New tetrasubstituted thioureas containing the 1-iminoethyl moiety*

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The reactions of 1,1,3-trisubstituted thioureas with acetonitrile afforded the corresponding tetrasubstituted thioureas containing the *N*-(1-iminoethyl) moiety.

Key words: thioureas, acetonitrile, amidines.

Thioureas belong to a class of compounds that hold promise in chemical and pharmacological aspects. In medicinal chemistry, thioureas are used in the synthesis of neuroactive acyclic isothioureas[1,2] and various sulfur-containing heterocycles bearing the pharmacophoric isothiouronium group.[3] Thioureas can suppress HIV reverse transcriptase,[5] exhibit antifungal[5] and antibacterial[6] properties, and inhibit NO synthase.[7]

The aim of the present study was to search for new reactions giving tetrasubstituted thioureas. We developed a convenient one-pot method for the synthesis of the previously unknown tetrasubstituted thioureas containing the 1-iminoethyl group as one of *N*-substituents. This method is based on the reaction of 1,1,3-trisubstituted thioureas **1a—g** with acetonitrile. The reaction can be performed with the use of aqueous solutions of hydrochloric or hydrobromic acid (method *A*, products **2a—f**), as well as under milder conditions with the use of triphenylphosphine and carbon tetrachloride (method *B*, product **2g**). The reaction produces acetimidoyl halides, which react with thiourea to give the corresponding iminoethyl derivatives **2** (Scheme 1).

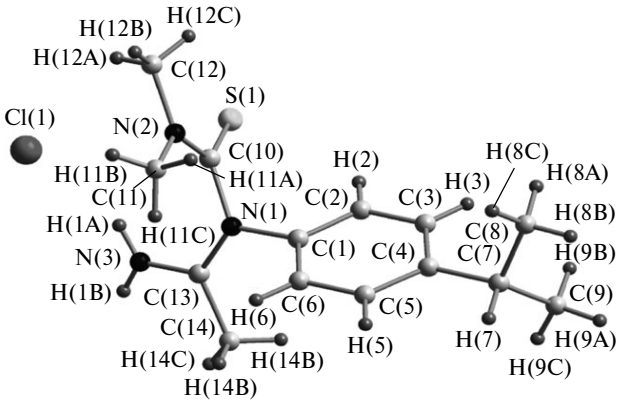
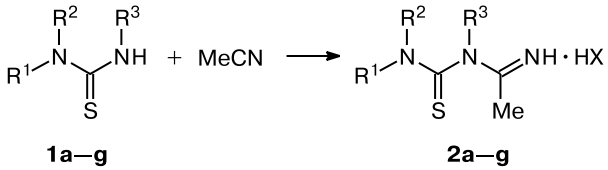


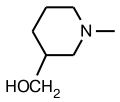
Fig. 1. Molecular structure of compound **2d** in the crystal.

Scheme 1



1a—g **2a—g**

Compound	R^1	R^2	R^3	X
a	Me	Me	Ph	Br
c	Me	Me	4-$Me_2CHC_6H_4$	Cl
d	Me	Me	4-$Me_2CHC_6H_4$	Br

Compound	NR^1R^2	R^3	X
b		Ph	Br
e		4-$Me_2CHC_6H_4$	Cl
f		4-$Me_2CHC_6H_4$	Br
g		4-$Me_2CHC_6H_4$	Cl

Conditions: *A*, HX; *B*, Ph_3P, CCl_4.

The structures of the resulting compounds were confirmed by the X-ray diffraction data for thiourea **2d** (Fig. 1).

Experimental

The ^1H NMR spectra were recorded on a Bruker CXP-200 spectrometer operating at 200 MHz in DMSO-d_6 with tetrame-

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thylsilane as the internal standard. The electrospray ionization mass spectra were obtained on a Shimadzu LCMS-2010A quadrupole mass spectrometer. The elemental analysis was performed on a Carlo-Erba CHN analyzer.

1-(1-Iminoethyl)thioureas 2a—f (general procedure). Method *A*. The starting thiourea **1a—f** (1 mmol) was dissolved with stirring in acetonitrile (3—4 mL). Then an aqueous solution of hydrochloric or hydrobromic acid (1 mmol) was added. The reaction mixture was stirred for 2—4 h and left for 16 h. The crystalline precipitate that formed was filtered off and washed with diethyl ether.

1-(1-Iminoethyl)-3,3-dimethyl-1-phenylthiourea hydrobromide (2a). The yield was 60%, m.p. 143—144 °C. Found (%): C, 44.02; H, 5.13; N, 14.07; S, 10.43. $C_{11}H_{15}N_3S \cdot HBr$. Calculated (%): C, 43.71; H, 5.34; N, 13.90; S, 10.61. ^{1}H NMR, δ: 2.30 (s, 3 H, CH_3); 3.33 (s, 3 H, C$\underline{H}_3$); 3.50 (s, 3H, C$\underline{H}_3$); 7.43—7.95 (m, 5 H, Ar); 9.75 (br.s, 1 H, NH); 10.85 (br.s, 1 H, N^+H).

***N*-(1-Iminoethyl)-*N*-phenylpyrrolidine-1-carbothioamide hydrobromide (2b).** The yield was 75%, m.p. 137—138 °C. Found (%): C, 47.28; H, 5.11; N, 13.06; S, 9.38. $C_{13}H_{17}N_3S \cdot HBr$. Calculated (%): C, 47.57; H, 5.53; N, 12.80; S, 9.77. ^{1}H NMR, δ: 1.80—2.20 (m, 4 H, C$\underline{H}_2$C$\underline{H}_2$); 2.32 (s, 3 H, CH_3); 3.40—4.30 (m, 4 H, C$\underline{H}_2$NC$\underline{H}_2$); 7.52—7.83 (m, 5 H, Ar); 9.73 (br.s, 1 H, NH); 10.86 (br.s, 1 H, N^+H).

1-(1-Iminoethyl)-1-(4-isopropylphenyl)-3,3-dimethylthiourea hydrochloride (2c). The yield was 65%, m.p. 168—169 °C. Found (%): C, 55.81; H, 7.12; N, 13.72; S, 10.24. $C_{14}H_{21}N_3S \cdot HCl$. Calculated (%): C, 56.08; H, 7.40; N, 14.01; S, 10.69. ^{1}H NMR, δ: 1.23 (d, 6 H, CH(C$\underline{H}_3$)$_2$, J = 7.3 Hz); 2.25 (s, 3 H, CH_3); 2.95 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$); 3.42 (s, 3 H, C$\underline{H}_3$); 3.50 (s, 3 H, C$\underline{H}_3$); 7.37 (d, 2 H, Ar, J = 8.6 Hz); 7.75 (d, 2 H, Ar, J = 8.6 Hz); 9.71 (br.s, 1 H, NH); 11.30 (br.s, 1 H, N^+H).

1-(1-Iminoethyl)-1-(4-isopropylphenyl)-3,3-dimethylthiourea hydrobromide (2d). The yield was 85%, m.p. 159—160 °C. Found (%): C, 48.52; H, 6.14; N, 12.44; S, 9.12. $C_{14}H_{21}N_3S \cdot HBr$. Calculated (%): C, 48.84; H, 6.404; N, 12.20; S, 9.31. ^{1}H NMR, δ: 1.28 (d, 6 H, CH(C$\underline{H}_3$)$_2$, J = 7.3 Hz); 2.25 (s, 3 H, CH_3); 3.02 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$); 3.40 (s, 3 H, C$\underline{H}_3$); 3.50 (s, 3 H, C$\underline{H}_3$); 7.40 (d, 2 H, Ar, J = 8.6); 7.75 (d, 2 H, Ar, J = 8.6 Hz); 8.50—11.20 (br.s, 2 H, N^+H+NH).

***N*-(1-Iminoethyl)-*N*-(4-isopropylphenyl)piperidine-1-carbothioamide hydrochloride (2e).** The yield was 74%, m.p. 178—180 °C. Found (%): C, 60.32; H, 7.94; N, 12.59; S, 9.08. $C_{17}H_{25}N_3S \cdot HCl$. Calculated (%): C, 60.07; H, 7.71; N, 12.36; S, 9.43. ^{1}H NMR, δ: 1.20 (d, 6 H, CH(C$\underline{H}_3$)$_2$, J = 7.3 Hz); 1.30—1.80 (m, 6 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$); 2.25 (s, 3 H, CH_3); 2.95 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$); 3.60—4.50 (m, 4 H, C$\underline{H}_2$NC$\underline{H}_2$)); 7.42 (d, 2 H, Ar, J = 8.6 Hz); 7.70 (d, 2 H, Ar, J = 8.6 Hz); 9.80 (br.s, 1 H, NH); 11.20 (br.s, 1 H, N^+H).

***N*-(1-Iminoethyl)-*N*-(4-isopropylphenyl)piperidine-1-carbothioamide hydrobromide (2f).** The yield was 86%, m.p. 175—176 °C. Found (%): C, 53.44; H, 6.68; N, 10.75; S, 8.12. $C_{17}H_{25}N_3S \cdot HBr$. Calculated (%): C, 53.12; H, 6.82; N, 10.93; S, 8.34. ^{1}H NMR, δ: 1.18 (d, 6 H, CH(C$\underline{H}_3$)$_2$, J = 7.3 Hz); 1.45—1.95 (m, 6 H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$); 2.15 (s, 3 H, CH_3); 2.95 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$); 3.60—4.60 (m, 4 H, C$\underline{H}_2$NC$\underline{H}_2$); 7.35 (d, 2 H, Ar, J = 8.6 Hz); 7.65 (d, 2 H, Ar, J = 8.6 Hz); 9.55 (br.s, 1 H, NH); 10.60 (br.s, 1 H, N^+H).

3-Hydroxymethyl-*N*-(1-iminoethyl)-*N*-(4-isopropylphenyl)-piperidine-1-carbothioamide hydrochloride (2g). Method *B*. A mixture of 3-hydroxymethyl-*N*-(4-isopropylphenyl)piperidine-1-carbothioamide (0.1 g, 0.34 mmol) and triphenylphosphine (0.1 g, 0.38 mmol) was dissolved in acetonitrile (2.6 mL). Then CCl_4 (0.5 mL) was added, and the mixture was kept for 16 h. The crystalline precipitate that formed was filtered off and recrystallized from acetone. Product **2g** was obtained in a yield of 0.07 g (63%). M.p. 125—126 °C. Found (%): C, 58.65; H, 7.43; N, 11.30; S, 8.61. $C_{18}H_{27}N_3OS \cdot HCl$. Calculated (%): C, 58.44; H, 7.63; N, 11.36; S, 8.67. ^{1}H NMR, δ: 1.25 (d, 6 H, C(C$\underline{H}_3$)$_2$); 1.3—1.9 (m, 5 H, CH_2CH_2CH); 2.25 (br.s, 3 H, HN=CC$\underline{H}_3$); 2.80 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$); 3.0—3.4 (m, 4 H, CHNCH, CH_2O); 4.30—4.60 (m, 3 H, CHNCH, OH); 7.05—7.50 (m, 4 H, Ar); 9.50—10.30 (br.s, 2 H, NH+N^+H). MS, m/z: 333 $[M]^+$, 292 $[M - CH_3{=}NH]^+$, 249 $[M - CH_3{=}NH{-}C(CH_3)_3]^+$, 232 $[M - CH_3{=}NH{-}C(CH_3)_3{-}OH]^+$, 219 $[M - CH_3{=}NH{-}C(CH_3)_3{-}CH_2OH]^+$.

Principal crystallographic data for compound 2d. The unit cell parameters: a = 14.9503(5) Å, b = 9.2691(2) Å, c = = 12.1751(4) Å, α = 90.00°, β = 110.553(2)°, γ = 90.00°, V = 1579.78(8) Å^3, space group $P2_1/c$, Z = 2. The X-ray diffraction data were collected on a KAPPA APEX II single-crystal diffractometer (Mo-Kα radiation, λ = 0.71073 Å). Single crystals were attached to a glass fiber and mounted on a goniometer. The crystals were cooled with liquid nitrogen at 100 K. The unit cell parameters were refined based on the total X-ray diffraction data set. The experimental intensities were corrected for absorption.[8] The structure was solved by direct methods with the use of the SHELXTL program package[9] and refined by the full-matrix least-squares method based on F^2 using the total X-ray data set with anisotropic displacement parameters for all nohydrogen atoms. The structure was deposited to the Cambridge Crystallographic Data Centre (CCDC 763757).

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