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–c. 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–f.j–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 and on solid support. Thermal decomposition of N-aryliminothioureas gives aryl isothiocyanates. Oxidation of arylthioureas with lead tetraacetate or iodic acid affords aryl isothiocyanates. 3 Oxidation of arylthioureas with lead tetraacetate or iodic acid affords aryl isothiocyanates.

Acylthioureas are valuable starting materials for numerous transformations: acylthioureas were used for the preparation of four-, five-, six- and seven-membered heterocyclic ring systems. N,N-Dialkyl-N’-acyl(aryl)thioureas are efficient ligands for the separation and refinement of platinum group metals (Pd, Rh, Ru, Ir, and Os). Acylthiourea derivatives have been patented as antidiabetic, antiarthritic, antineoplastic, and anticoagulant agents and for treatment of cognitive problems and prostate disorder. Herbicidal, fungicidal, bactericidal, insecticidal 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; (ii) acylation of N,N-disubstituted thioureas; (iii) reaction of N-acyliminoimidoyl chlorides or (iv) N-acylisothioureas with hydrogen sulfide, reactions of amines with (v) methyl N-acylcarbamodithioates and (vi) acyl isothiocyanates; (vii) reactions of iminophosphorane derivatives of thioureas with carboxylic acids, and (viii) hydrolysis of N-aminothiocarbonylcarbodiimides with mineral acids.

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-carboxothioamide from the previously described benzotriazole-1-carboxylic acid amide45 with Lawesson's reagent gave only benzotriazole. Reactions of benzotriazole or its trimethylsilyl derivative with sodium thioctanate, sodium hydrogen sulfide, trimethylsilyl isothiocyanate all failed under various conditions. Finally, the desired 1-benzotriazole-1-carboxothioamide (2) was prepared in 84% yield from 1-cyanobenzotriazole (1) in DME saturated with gaseous hydrogen sulfide (Scheme 3).

Scheme 3

1-Benzotriazole-1-carboxothioamide (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 procedure46 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 reports46,47 indicate that mono-substituted (benzotriazol-1-yl)carboximidamides 4a.d.h.i.j are stable compounds which are resistant to displacement of benzotriazole by amines46 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 (R3 = alkyl or aryl) and aroylaminocarbonyl 5 (R3 = NHAr) (benzotriazol-1-yl)carboximidamides 5a–k are efficient reagents for the preparation of

<table>
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<th>Entry</th>
<th>Starting Material</th>
<th>Product 3</th>
<th>R1</th>
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<th>Yield (%)</th>
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<td>54*</td>
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<td>3b</td>
<td>Bn</td>
<td>Bn</td>
<td>67*</td>
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<td>3e</td>
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<td>3j</td>
<td>4-ClC6H4</td>
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* Toluene, reflux.

** THF, sealed tube, 90 °C.

* THF, r.t.
acylguanidines and also provide three atom synths for the preparation of 5-amino-1,2,8-triazoles and 4(6)-amino-1,3,5-triazine-2-ones. Compounds 5a–k were prepared by a previously published procedure. We first attempted displacement of benzotriazole from 5 (R1 = Ph, R2 = R3 = 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 (benzotriazol-1-yl)carboximidamides 5a–k depends on the nature of the acyl group, R’CO. The presence of electron-donating substitutents 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 benzotriazole, whereas the presence of electron-withdrawing groups extends the reaction time. A continuous flow of benzotriazole from 6 into desired substituted thioureas 6 was not converted into mono and N,N-disubstituted thioureas in analogy to a recently reported O-analog benzotriazole-1-carboxylic acid amide.

In summary, 1-benzotriazole-1-carboxylic acid amide (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. Pure, stable, key intermediate 2 was prepared from readily available 1-cyanobenzotriazole 1 with hydrogen sulfide in mild conditions. Purification of 1-benzotriazole-1-carboxylic acid amide is possible by the same mild procedure developed for the preparation of thioureas.

Use of acyl- 5a–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 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.

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

<table>
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<th>R2</th>
<th>R1</th>
<th>Index for 5,6</th>
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<tr>
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<td>n-Bu</td>
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<td>Et</td>
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The preparation of (benzotriazol-1-yl)carboximidamides $^{31}$ and their acyl analogues $^{32}$ 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 $^{33}$ as off-white microcrystals (90%, mp 74–76 °C, Lit. $^{47}$ mp 97–98 °C). Compounds 3a–e from 2: General Procedure

1. N,B-Dibenzyliourea (3b)

White microcrystals from ethylene ether–CHCl$_3$ (67%); mp 137–138 °C (Lit. $^{54}$ mp 138–139 °C).

2. 1-Thiocarbamoylpyrrolidine (3c)

White microcrystals from acetone (71%); mp 153–154 °C (Lit.$^{55}$ mp 154 °C).

3. Phenylthiourea (3d)

White microcrystals from EtOAc–hexanes (71%); mp 153–154 °C (Lit.$^{55}$ mp 154 °C).

4. 1-Phenylthiosemicarbazide (3e)

Off-white microcrystals from EtOAc–hexanes (39%), mp 203–204 °C (Lit.$^{56}$ mp 202–203 °C).

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

$H_2$S 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,e–f) 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 $H_2$S 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$_2$Cl$_2$ and washed with 10% aq solution of Na$_2$CO$_3$. The organic layer was separated, dried (MgSO$_4$) and concentrated under reduced pressure. For thioureas $3b$–c,e 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 EtOH (54%); mp 209–210 °C (Lit.$^{53}$ mp 210 °C).

1. N,N-Dibenzyliourea (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 (78%); mp 158–159 °C (Lit.58 mp 156 °C).

Benzylthiourea (3h)
Light-pink microcrystals from EtOAc–hexanes (44%); mp 94–95 °C (Lit.52 mp 97–98 °C).

1,1-Diethylthiourea (3i)
Colorless microcrystals from EtOAc–hexanes (99%); mp 92–93 °C (Lit.22 mp 98–101 °C).

(4-Chlorophenyl)thiourea (3j)
Colorless microcrystals from EtOAc–hexanes (76%); mp 161–162 °C (Lit.61 mp 161 °C).

Compounds 6a–k; General Procedure
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1H 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).

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

Anal. Caled for C_{13}H_{14}N_{2}O_{2}S: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.76; H, 5.76; N, 10.85.

p-Methoxy-N-(morpholinocarbothioyl)benzamide (6c)
Colorless microcrystals from EtOAc–CH_{2}Cl_{2} (68%); mp 127–128 °C (Lit.61 mp 134 °C).

-(Morpholinocarbothioyl)-4-nitrobenzamide (6d)
Yellow microcrystals from EtOAc–hexanes (46%); mp 158–159 °C (Lit.62 mp 161 °C).

(4-Chloro-(morpholinocarbothioyl)benzamide (6e)
Colorless microcrystals from EtOAc–hexanes (44%); mp 137–138 °C (Lit.39 mp 152–153 °C).

4-Chloro-(morpholinocarbothioyl)benzamide (6f)
Colorless microcrystals from EtOAc–hexanes (37%); mp 137–138 °C.

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

1H 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).

13C NMR: δ = 51.5, 52.4, 66.1, 129.19, 134.3, 138.9, 149.6, 162.5, 179.1.

Anal. Caled for C_{13}H_{13}ClN_{2}O_{2}S: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.76; H, 5.76; N, 10.85.

1-(Butylaminocarbothioyl)amine (6g)
Colorless microcrystals from EtO–CH_{2}Cl_{2} (44%); mp 111–112 °C.

1H 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 (d, 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).

$\text{1}^{13}$C NMR: $\delta = 13.6, 20.1, 30.5, 45.3, 120.0, 124.5, 129.1, 136.7, 152.2, 179.3.$

Anal. Calcd for C$_{11}$H$_{15}$N$_{3}$O$_{2}$S: C, 55.67; H, 6.37. Found: C, 55.38; H, 6.53.

$\text{N,N-Diethyl-N'}-$isonicotinilythiourea (6j)

Colorless microcrystals from EtOAc–hexanes (35%); mp 108–109 °C.

$\text{1H NMR:} \delta = 1.26–1.38 \text{ (m, 6 H), 3.50–3.70 \text{ (m, 2 H), 4.00–4.02 \text{ (m, 2 H), 7.70 \text{ (br s, 2 H), 8.76–8.78 \text{ (m, 2 H), 9.1 \text{ (br s, 1 H).}}}$

$\text{13C NMR:} \delta = 11.3, 13.3, 47.5, 47.8, 121.4, 139.8, 150.6, 162.3, 178.6.$

Anal. Calcd for C$_{12}$H$_{17}$N$_{3}$O$_{2}$S: C, 57.34; H, 6.82. Found: C, 56.98; H, 6.82, 152.2, 179.3.


$\text{N,N-Diethyl-N'}-$isonicotinilythiourea (6j)

Light-brown microcrystals from CH$_2$Cl$_2$ (80%); mp 108–109 °C.

$\text{1H NMR:} \delta = 1.20–1.45 \text{ (m, 6 H), 3.64 \text{ (br s, 2 H), 4.01 \text{ (br s, 2 H), 6.56 \text{ (dd, J = 3.3, 1.8 Hz, 1 H), 7.24 \text{ (d, J = 3.3 Hz, 1 H), 7.54 \text{ (d, 2 H, J = 0.9 Hz).}}}$

$\text{13C NMR:} \delta = 11.3, 13.1, 47.8, 112.7, 117.0, 145.2, 146.2, 153.7, 178.1.$

References


