# Synthesis of Mono- and N,N-Disubstituted Thioureas and *N*-Acylthioureas

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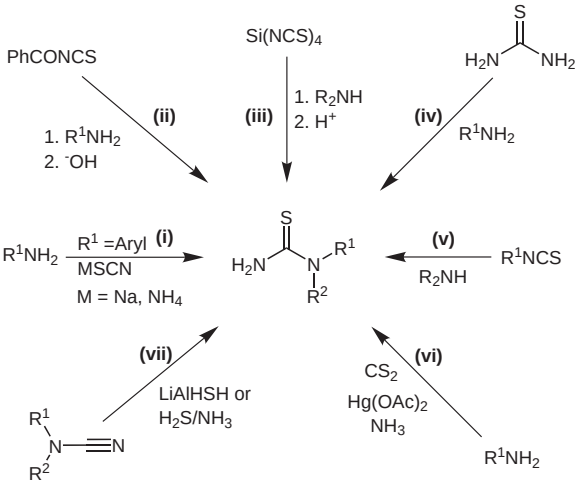
**Abstract:** 1-Benzotriazole-1-carbothioamide (**2**), prepared from 1-cyanobenzotriazole (**1**) and hydrogen sulfide, reacts with amines to give thioureas **3a–e**. Reactions of (benzotriazol-1-yl)carboximidamides **4a–d**,**f–j** and acyl- **5a–f**,**i–k** or arylaminocarbonyl- **5g**,**h** (benzotriazol-1-yl)carboximidamides with hydrogen sulfide give the corresponding thioureas **3a–d**,**f–j**, and *N*-acylthioureas **6a–f**,**i–k** or *N*-carbamoylthioureas **6g**,**h**, respectively.

**Key words:** thioureas, benzotriazole, acylations, nucleophilic substitution, substituent effects

Thiourea moieties are important chemical building blocks that have numerous chemical and pharmaceutical applications. For example, recent reports describe thiourea derivatives as efficient guanylating agents both in solution[1] and on solid support.[2] Thermal decomposition of *N*-arylthioureas gives aryl isothiocyanates.[3] Oxidation of arylthioureas with lead tetraacetate[4] or iodic acid[5] affords arylcyanamides. Thioureas condense with α-halocarbonyl compounds to afford 2-amino-1,3-thiazoles.[6] Benzothiazoles can be prepared from arylthioureas in the presence of bromine.[7] Solid-phase Biginelli pyrimidine synthesis[8] and synthesis of imidazolone derivatives[9] using resin-bound thioureas have been reported. The uses of thioureas to make 1,3-thiazines,[10] 1,3-diazines,[11] 1,3-quinazolines[12] and 1,2,4-triazines[13] were also described recently.

Synthetic approaches to thioureas have been long investigated.[14] Well-known routes to substituted thioureas (Scheme 1) involve reactions of (i) anilines with sodium[15] or ammonium thiocyanate[16] in the presence of strong acids (TFA or concentrated HCl); (ii) aroyl isothiocyanates with amines followed by basic hydrolysis;[17] (iii) silicon tetraisothiocyanate with primary and secondary amines;[18] (iv) unsubstituted thioureas with primary alkyl amines at 170–180 °C;[19] (v) isothiocyanates with ammonia or amines;[20] (vi) primary amines with carbon disulfide in the presence of mercury acetate and aqueous ammonia;[21] and (vii) disubstituted cyanamides with hydrogen chloride and LiAlHSH[22] or hydrogen sulfide in the presence of ammonia.[23] Mono and *N*,*N*-disubstituted thioureas were also prepared on solid support from Fmoc-isothiocyanate with subsequent deprotection.[9]




**Scheme 1**

Acylthioureas are valuable starting materials for numerous transformations: acylthioureas were used for the preparation of four-,[24] five-,[25] six-[25c,26] and seven-[27] membered heterocyclic ring systems. *N*,*N*-Dialkyl-*N*′-acyl(aroyl)thioureas are efficient ligands for the separation and refinement of platinum group metals (Pd, Rh, Ru, Ir, and Os).[28] Acylthiourea derivatives have been patented as antidiabetic,[29] antiarthritic,[30] antineoplastic,[31] and anticoagulant[32] agents and for treatment of cognitive problems[33] and prostate disorder.[34] Herbicidal,[35] fungicidal,[35] bactericidal,[35] insecticidal[36] and plant growth regulator activities have also been reported.

Common routes to acylthioureas are presented in Scheme 2. Acylthioureas can be prepared by (i) reaction of aminothiocarbonylimidoyl chlorides with potassium thiocyanate followed by hydrolysis;[37] (ii) acylation of N,N-disubstituted thioureas;[38] (iii) reaction of *N*-acyl aminoimidoyl chlorides[39] or (iv) *N*-acylisothioureas[40] with hydrogen sulfide, reactions of amines with (v) methyl *N*-acylcarbamodithioates[41] and (vi) acyl isothiocyanates;[42] (vii) reactions of iminophosphorane derivatives of thioureas with carboxylic acids,[43] and (viii) hydrolysis of *N*-aminothiocarbonylcarbodiimides with mineral acids.[44]

This sustained interest in thiourea and acylthiourea derivatives prompted us to investigate new approaches to their synthesis. We now report the synthesis of mono and N,N-disubstituted thioureas from (benzotriazol-1-yl)carboximidamides and 1-benzotriazole-1-carbothioamide, and acylthioureas from *N*-acyl(benzotriazol-1-yl)carboximidamides.

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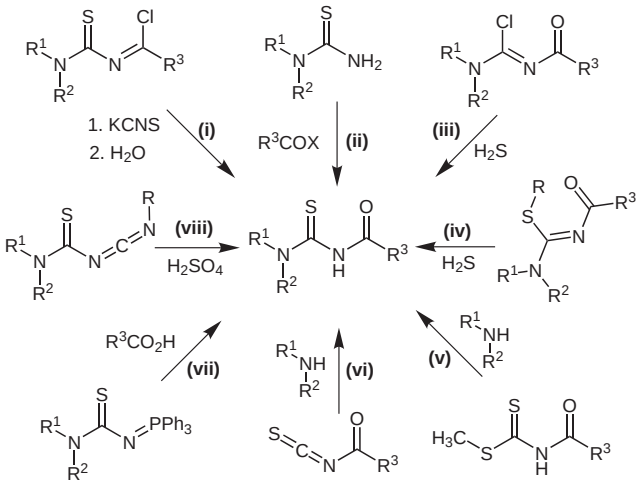
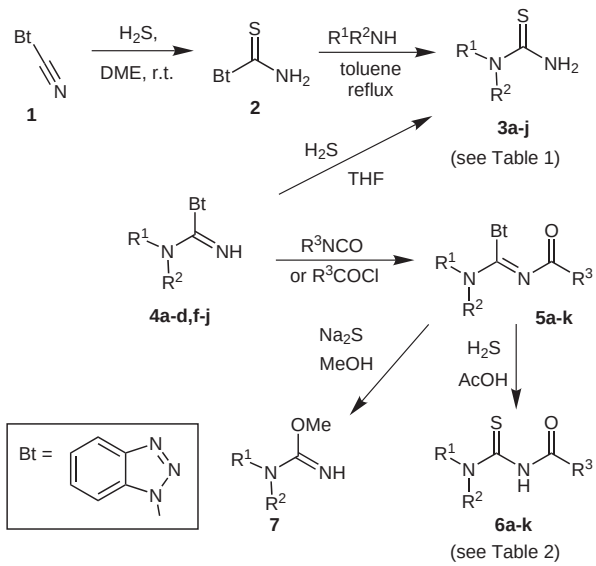


**Scheme 2**

Recently we described a new and efficient reagent for the preparation of mono and N,N-disubstituted ureas.[45] However, attempts to prepare 1-benzotriazole-1-carbothioamide from the previously described benzotriazole-1-carboxylic acid amide[45] with Lawesson's reagent gave only benzotriazole. Reactions of benzotriazole or its trimethylsilyl derivative with sodium thiocyanate, sodium hydrogen sulfide, trimethylsilyl isothiocyanate all failed under various conditions. Finally, the desired 1-benzotriazole-1-carbothioamide (**2**) was prepared in 84% yield from 1-cyanobenzotriazole (**1**) in DME saturated with gaseous hydrogen sulfide (Scheme 3).



**Scheme 3**

1-Benzotriazole-1-carbothioamide (**2**) did not react with amines in THF at 20 °C and only very slowly at reflux. Heating **2** under reflux with *p*-anisidine in toluene for 18 hours gave *p*-methoxyphenylthiourea (**3a**) in 54% yield, and reaction of **2** with different amines gave the corresponding thioureas **3b**–**e** in moderate yields (39–71%) (Scheme 3, Table 1).

The moderate yields of thioureas **3a**–**e** (Table 1), under relatively harsh reaction conditions prompted us to investigate an alternative route starting from (benzotriazol-1-yl)carboximidamides **4a**–**d**,**f**–**j**. Nucleophilic displacement of benzotriazole from **4a**–**d**,**f**–**j** by a variety of amines with the formation of tri- and tetrasubstituted guanidines has been reported previously.[46] (Benzotriazol-1-yl)carboximidamides **4a**–**d**,**f**–**j** were prepared by a previously published procedure[46] and reaction of (benzotriazol-1-yl)carboximidamides **4a**–**d**,**f**–**j** in THF with hydrogen sulfide at 20 °C in most cases gave the desired mono and N,N-disubstituted thioureas **3a**–**d**,**f**–**j**. It was found, however, that *N*-aryl(benzotriazol-1-yl)carboximidamides **4a**,**d**,**j** did not react at room temperature. In refluxing THF, rapid loss of hydrogen sulfide from the reaction mixture apparently occurred. Previous reports[46,47] indicate that mono-substituted (benzotriazol-1-yl)carboximidamides **4a**,**d**,**h**,**i**,**j** are stable compounds which are resistant to displacement of benzotriazole by amines[46] and to elimination at highly basic conditions.[47] However, *N*-aryl substituted compounds **4a**,**d**,**j** were successfully converted into the desired thioureas **3a**,**d**,**j** (21–78% isolated yields) by heating a THF solution of **4a**,**d**,**j** saturated with hydrogen sulfide at 90 °C in sealed tubes (Scheme 3, Table 1).

Acyl- **5** ($R^3$ = alkyl or aryl) and arylaminocarbonyl **5** ($R^3$ = NHAr) (benzotriazol-1-yl)carboximidamides **5a**–**k** are efficient reagents for the preparation of

**Table 1** Preparation of Mono- and N,N-Disubstituted Thioureas **3a**–**j**

| Entry | Starting Material | Product **3** | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|---|---|
| 1 | **2** | **3a** | 4-$CH_3OC_6H_4$ | H | 54[a] |
| 2 | **2** | **3b** | Bn | Bn | 67[a] |
| 3 | **2** | **3c** | pyrrolidinyl | | 54[a] |
| 4 | **2** | **3d** | Ph | H | 71[a] |
| 5 | **2** | **3e** | PhNH | H | 39[a] |
| 6 | **4a** | **3a** | 4-$CH_3OC_6H_4$ | H | 59[b] |
| 7 | **4b** | **3b** | Bn | Bn | 86[c] |
| 8 | **4c** | **3c** | pyrrolidinyl | | 85[c] |
| 9 | **4d** | **3d** | Ph | H | 78[b] |
| 10 | **4f** | **3f** | $(CH_2)_2O(CH_2)_2$ | | 99[c] |
| 11 | **4g** | **3g** | Et | Et | 92[c] |
| 12 | **4h** | **3h** | Bn | H | 76[c] |
| 13 | **4i** | **3i** | *n*-Bu | H | 94[c] |
| 14 | **4j** | **3j** | 4-$ClC_6H_4$ | H | 21[b] |

[a] Toluene, reflux.
[b] THF, sealed tube, 90 °C.
[c] THF, r.t.

acylguanidines[48] and also provide three atom synthons for the preparation of 5-amino-1,2,8-triazoles[49] and 4(6)-amino-1,3,5-triazine-2-ones.[50] Compounds **5a**–**f**,**i**–**k** were prepared by a previously published procedure.[46,49] We first attempted displacement of benzotriazole from **5** ($R^3$ = Ph, $R^1$ = $R^2$ = *i*-Pr) by the action of sodium sulfide in methanol at room temperature (Scheme 3). The only product isolated was the corresponding *O*-methylisourea **7** as the result of displacement of benzotriazole by the methoxy anion formed in situ.

Reactions of substituted (benzotriazol-1-yl)carboximidamides **5a**–**k** in acetic acid at room temperature with hydrogen sulfide gave the desired substituted thioureas **6a**–**k** in 35–80% isolated yields (Scheme 3, Table 2). Benzotriazole is the only by-product observed. The time of conversion of starting (benzotriazol-1-yl)carboximidamides **5a**–**k** depends on the nature of the acyl group, $R^3CO$. The presence of electron-donating substituents promotes the nucleophilic displacement of benzotriazole, whereas the presence of electron-withdrawing groups extends the reaction time. A continuous flow of hydrogen sulfide through a solution of **5c** ($R^3$ = 4-$CH_3OC_6H_4$), gave complete conversion of starting material during 2 hours. When compounds **5d** ($R^3$ = 4-$NO_2C_6H_4$) and **5j** ($R^3$ = 4-pyridyl) were reacted with hydrogen sulfide under the same conditions, starting material was observed after 5 hours. Increasing the reaction temperature to 80 °C decreased the reaction time, but in some cases the isolated yield of final substituted thioureas **6** was not improved. The influence of substituents within the amino function is less recognizable.

We extended the application of the procedure developed for the preparation of aminocarbonyl derivatives of substituted thioureas. The efficient preparation of the starting aminocarbonyl (benzotriazol-1-yl)carboximidamides **5g**,**h** has been described previously.[48] The substitution of benzotriazole appears to be general and no additional modification of the reaction conditions is necessary. The desired aminocarbonyl thiourea derivatives **6g**,**h** were obtained in 44 and 62% isolated yields, respectively (Scheme 3, Table 2).

In summary, 1-benzotriazole-1-carbothioamide (**2**) was developed as a new reagent for the synthesis of mono and N,N-disubstituted thioureas in analogy to a recently reported O-analog benzotriazole-1-carboxylic acid amide.[45] Pure, stable, key intermediate **2** was prepared from readily available 1-cyanobenzotriazole **1** with hydrogen sulfide in mild conditions. Purification of 1-benzotriazole-1-carbothioamide (**2**) is simple. However, the displacement of benzotriazole from **2** was less favorable in comparison to benzotriazole-1-carboxylic acid amide.

Di(benzotriazolyl)methanimine[46] reacts with primary and secondary amines to give an almost unlimited number of (benzotriazol-1-yl)carboximidamides **4a**–**d**,**f**–**j** which are easily converted into mono and *N*,*N*-disubstituted thioureas **3a**–**d**,**f**–**j** with hydrogen sulfide utilizing mild conditions. Our new procedure is advantageous in comparison to literature methods from amines by avoiding the use of strong acids,[15,16] hydrolysis at basic conditions,[17] difficult to handle reagents (such as silicon tetraisothiocyanate[18] or $LiAlHSH$[22]), high reaction temperatures[19] and environmentally unsafe heavy metal salts.[21]

Use of acyl- **5a**–**f**,**i**–**k** and arylaminocarbonyl- **5g**,**h** (benzotriazol-1-yl)carboximidamides readily available from (benzotriazol-1-yl)carboximidamides of type **4** for the preparation of acyl- and carbamoyl thioureas **6a**–**k** is a valuable addition to known methods[37–44] and allowed us to introduce an additional diversity in the acyl group. The conversion of **5a**–**k** into desired substituted thioureas **6a**–**k** is possible by the same mild procedure developed for the preparation of thioureas **3**. The dependence of yields of the final products and the reaction time on the nature of substituents is discussed.

**Table 2** Preparation of *N*-Acylthioureas **6a**–**f**,**i**–**k** and *N*-Carbamoylthioureas **6g**,**h**

| Entry | Starting Material | $R^1$ | $R^2$ | $R^3$ | Index for **5**,**6** | Yield (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | **5** | **6** |
| 1 | **4f** | $(CH_2)_2O(CH_2)_2$ | | Ph | **a** | 71 | 63 |
| 2 | **4g** | Et | Et | Ph | **b** | 60 | 77 |
| 3 | **4f** | $(CH_2)_2O(CH_2)_2$ | | 4-$CH_3OC_6H_4$ | **c** | 79 | 68 |
| 4 | **4f** | $(CH_2)_2O(CH_2)_2$ | | 4-$NO_2C_6H_4$ | **d** | 88 | 46 |
| 5 | **4f** | $(CH_2)_2O(CH_2)_2$ | | 4-$ClC_6H_4$ | **e** | 89 | 44 |
| 6 | **4b** | Bn | Bn | 4-$ClC_6H_4$ | **f** | 35 | 37 |
| 7 | **4i** | *n*-Bu | H | PhNH | **g** | 81 | 44 |
| 8 | **4g** | Et | Et | 4-$CH_3OC_6H_4NH$ | **h** | 85 | 62 |
| 9 | **4f** | $(CH_2)_2O(CH_2)_2$ | | Et | **i** | 88 | 56 |
| 10 | **4g** | Et | Et | 4-pyridyl | **j** | 73 | 35 |
| 11 | **4g** | Et | Et | 2-furyl | **k** | 91 | 80 |

The preparation of (benzotriazol-1-yl)carboximidamides[51] and their acyl analogues[52] on solid support has been described and such development of the protocol of this report could be of great value for combinatorial synthesis.

All reactions were carried out under $N_2$. THF and DME were distilled over sodium/benzophenone. Toluene was distilled over sodium. Other materials were used as supplied. Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Varian Gemini 300 spectrometer in $CDCl_3$ (with TMS for $^1$H and solvent for $^{13}$C as the internal reference), unless otherwise stated. The elemental analyses were performed on a Carlo Erba EA–1108 instrument. Column chromatography was conducted on silica gel 200–425 meshes.

The 1-cyanobenzotriazole **(1)** was prepared by a previously published procedure[47] as off-white microcrystals (90%, mp 74–76 °C, Lit.[47] mp 74–76 °C). Compounds **4a**–**d**,**f**–**j** were prepared according to the previously published procedures:[46,49] benzotriazol-1-yl(tetrahydro-1*H*-pyrrol-1-yl)methanimine **(4c)**, yellow oil[46] (70%); *N*′-phenylbenzotriazole-1-carboximidamide **(4d)**, white prisms from MeOH (56%), mp 123–124 °C (Lit.[46] mp 123–124 °C); benzotriazol-1-yl(tetrahydro-4*H*-1,4-oxazin-4-yl)methanimine **(4f)**, light yellow oil[46] (65%); *N*,*N*-diethyl-1*H*-benzotriazole-1-carboximidamide **(4g)**, yellow oil[49] (60%); *N*-(benzyl)benzotriazole-1-carboximidamide **(4h)**, colorless needles from hexanes (82%), mp 97–98 °C (Lit.[46] mp 97–98 °C).

**1*H*-1,2,3-Benzotriazole-1-carbothioamide (2)**

$H_2S$ was passed (approximately six times per 48 h, each time about 3–4 h) into a stirred solution of the 1-cyano-1*H*-benzotriazole (**1**; 1.0 g, 7.0 mmol) in anhyd DME at r.t. (the reaction was monitored by TLC). The reaction mixture was filtered through cotton-Celite 545 to remove a small amount (less than 3%) of precipitate. The filtrate was concentrated under reduced pressure. The crude residue was purified by recrystallization from $CHCl_3$ to give the pure product as yellow microcrystals (1.05 g, 84%); mp 126–127 °C.

$^1$H NMR (DMSO-$d_6$): δ = 7.60 (t, *J* = 7.7 Hz, 1 H), 7.78 (t, *J* = 7.7 Hz, 1 H), 8.25 (d, *J* = 8.2 Hz, 1 H), 8.83 (d, *J* = 8.5 Hz, 1 H), 10.19 (br s, 1 H), 10.37 (br s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 115.6, 120.1, 125.8, 130.2, 132.0, 146.4, 176.3.

Anal. Calcd for $C_7H_6N_4S$: C, 47.18; H, 3.39; N, 31.44. Found: C, 47.55; H, 3.07; N, 31.46.

**Compounds 3a–e from 2; General Procedure**

The appropriate amine (1.0 mmol) was added to a solution of 1*H*-benzotriazole-1-carbothioamide (**2**; 0.178 g, 1.0 mmol) in toluene (10 mL). The mixture was allowed to react under reflux for 18 h. Completion of the reaction was monitored by TLC analysis and the reaction mixture was then cooled down. The solvent was evaporated under reduced pressure. The residue obtained was dissolved in $CHCl_3$ (15–20 mL) and washed with 10% aq solution of $Na_2CO_3$ (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude thioureas **3b**,**c** were purified by recrystallization; thioureas **3d**,**e** were purified by gradient column chromatography (silica gel) with EtOAc–hexanes from 1:4 to 1:1 (for **3d**) and from 1:6 to 1:1 (for **3e**). Compound **3a** precipitated from the reaction mixture, was filtered off and purified by recrystallization.

***p*-Methoxyphenylthiourea (3a)**

Off-white microcrystals from EtOH (54%); mp 209–210 °C (Lit.[53] mp 210 °C).

$^1$H NMR (DMSO-$d_6$): δ = 3.74 (s, 3 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.24–7.62 (m, 2 H, $NH_2$), 9.48 (s, 1 H, NH).

$^{13}$C NMR (DMSO-$d_6$): δ = 55.2, 114.0, 125.6, 131.7, 156.6, 181.1.

***N*,*N*-Dibenzylthiourea (3b)**

White microcrystals from petroleum ether–$CHCl_3$ (67%); mp 137–138 °C (Lit.[54] mp 138–139 °C).

$^1$H NMR: δ = 4.92 (br s, 4 H), 5.84 (br s, 2 H), 7.26–7.39 (m, 10 H).

$^{13}$C NMR: δ = 54.6, 126.9, 127.9, 129.0, 135.2, 183.8.

**1-Thiocarbamoylpyrrolidine (3c)**

Off-white microcrystals from propan-2-ol (54%); mp 194–196 °C (Lit.[55] mp 193–197 °C).

$^1$H NMR (DMSO-$d_6$): δ = 1.80–1.92 (m, 4 H), 3.27–3.38 (m, 2 H), 3.54–3.60 (m, 2 H), 7.09 (br s, 2 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 24.6, 25.9, 47.5, 51.4, 178.3.

**Phenylthiourea (3d)**

White microcrystals from EtOAc-hexanes (71%); mp 153–154 °C (Lit.[53] mp 154 °C).

$^1$H NMR (acetone-$d_6$): δ = 6.90–7.10 (m, 4 H), 7.20 (t, *J* = 7.2 Hz, 1 H), 7.35–7.46 (m, 4 H), 9.16 (br s, 1 H).

$^{13}$C NMR (acetone-$d_6$): δ = 124.8, 126.3, 130.0, 139.7, 183.3.

**1-Phenylthiosemicarbazide (3e)**

Off-white microcrystals from EtOAc–hexanes (39%), mp 203–204 °C (Lit.[56] mp 202–203 °C).

$^1$H NMR (acetone-$d_6$): δ = 6.80–6.89 (m, 3 H), 7.20–7.26 (m, 3 H), 7.35–7.47 (m, 2 H), 8.57 (br s, 1 H).

$^{13}$C NMR (acetone-$d_6$): δ = 114.0, 121.4, 129.9, 148.9, 185.5.

**Compounds 3a–d,f–j from 4a–d,f–j; General Procedure**

$H_2S$ was bubbled into THF (40 mL) for 2 min under dry conditions. The (benzotriazol-1-yl)carboximidamide **4** (2.0 mmol) was added and the reaction mixture was stirred at r.t. for 1 h (for **3b–c**,**f–i**) under a flow of hydrogen sulfide. Completion of the reaction was monitored by TLC analysis. For compounds **3a**,**d**,**j**, the reaction was very slow at r.t. After bubbling $H_2S$ for 1 h at r.t., the flow was stopped and the reaction mixture was allowed to react at 90 °C for 4 h in a sealed tube. The solvent was removed under reduced pressure and the residue was dissolved in $CH_2Cl_2$ and washed with 10% aq solution of the $Na_2CO_3$. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. For thioureas **3b**,**c**,**g** no further purification was required; **3d**,**f**,**h**–**j** were purified by gradient column chromatography (silica gel) with EtOAc–hexanes from 1:6 to 1:1. Compound **3a** was precipitated from the reaction mixture, it was filtered off and washed with hexanes.

***p*-Methoxyphenylthiourea (3a)**

Off-white microcrystals from hexanes (59%), identical with compound **3a** prepared following the procedure for **3a**–**e** from **2**.

***N*,*N*-Dibenzylthiourea (3b)**

White microcrystals from petroleum ether–$CHCl_3$ (86%), identical with compound **3b** prepared following the procedure for **3a**–**e** from **2**.

**1-Thiocarbamoylpyrrolidine (3c)**
Off-white microcrystals from propan-2-ol (85%), identical with compound **3c** prepared following the procedure for **3a**–**e** from **2**.

**Phenylthiourea (3d)**
White microcrystals from EtOAc–hexanes (78%), identical with compound **3d** prepared following the procedure for **3a**–**e** from **2**.

**4-Thiocarbamoylmorpholine (3f)**
White microcrystals from EtOAc–hexanes (99%), mp 159–161 °C (Lit.[57] mp 160–161 °C).

$^1$H NMR (DMSO-$d_6$): δ = 3.55–3.58 (m, 4 H), 3.70–3.73 (m, 4 H), 7.50 (br s, 2 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 47.9, 66.0, 182.7.

**1,1-Diethylthiourea (3g)**
Light-yellow microcrystals from EtOAc–hexanes (92%); mp 82–84 °C (Lit.[22] mp 98–101 °C).

$^1$H NMR: δ = 1.18 (t, *J* = 7.1 Hz, 6 H), 3.58 (br s, 4 H), 5.91 (br s, 2 H).

$^{13}$C NMR: δ = 12.3, 46.0, 180.3.

**Benzylthiourea (3h)**
Colorless microcrystals from EtOAc–hexanes (76%); mp 154–155 °C (Lit.[58] mp 156 °C).

$^1$H NMR (DMSO-$d_6$): δ = 4.66 (s, 2 H), 6.60 (s, 1 H), 7.11 (br s, 1 H), 7.28–7.39 (m, 5 H), 8.03 (br s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 47.5, 127.0, 127.4, 128.4, 139.3, 183.5.

**Butylthiourea (3i)**
White microcrystals from EtOAc–hexanes (94%); mp 67–69 °C (Lit.[59] mp 71–72 °C).

$^1$H NMR (mixture of rotamers): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 1.36–1.43 (m, 2 H), 1.55–1.65 (m, 2 H), 3.20 (br s, 2 H), 5.88 (br s, 2 H), 6.39 (br s, 1 H).

$^{13}$C NMR: δ = 13.5, 19.9, 30.5, 44.2, 44.9, 180.4, 182.8.

**(4-Chlorophenyl)thiourea (3j)**
Off-white microcrystals from EtOAc–hexanes (21%); mp 178–179 °C (Lit.[60] mp 180–181 °C).

$^1$H NMR (DMSO-$d_6$): δ = 7.37–7.51 (m, 6 H), 9.78 (s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 124.6, 128.1, 128.5, 138.2, 181.2.

**Compounds 6a–k; General Procedure**
$H_2S$ was bubbled into AcOH (10 mL) for 5 min under dry conditions. Benzotriazole-1-ylcarboximidamine **5a**–**k** (0.626 mmol) was added to the latter solution and the reaction mixture was stirred at r.t. under a flow of $H_2S$. Completion of the reaction was monitored by TLC analysis. Then the mixture was poured into brine and extracted with EtOAc (2 ×). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The desired substituted thioureas **6a**–**f**,**i**–**k** were obtained after purification by column chromatography (silica gel); **6a**,**e**: EtOAc–hexanes (1:2); **6b**: EtOAc–hexanes (1:4); **6c**: EtOAc–$CH_2Cl_2$ (1:19); **6d**: gradient elution with EtOAc–hexanes from (1:2 to 2:3); **6f**: EtOAc–hexanes (1:9); **6g**: gradient elution with $Et_2O$–$CH_2Cl_2$ from pure $CH_2Cl_2$ to 1:49; **6h**: EtOAc–$CH_2Cl_2$ (1:49); **6i**: MeOH–$CH_2Cl_2$ (1:24); **6j**: gradient elution with EtOAc–hexanes from 2:3 to 1:1; **6k**: $CH_2Cl_2$.

***N*-(Morpholinocarbothioyl)benzamide (6a)**
Colorless microcrystals from EtOAc–hexanes (63%); mp 137–138 °C (Lit.[61] mp 143 °C).

$^1$H NMR: δ = 3.54–3.94 (m, 6 H), 4.14–4.32 (m, 2 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 8.71 (s, 1 H).

$^{13}$C NMR: δ = 51.4, 52.3, 66.1, 127.8, 128.8, 132.1, 133.1, 163.2, 179.1.

Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.76; H, 5.76; N, 10.85.

***N*-Benzoyl-*N*′,*N*′-diethylthiourea (6b)**
Light-pink microcrystals from EtOAc–hexanes (77%); mp 94–95 °C (Lit.[62] mp 97–98 °C).

$^1$H NMR: δ = 1.29–1.36 (m, 6 H), 3.60–3.31 (m, 2 H), 4.01–4.03 (m, 2 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 8.54 (s, 1 H).

$^{13}$C NMR: δ = 11.5, 13.2, 47.7, 127.8, 128.8, 132.6, 132.8, 163.7, 179.3.

***p*-Methoxy-*N*-(morpholinocarbothioyl)benzamide (6c)**
Colorless microcrystals from EtOAc–$CH_2Cl_2$ (68%); mp 127–128 °C (Lit.[61] mp 134 °C).

$^1$H NMR: δ = 3.58–3.70 (m, 2 H), 3.76–3.90 (m, 4 H), 3.87 (s, 3 H), 4.18–4.28 (m, 2 H), 6.95 (d, *J* = 8.7 Hz, 2 H), 7.81 (d, *J* = 8.7 Hz, 2 H), 8.59 (s, 1 H).

$^{13}$C NMR: δ = 51.5, 52.3, 55.5, 66.1, 114.0, 124.3, 129.9, 162.8, 163.4, 179.5.

Anal. Calcd for $C_{13}H_{16}N_2O_3S$: N, 9.99. Found: N, 9.83.

***N*-(Morpholinocarbothioyl)-4-nitrobenzamide (6d)**
Yellow microcrystals from EtOAc–hexanes (46%); mp 158–159 °C (Lit.[61] mp 161 °C).

$^1$H NMR (DMSO-$d_6$): δ = 3.56–3.80 (m, 6 H), 4.20–4.26 (m, 2 H), 8.15 (d, *J* = 8.7 Hz, 2 H), 8.34 (d, *J* = 8.7 Hz, 2 H), 11.22 (s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 50.3, 50.9, 65.6, 123.4, 129.9, 138.3, 149.6, 162.5, 179.1.

**4-Chloro-*N*-(morpholinocarbothioyl)benzamide (6e)**
Colorless microcrystals from EtOAc–hexanes (44%); mp 137–138 °C (Lit.[25g] mp 152–153 °C).

$^1$H NMR: δ = 3.48–4.00 (m, 6 H), 4.05–4.35 (m, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.78 (d, *J* = 8.7 Hz, 2 H), 8.68 (s, 1 H).

$^{13}$C NMR: δ = 51.5, 52.4, 66.1, 129.19, 129.23, 130.6, 139.6, 162.3, 178.9.

Anal. Calcd for $C_{12}H_{13}ClN_2O_2S$: C, 50.61; H, 4.60; N, 9.84. Found: C, 51.04; H, 4.64; N, 9.45.

***N*,*N*-Dibenzyl-*N*′-(4-chlorobenzoyl)thiourea (6f)**
Colorless microcrystals from EtOAc–hexanes (37%); mp 137–138 °C.

$^1$H NMR: δ = 4.68 (br s, 2 H), 5.22 (br s, 2 H), 7.02–7.18 (m, 2 H), 7.32–7.42 (m, 10 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 8.75 (s, 1 H).

$^{13}$C NMR: δ = 55.9, 56.7, 127.5, 127.8, 128.1, 128.8, 128.9, 129.1, 129.3, 130.7, 134.5, 135.1, 139.5, 163.0, 181.6.

Anal. Calcd for $C_{22}H_{19}ClN_2OS$: C, 66.91; H, 4.85; N, 7.09. Found: C, 66.47; H, 4.85; N, 6.89.

**1-[({[Butylaminocarbothioyl]amino}carbonyl)amino]benzene (6g)**
Colorless microcrystals from $Et_2O$–$CH_2Cl_2$ (44%); mp 111–112 °C.

$^1$H NMR: δ = 0.94 (t, *J* = 7.2 Hz, 3 H), 1.38–1.46 (m, 2 H), 1.61–1.69 (m, 2 H), 3.67–3.74 (m, 2 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 7.32 (t,

*J* = 7.8 Hz, 2 H), 7.41 (d, *J* = 7.8 Hz, 2 H) 8.32 (s, 1 H), 10.27 (s, 1 H), 10.37 (s, 1 H).

$^{13}$C NMR: δ = 13.6, 20.1, 30.5, 45.3, 120.0, 124.5, 129.1, 136.7, 152.2, 179.3.

Anal. Calcd for $C_{12}H_{17}N_3OS$: C, 57.34; H, 6.82. Found: C, 56.98; H, 6.90.

**1-[({[Diethylaminocarbothioyl]amino}carbonyl)amino]-4-methoxybenzene (6h)**
Colorless microcrystals from EtOAc–$CH_2Cl_2$ (62%); mp 104–105 °C.

$^1$H NMR: δ = 1.26 (t, *J* = 7.2 Hz, 6 H), 3.67–3.88 (m, 7 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 8.16 (s, 1 H), 12.25 (s, 1 H).

$^{13}$C NMR: δ = 12.3, 45.8, 55.4, 114.0, 122.3, 130.3, 151.7, 156.3, 176.0.

Anal. Calcd for $C_{13}H_{19}N_3O_2S$: N, 14.93. Found: N, 14.59.

***N*-(Morpholinocarbothioyl)propanamide (6i)**
Colorless microcrystals from MeOH–$CH_2Cl_2$ (56%); mp 116–117 °C (Lit.[61] mp 154 °C).

$^1$H NMR: δ = 1.18 (t, *J* = 7.5 Hz, 3 H), 2.37 (q, *J* = 7.5 Hz, 2 H), 3.46–4.50 (m, 8 H), 8.02 (br s, 1 H).

$^{13}$C NMR: δ = 8.9, 30.3, 51.9, 66.2, 169.6, 178.8.

Anal. Calcd for $C_8H_{14}N_2O_2S$: C, 47.50; H, 6.98; N, 13.85. Found: C, 47.62; H, 6.98; N, 13.80.

***N*,*N*-Diethyl-*N*′-isonicotinoylthiourea (6j)**
Colorless microcrystals from EtOAc–hexanes (35%); mp 108–109 °C.

$^1$H NMR: δ = 1.26–1.38 (m, 6 H), 3.50–3.70 (m, 2 H), 4.00–4.02 (m, 2 H), 7.70 (br s, 2 H), 8.76–8.78 (m, 2 H), 9.1 (br s, 1 H).

$^{13}$C NMR: δ = 11.3, 13.3, 47.5, 47.8, 121.4, 139.8, 150.6, 162.3, 178.6.

Anal. Calcd for $C_{11}H_{15}N_3OS$: C, 55.67; H, 6.37. Found: C, 55.38; H, 6.53.

***N*,*N*-Diethyl-*N*′-(2-furylcarbonyl)thiourea (6k)**
Light-brown microcrystals from $CH_2Cl_2$ (80%); mp 74–75 °C (Lit.[63] mp 78–79 °C).

$^1$H NMR: δ = 1.20–1.45 (m, 6 H), 3.64 (br s, 2 H), 4.01 (br s, 2 H), 6.56 (dd, *J* = 3.3, 1.8 Hz, 1 H), 7.24 (d, *J* = 3.3 Hz, 1 H), 7.54 (d, 2 H, *J* = 0.9 Hz).

$^{13}$C NMR: δ = 11.3, 13.1, 47.8, 112.7, 117.0, 145.2, 146.2, 153.7, 178.1.

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