation.[17] Apparently, the nucleophilic *N*-attack of **2**−**4** is hindered sterically and by electronic repulsion of the *axial* nitrile group.



Scheme 1. Preparation of *O*-amidinylhydroxylamines **5**−**7** and thiocarbamoylsulfenamides **8**−**10**

When the ratio of **1/2** was 2:1, so that no hydroxylamine was left after the initial reaction, the substrate was still present. Thus, from our findings it can be inferred that the products **5**−**7** react with excess **1** and upon workup give back the substrates **2**−**4** and 1-(4,5-dihydroimidazol-2-yl)-2-imidazolidinone as the only identified side product (see Exp. Sect.).

Treatment of **5**−**7** with carbon disulfide in acetone at room temperature in the presence of Et_3N gave rise to the desired thiocarbamoylsulfenamides **8**−**10** in 39−40% yields. The structures of these compounds was confirmed by IR and NMR spectroscopic data as well as by the X-ray diffraction analysis of **10** (Figure 2).

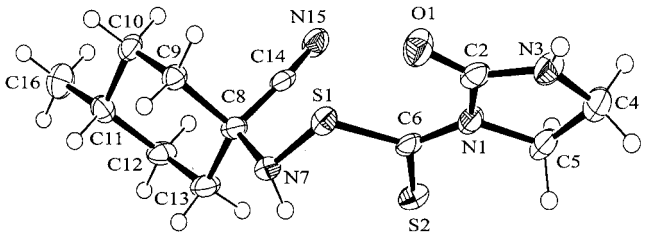
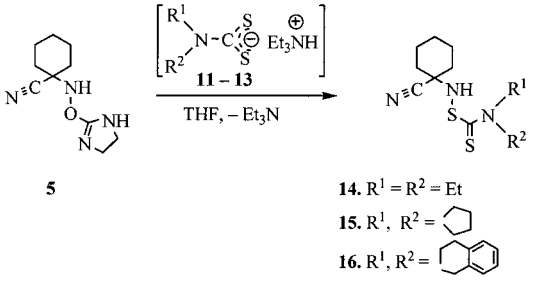


Figure 2. ORTEP drawing of **10** with the atom labeling scheme

A proposed mechanism for this reaction is shown in Scheme 1. Since the reaction was performed under basic conditions, the dithiocarbamic acid initially formed should exist in the anionic form **B**. Then, intramolecular O→S amine migration with simultaneous cleavage of the rather weak N−O bond produces the thiocarbamoylsulfenamides **8**−**10**.

Another possible mechanism is the concerted base-mediated [1,5]-sigmatropic rearrangement of **B**, which is not ruled out by the present evidence. However, the next logical step in the development of this chemistry was to study the intermolecular version of this process by using preformed triethylammonium dithiocarbamates **11**−**13**. As can be seen from the results shown in Scheme 2, the use of secondary aliphatic amines allows the preparation of thiocarbamoylsulfenamides **14**−**16** in 33−64% yields. The structure of **14** thus obtained was analyzed by X-ray diffraction (Figure 3).



Scheme 2. Preparation of thiocarbamoylsulfenamides **14**−**16**

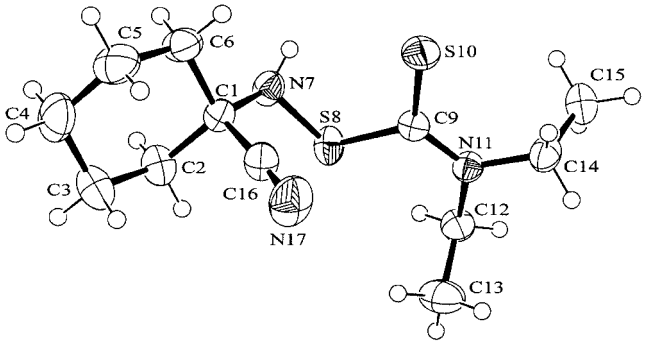
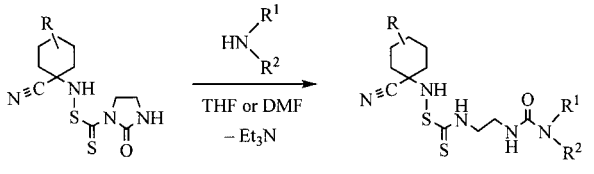


Figure 3. ORTEP drawing of **14** with the atom labeling scheme

Compounds **8** and **9** were used in the synthesis of functionalized ethylenediamines **17**−**19** (Scheme 3). The method is based on our finding that the 2-oxoimidazolidine

derivatives react with primary and secondary amines to give the products of a nucleophilic ring-opening reaction. The structure of **17** thus obtained was analyzed by X-ray diffraction (Figure 4).



8. R = H
9. R = 3-Me

17. R = H; $R^1 = R^2$ = Et
18. R = 3-Me; R^1, R^2 = cyclopentyl
19. R = H; R^1 = H; R^2 = Bzl

Scheme 3. Preparation of functionalized ethylenediamines **17**–**19**

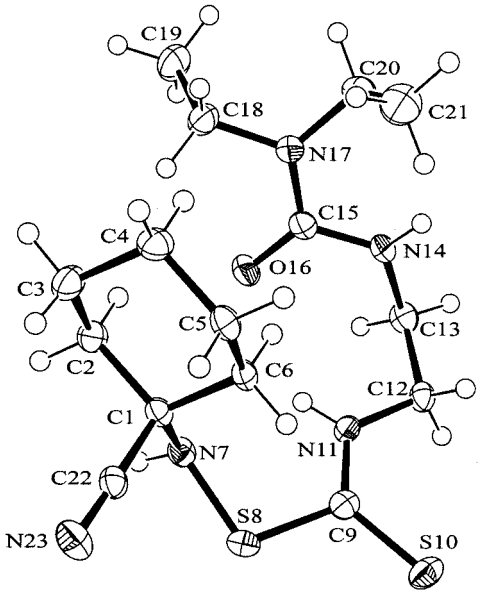


Figure 4. ORTEP drawing of **17** with the atom labeling scheme

The structures of the newly prepared compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopic data (see Supporting Information).

Biological Evaluation

It is well known that unstable *O*-acylhydroxylamines react as electrophiles to form DNA adducts which cause primary cancer lesion.[18] On the other hand, solid tumors have lower extracellular pH levels than normal tissues due to the accumulation of metabolic acids in hypoxic cells.[19] This difference (0.6–0.8 units) provides new strategies for tumor-selective activation of cytocidal drugs.[20] We reasoned that the electrophilic character of nitrogen electrophiles like **5**–**7** should be enhanced upon protonation of the imidazoline ring in hypotoxic cells. Therefore, compounds **5**–**7** were submitted to the National Cancer Institute (Bethesda, USA) for evaluation against human tumor cell lines, and compounds **6** and **7** were found to exhibit activity against the NCI-H460 cell line (lung cancer) in the preliminary anticancer assay.

The minimum inhibitory concentration (MIC) and minimum bactericide concentration (MBC) of compounds **8**–**10**, **15** and **17** in liquid media were also determined by the standard broth dilution technique[21] with an innoculum of approximately 4×10^5 CFU·mL^{-1}. Compounds were tested against three bacterial strains: *Escherichia coli* (NCTC 8196), *Staphylococcus aureus* (NCTC 4163) and *Pseudomonas aeruginosa* (NCTC 6749) at concentrations in the range of 1.9–250μg·mL^{-1}. Compounds **9**, **15** and **17** were inactive (MIC ⩾ 62.5 μg·mL^{-1}), while thiocarbamoylsulfenamides **8** and **10** showed activity against gram-positive *Staphylococcus aureus* with MIC and MBC values of 15.6 μg·mL^{-1}.

Conclusion

We have described the first synthesis of stable *O*-amidinylhydroxylamines **5**–**7**, which are easy to separate and may be stored under anhydrous conditions for several months without significant decomposition.

A novel tandem nucleophilic addition-electrophilic amination rearrangement as a key step provides access to the otherwise not readily available thiocarbamoylsulfenamides, for example, **8**–**10**, **14**–**16** and **17**–**19**.

Experimental Section

General Remarks: Melting points were measured with a Büchi S35 apparatus and are uncorrected. FT-IR spectra were recorded with a Perkin-Elmer 1600 spectrophotometer as KBr pellets. NMR spectra were recorded with Varian Gemini 200 and Varian Unity Plus 500 spectrometers at 200 or 500 MHz for proton and at 125 MHz for carbon nuclei. Chemical shifts (δ) were measured relative to the residual solvent signal at δ = 2.50 or 7.26 ppm and δ = 39.5 or 77 ppm for ^{1}H and ^{13}C NMR, respectively. Mass spectra were recorded at 70 eV. All reagents were used directly as obtained commercially. 2-Chloro-4,5-dihydroimidazole[22] (**1**) and the 1-(hydroxyamino)cyclohexanecarbonitriles[23,24] **2**–**4** were prepared according to previously described procedures.

Reaction of 2-Chloro-4,5-dihydroimidazole (1) with 1-(Hydroxyamino)cyclohexanecarbonitrile (2). Preparation of 1-[(4,5-Dihydro-1*H*-imidazol-2-yloxy)amino]cyclohexanecarbonitrile (5): 1-(Hydroxyamino)cyclohexanecarbonitrile (**2**) (2.31 g, 16.5 mmol) was added to a solution of 2-chloro-4,5-dihydroimidazole (**1**) (2.5 g, 24 mmol) in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at room temperature for 12 h. The solid that precipitated (1.82 g), which consists of a mixture of **5**·HCl and 1-(4,5-dihydroimidazol-2-yl)-2-imidazolidinone (NMR evidence), was filtered off (the filtrate denoted as **I** was stored for further workup), dissolved in water (15 mL) and the resulting solution was made alkaline (pH = 9) with 10% aqueous NaOH. The precipitated solid was collected by filtration, washed with water and dried to give free base **5** (0.64 g, 19%) as a white solid; m.p. 111–113 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.18–1.25 (m, 1 H), 1.34–1.42 (m, 2 H), 1.47–1.52 (m, 2 H), 1.59–1.61 (m, 1 H), 1.75 (dd, *J* = 4.12, 9.34 Hz, 2 H), 1.93 (d, *J* = 12.9 Hz, 2 H), 3.42 (s, 4 H), 6.23 (br. s, 1 H), 8.35 (s, 1 H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 22.17 (two overlapping signals), 25.09, 32.52 (two overlapping signals), 48.63 (two overlap-

ping signals), 59.86, 121.57, 167.44 ppm. IR (KBr): $\tilde{\nu}$ = 3415, 3115, 2935, 2920, 2860, 2230, 1630, 1610, 1545, 1490, 1450, 1285 cm^{-1}. $C_{10}H_{16}N_4O$ (208.27): calcd. C 57.68, H 16.13, N 26.93; found C 57.65, H 16.10, N 26.74. The filtrate **I** was concentrated under reduced pressure, and the oily residue was treated with diethyl ether. The precipitated solid was collected by suction and dried to give 1-(hydroxyamino)cyclohexanecarbonitrile (**2**) (0.3 g, 13%). The following compounds were prepared analogously by treating **1** with the appropriate 1-(hydroxyamino)cyclohexanecarbonitrile **3** or **4**.

1-[(4,5-Dihydro-1*H*-imidazol-2-yloxy)amino]-3-methylcyclohexanecarbonitrile (6): This compound was prepared from 1-(hydroxyamino)-3-methylcyclohexanecarbonitrile (**3**) (2.51 g, 16.5 mmol); white solid; yield 0.7 g (20%); m.p. 102−104 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.84−0.89 (m, 1 H), 0.92 (d, *J* = 6.35 Hz, 3 H), 1.09 (t, *J* = 12.7 Hz, 1 H), 1.30−1.46 (m, 2 H), 1.57−1.59 (m, 1 H), 1.68 (d, *J* = 12.69 Hz, 1 H), 1.77−1.80 (m, 1 H), 1.94−1.96 (m, 2 H), 3.42 (s, 4 H), 6.27 (br. s, 1 H), 8.38 (s, 1 H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 22.4, 22.44, 29.3 (two overlapping signals), 32.3, 33.9, 48.7 (two overlapping signals), 60.6, 121.5, 167.5 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 3110, 2920, 2860, 2225, 1634, 1615, 1535, 1445, 1285 cm^{-1}. $C_{11}H_{18}N_4O$ (222.29): calcd. C 59.43, H 8.16, N 25.20; found C 59.65, H 7.83, N 25.36.

1-[(4,5-Dihydro-1*H*-imidazol-2-yloxy)amino]-4-methylcyclohexanecarbonitrile (7): This compound was prepared from 1-(hydroxyamino)-4-methylcyclohexanecarbonitrile (**4**) (2.51 g, 16.5 mmol); white solid; yield 0.8 g (22%); m.p. 104−105 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.9 (d, *J* = 6.59 Hz, 3 H), 1.08 (q, *J* = 11.67 Hz, 2 H), 1.33−1.40 (m, 1 H), 1.44−1.48 (m, 2 H), 1.75 (d, *J* = 12.36 Hz, 2 H), 1.97 (d, *J* = 12.91 Hz, 2 H), 3.42 (s, 4 H), 6.27 (br. s, 1 H), 8.38 (s, 1 H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 21.7, 30.3 (two overlapping signals), 31.0, 31.9 (two overlapping signals), 48.0 (two overlapping signals), 59.6, 120.7, 166.8 ppm. IR (KBr): $\tilde{\nu}$ = 3145, 2945, 2925, 2870, 2225, 1625, 1610, 1515, 1445, 1285 cm^{-1}. $C_{11}H_{18}N_4O$ (222.29): calcd. C 59.43, H 8.16, N 25.20; found C 59.68, H 7.92, N 24.95.

Preparation of 1-({[(2-Oxoimidazolidin-1-yl)carbonothioyl]thio}amino)cyclohexanecarbonitriles 8−10. General Procedure: Triethylamine (0.27 mL, 2 mmol) was added dropwise to a mixture of the appropriate nitrile **5**−**7** (2 mmol) and carbon disulfide (1.2 mL, 20 mmol) in anhydrous acetone (10 mL), and the reaction suspension was stirred at room temperature for 20 h. Then the insoluble by-product (0.02 g) was filtered off. The solvent of the filtrate and excess of carbon disulfide were evaporated under reduce pressure, and the residue was treated with anhydrous methanol (3 mL). The precipitate thus obtained was filtered and dried. The following compounds were obtained according to the above procedure.

1-({[(2-Oxoimidazolidin-1-yl)carbonothioyl]thio}amino)cyclohexanecarbonitrile (8): This compound was prepared from nitrile **5** (410 mg, 2 mmol); yellow solid; yield 220 mg (40%); m.p. 141−143 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.18−1.23 (m, 1 H), 1.33−1.40 (m, 2 H), 1.54−1.56 (m, 1 H), 1.60−1.66 (m, 2 H), 1.70−1.73 (m, 2 H), 2.27 (d, *J* = 12.7 Hz, 2 H), 3.49−3.52 (m, 2 H), 4.13−4.16 (m, 2 H), 5.39 (s, 1 H), 8.30 (s, 1 H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 22.8 (two overlapping signals), 24.9, 36.7 (two overlapping signals), 38.0, 50.7, 59.3, 121.9, 155.5, 203.5 ppm. IR (KBr): $\tilde{\nu}$ = 3240, 3130, 2930, 2855, 2225, 1740, 1345, 1265, 1170 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 284.1 (10.4) [M$^+$], 129.0 (100), 128 (17.8), 86 (18.8), 72 (18.7). $C_{11}H_{16}N_4OS_2$ (284.41): calcd. C 46.45, H 5.67, N 19.70; found C 46.32, H 5.83, N 19.73.

3-Methyl-1-({[(2-oxoimidazolidin-1-yl)carbonothioyl]thio}amino)cyclohexanecarbonitrile (9): This compound was prepared from nitrile **6** (440 mg, 2 mmol); yellow solid; yield 230 mg (39%); m.p. 136−138 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.80−0.88 (m, 1 H), 0.91 (d, *J* = 6.35 Hz, 3 H), 1.24 (t, *J* = 12.70 Hz, 1 H), 1.36−1.51 (m, 2 H), 1.55−1.57 (m, 1 H), 1.64 (d, *J* = 12.69 Hz, 1 H), 1.74−1.76 (m, 1 H), 2.11 (d, *J* = 12.70 Hz, 2 H), 3.50−3.53 (m, 2 H), 4.14−4.17 (m, 2 H), 5.45 (s, 1 H), 8.31 (s, 1 H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 22.3, 23.1, 29.9, 33.7, 36.6, 38.0, 44.7, 50.7, 60.1, 121.8, 155.5, 205.8 ppm. IR (KBr): $\tilde{\nu}$ = 3240, 3125, 2950, 2920, 2225, 1730, 1340, 1265 cm^{-1}. $C_{12}H_{18}N_4OS_2$ (298.43): calcd. C 48.30, H 6.08, N 18.77; found C 48.37, H 6.21, N 18.52.

4-Methyl-1-({[(2-oxoimidazolidin-1-yl)carbonothioyl]thio}amino)cyclohexanecarbonitrile (10): This compound was prepared from nitrile **7** (440 mg, 2 mmol); yellow solid; yield 240 mg (41%); m.p. 139−140 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.88 (d, *J* = 6.83 Hz, 3 H), 1.08 (q, *J* = 11.72 Hz, 2 H), 1.32−1.41 (m, 1 H), 1.59−1.64 (m, 2 H), 1.72 (d, *J* = 12.7 Hz, 2 H), 2.12 (d, *J* = 12.21 Hz, 2 H), 3.50−3.52 (m, 2 H), 4.14−4.17 (m, 2 H), 5.46 (s, 1 H), 8.30 (s, 1 H) ppm. ^{13}C NMR (500 MHz, [D$_6$]DMSO): δ = 22.4, 31.5, 31.7 (two overlapping signals), 36.7 (two overlapping signals), 38.0, 50.7, 59.77, 121.7, 155.5, 205.8 ppm. IR (KBr): $\tilde{\nu}$ = 3250, 3130, 2925, 2855, 2220, 1730, 1340, 1265 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 298.1 (35.2) [M$^+$], 143.1 (61.6), 129.1 (100), 128.1 (39.8), 111 (15.5). $C_{12}H_{18}N_4OS_2$ (298.43): calcd. C 48.30, H 6.08, N 18.77; found C 48.15, H 5.92, N 18.51.

Reaction of 5 with Triethylammonium Dithiocarbamates. Preparation of 1-({[(Amino)carbonothioyl]thio}amino)cyclohexanecarbonitriles 14−16. General Procedure: Carbon disulfide (0.11 mL, 1.9 mmol) and Et_3N (0.26 mL, 1.9 mmol) were added to a solution of the appropriate amine **11**−**13** (1.9 mmol) in anhydrous THF (10 mL). After stirring at room temperature for 30 min, a solution of **5** (320 mg, 1.6 mmol) in anhydrous THF (30 mL) was added dropwise to the solution or mixture (in the case of pyrrolidine or 1,2,3,4-tetrahydroisoquinoline) . The resulting solution was stirred at room temperature for 20 h. Then the solvent was evaporated under reduced pressure, and the residue was treated with methanol (5 mL). The insoluble product (**14**−**16**) thus obtained was collected by filtration, washed with methanol (2 mL), dried and purified by crystallization from a suitable solvent. The following compounds were obtained according to the above procedure.

1-({[(Diethylamino)carbonothioyl]thio}amino)cyclohexanecarbonitrile (14): This compound was prepared from diethylamine (140 mg, 1.9 mmol); white solid; yield 270 mg (64%); m.p. 104−106 °C (ethanol). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25−1.34 (m, 7 H), 1.48−1.59 (m, 2 H), 1.62−1.66 (m, 3 H), 1.78−1.80 (m, 2 H), 2.18 (d, *J* = 11.72 Hz, 2 H), 3.67 (q, *J* = 6.84 Hz, 2 H), 4.02 (q, *J* = 6.84 Hz, 2 H), 4.77 (s, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 11.8, 13.2, 22.7 (two overlapping signals), 25.0, 37.2 (two overlapping signals), 46.2, 50.8, 61.0, 120.5, 199.8 ppm. IR (KBr): $\tilde{\nu}$ = 3125, 2985, 2955, 2935, 2855, 2230, 1500, 1455, 1445, 1425, 1350, 1270, 1205, 1150 cm^{-1}. $C_{12}H_{21}N_3S_2$ (271.45): calcd. C 53.10, H 7.80, N 15.48; found C 53.35, H 7.61, N 15.17.

1-({[(Pyrrolidin-1-yl)carbonothioyl]thio}amino)cyclohexanecarbonitrile (15): This compound was prepared from pyrrolidine (130 mg, 1.9 mmol); white solid; yield 160 mg (39%); m.p. 108−111 °C (ethanol). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19−1.31 (m, 1 H), 1.60−1.66 (m, 5 H), 1.74−1.83 (m, 2 H), 1.95−2.03 (m, 2 H), 2.11−2.18 (m, 4 H), 3.61 (s, 2 H), 3.96 (s, 2 H), 4.67 (s, 1 H) ppm. ^{13}C NMR (500, $CDCl_3$): δ = 22.7 (two overlapping signals), 23.9,

25.0, 26.1, 37.1 (two overlapping signals), 49.1, 55.4, 60.9, 120.6, 196.6 ppm. IR (KBr): $\tilde{\nu}$ = 3070, 2930, 2860, 2225, 1480, 1440, 1325, 1250, 1160 cm^{-1}. $C_{12}H_{19}N_3S_2$ (269.43): calcd. C 53.50, H 7.11, N 15.59; found C 53.32, H 7.43, N 15.80.

1-({[(1,2,3,4-Tetrahydroisoquinolin-2-yl)carbonothioyl]thio}amino)-cyclohexanecarbonitrile (16): This compound was prepared from 1,2,3,4-tetrahydroisoquinoline (250 mg, 1.9 mmol); white solid; yield 170 mg (33%); m.p. 89−92 °C (2-propanol). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.20−1.30 (m, 1 H), 1.60 (d, *J* = 12.7 Hz, 1 H), 1.64−1.71 (m, 4 H), 1.79−1.82 (m, 2 H), 2.21 (d, *J* = 12.2 Hz, 1 H), 3.02 (t, *J* = 5.61 Hz, 2 H), 3.99 (s, 1 H), 4.41 (br. s, 1 H), 4.80 (s, 1 H), 4.91 (br. s, 1 H), 5.31 (s, 1 H), 7.20−7.26 (m, 4 H) ppm. IR (KBr): $\tilde{\nu}$ = 3020, 2935, 2855, 2225, 1485, 1440, 1275, 1230 cm^{-1}. $C_{17}H_{21}N_3S_2$ (331.51): calcd. C 61.59, H 6.38, N 12.67; found C 61.35, H 6.17, N 12.79.

***N′*-{2-[({[(1-Cyanocyclohexyl)amino]thio}carbonothioyl)amino]-ethyl}ureas 17−19. General Procedure:** A solution of the nitriles **8** or **9** (1.1 mmol) and the appropriate amine (1.3 mmol) in anhydrous THF (15 mL) or DMF (5 mL, in the case of benzylamine) was stirred at room temperature for 20 h. Then the solvent was evaporated under reduced pressure, and the residue was treated with methanol (4 mL). The insoluble product (**17**−**19**) thus obtained was collected by filtration, washed with methanol, dried and purified by crystallization from a suitable solvent. The following compounds were obtained according to the above procedure.

***N′*-{2-[({[(1-Cyanocyclohexyl)amino]thio}carbonothioyl)amino]-ethyl}-*N*,*N*-diethylurea (17):** This compound was prepared from nitrile **8** (310 mg, 1.1 mmol) and diethylamine (95 mg, 1.3 mmol); white solid; yield 120 mg (32%); m.p. 119−121 °C (2-propanol). ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.01 (s, 6 H), 1.11−1.13 (m, 1 H), 1.33 (d, *J* = 10.74 Hz, 2 H), 1.55−1.66 (m, 3 H), 1.69−1.78 (m, 2 H), 2.08 (d, *J* = 9.77 Hz, 2 H), 3.18 (s, 4 H), 3.28 (s, 2 H), 3.63 (s, 2 H), 6.16 (s, 1 H), 6.51 (br. s, 1 H), 9.91 (br. s, 1 H) ppm. ^{13}C NMR (500 MHz, [D_6]DMSO): δ = 19.2 (two overlapping signals), 27.9 (two overlapping signals), 29.6, 39.7, 44.1, 44.5, 45.7 (two overlapping signals), 52.6, 64.5, 126.8, 163.1, 202.0 ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3215, 2975, 2935, 2860, 2225, 1615, 1525, 1505, 1320, 1270, 1120 cm^{-1}. $C_{15}H_{27}N_5OS_2$ (357.54): calcd. C 50.40, H 7.61, N 19.59; found C 50.23, H 7.73, N 19.34.

***N*-{2-[({[(1-Cyano-3-methylcyclohexyl)amino]thio}carbonothioyl)-amino]ethyl}pyrrolidine-1-carboxamide (18):** This compound was prepared from nitrile **9** (330 mg, 1,1 mmol) and pyrrolidine (90 mg, 1.3 mmol); white solid; yield 220 mg (55%); m.p. 127−129 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 0.80 (q, *J* = 11.72 Hz, 1 H), 0.90 (d, *J* = 5.86 Hz, 3 H), 1.28−1.40 (m, 2 H), 1.48−1.53 (m, 2 H), 1.66 (d, *J* = 11.72 Hz, 1 H), 1.78 (s, 5 H), 2.05−2.15 (m, 2 H), 3.20 (s, 4 H), 3.23 (s, 2 H), 3.61 (d, *J* = 3.9 Hz, 2 H), 6.19 (s, 1 H), 6.42 (br. s, 1 H), 9.90 (br. s, 1 H) ppm. ^{13}C NMR (500 MHz, [D_6]DMSO): δ = 22.3, 23.1, 25.7, 30.1 (two overlapping signals), 33.7, 34.6, 38.9, 42.8, 46.0 (two overlapping signals), 47.9, 59.9, 122.2, 157.9, 197.3 ppm. IR (KBr): $\tilde{\nu}$ = 3380, 3195, 3135, 2940, 2910, 2860, 2225, 1615, 1550, 1495, 1410, 1360, 1200 cm^{-1}. $C_{16}H_{27}N_5OS_2$ (369.55): calcd. C 52.0, H 7.36, N 18.95; found C 52.15, H 7.46, N 18.76.

***N*-Benzyl-*N′*-{2-[(1-Cyanocyclohexyl)amino]thio}carbonothioyl)-amino]ethyl}urea (19):** This compound was prepared from nitrile **8** (310 mg, 1.1 mmol) and benzylamine (140 mg, 1.3 mmol); white solid; yield 140 mg (32%); m.p. 128−129 °C (2-propanol). ^1H NMR (200 MHz, [D_6]DMSO): δ = 1.13−1.45 (m, 3 H), 1.58−1.78 (m, 5 H), 2.08−2.13 (m, 2 H), 3.25−3.31 (m, 2 H), 3.61−3.65 (m, 2 H), 4.25 (d, *J* = 5.4 Hz, 2 H), 6.22 (s, 1 H), 6.27−6.29 (m, 1 H), 6.56−6.60 (m, 1 H), 7.21−7.33 (m, 5 H), 9.82 (br. s, 1 H) ppm. ^{13}C NMR (200 MHz, [D_6]DMSO): δ = 22.8 (two overlapping signals), 24.4, 34.5 (two overlapping signals), 38.6, 43.3, 47.1, 59.3, 121.7, 126.9, 127.3 (two overlapping signals), 128.5 (two overlapping signals), 140.9, 159.1, 196.9 ppm. IR (KBr): $\tilde{\nu}$ = 3325, 3225, 3185, 2935, 2855, 2230, 1670, 1610, 1585, 1500, 1450, 1315, 1255 cm^{-1}. $C_{18}H_{25}N_5OS_2$ (391.56): calcd. C 55.21, H 6.43, N 17.88; found C 55.21, H 6.43, N 17.66.

X-ray Structure Analyses: The intensity data for the crystals were collected using a KumaCCD diffractometer. The crystal structures were solved with SHELXS-97[25] and refined with SHELXL-97.[26] Crystal data for $C_{12}H_{18}N_4OS_2$ (**10**): monoclinic, space group $P2_1/n$, *a* = 5.8706(6), *b* = 9.6441(9), *c* = 25.4777(19) Å, β = 95.626(7)°, *V* = 1435.5(2) $Å^3$, *Z* = 4, λ = 0.71073 Å, *T* = 140 K, R_1 = 0.0558, wR_2 = 0.1302 for 2056 independent reflections with $I > 2\sigma(I)$. Crystal data for $C_{12}H_{21}N_3S_2$ (**14**): triclinic, space group $P\bar{1}$, *a* = 7.433(1), *b* = 9.862(1), *c* = 11.172(1) Å, α = 70.05(1), β = 88.32(1), γ = 73.51(1)°, *V* = 736.1(1) $Å^3$, *Z* = 2, λ = 0.71073 Å, *T* = 293 K, R_1 = 0.0359, wR_2 = 0.0969 for 2366 independent reflections with $I > 2\sigma(I)$. Crystal data for $C_{15}H_{27}N_5OS_2$ (**17**): triclinic, space group $P\bar{1}$, *a* = 9.7937(7), *b* = 10.0943(6), *c* = 11.0112(9) Å, α = 66.388(7), β = 73.374(7), γ = 70.779(6)°, *V* = 926.75(11) $Å^3$, *Z* = 2, λ = 0.71073 Å, *T* = 140 K, R_1 = 0.0343, wR_2 = 0.0885 for 2892 independent reflections with $I > 2\sigma(I)$. CCDC-241618 (**10**), -241619 (**14**) and -241620 (**17**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Supporting Information: NMR spectra for compounds **5**, **6**, **9**, **18** (see also footnote on the first page of this article).

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