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Unexpected formation of 4-alkyl-5-(4-alkylthiosemicarbazido)-4,5-dihydro-1,2,4-triazine-3(2*H*)-thiones from 1,3-dialkyl-4,5-bis-(4-alkylthiosemicarbazido)imidazolidin-2-ones in acidic medium

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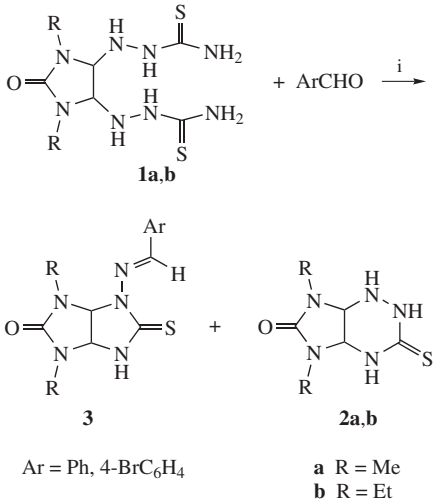
4-Alkyl-5-(4-alkylthiosemicarbazido)-4,5-dihydro-1,2,4-triazine-3(2*H*)-thiones are obtained either by heating 1,3-dialkyl-4,5-bis-(4-alkylthiosemicarbazido)imidazolidin-2-ones in acidic medium or the reaction of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones with 4-methylthiosemicarbazide.

Thiosemicarbazide derivatives are widely used for the synthesis of nitrogen- and sulfur-containing heterocyclic compounds.[1] They manifest antitumour,[2–4] antimicrobial,[2,5,6] antiparasitic[2,7–10] and other types of biological activity. Therefore, studies on the reactivity of thiosemicarbazide derivatives remain an issue of current interest.

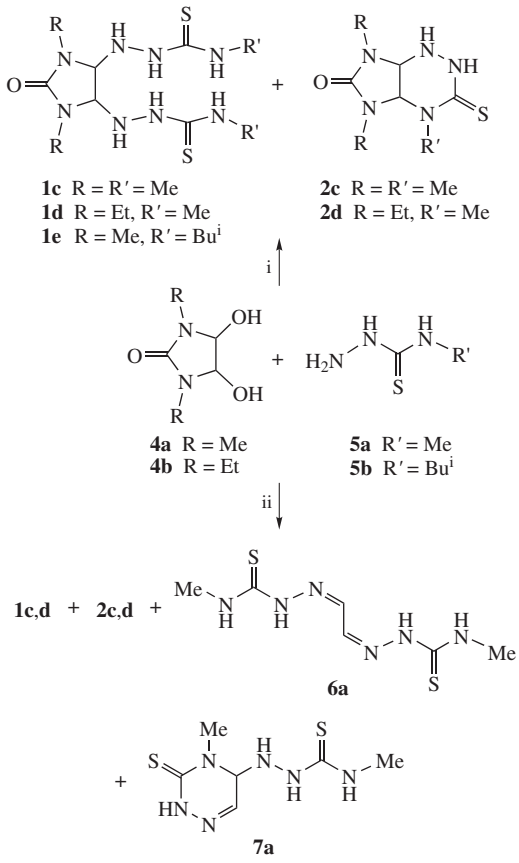
Our recent interests were aimed at the synthesis and chemical properties of five- and six-membered heterocyclic thiosemicarbazide derivatives.[1,11–15] For instance, we studied α-ureidoalkylation of thiosemicarbazide with 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones under acid catalysis affording 1,3-dialkyl-4,5-bis(thiosemicarbazido)imidazolidin-2-ones **1a**,**b** and 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones **2a**,**b** (Scheme 1).[11] Treatment of compounds **1a**,**b** with aromatic aldehydes in the presence of an acid caused their cyclization to give 1,3-dialkyl-4-{[(1*E*)-benzylidene]amino}-5-thioxohexahydroimidazo[4,5-*d*]-imidazol-2(1*H*)-ones **3** and traces of imidazotriazines **2**.[12]



Scheme 1 *Reagents and conditions*: i, MeOH, conc. HCl (cat.), reflux, 1.5 h.

This paper deals with the behaviour of 1,3-dialkyl-4,5-bis-(thiosemicarbazido)imidazolidin-2-ones **1a**–**e** on treatment with hydrochloric acid.

Hitherto unknown imidazolidinones **1c**–**e** were obtained similarly to derivatives **1a**,**b**[11] by α-ureidoalkylation of 4-alkylthiosemicarbazides **5a**,**b** with dihydroxyimidazolidinones **4a**,**b**



Scheme 2 *Reagents and conditions*: i, H_2O, 0.1 ml of conc. HCl, 70–80 °C, 1 h; ii, EtOH, H_2O, conc. HCl (10 : 1 : 0.1), reflux, 1 h (R′ = Me).

(Scheme 2). The reaction was carried out in water under HCl catalysis and produced compounds **1c**–**e** in 69–81% yields. In addition to imidazolidinones **1c**,**d**, imidazotriazines **2c**,**d** were also formed in 4–14% yields.

The reaction in aqueous ethanol (EtOH–H_2O–conc. HCl, 10 : 1 : 0.1) performed by portionwise addition of thiosemicarbazide **5a** to a solution of dihydroxyimidazolidinone **4a**,**b** afforded imidazolidinones **1c**,**d** (29–35%), imidazotriazines **2c**,**d** (21–35%), glyoxal thiosemicarbazone **6a** (5–10%) and 4-methyl-5-(4-methylthiosemicarbazido)-4,5-dihydro-1,2,4-triazine-3(2*H*)-thione **7a** (10–28%) (see Scheme 2). The products were separated by frac-

tional crystallization from ethanol and methanol. The formation of triazine **7a** was unexpected. The structure of the latter was confirmed by the combined IR, ^{1}H and ^{13}C NMR spectral data and its high resolution mass spectrum.†

The IR spectrum of triazinethione **7a** contains absorption bands of NH bonds at 3309, 3261 and 3168 cm^{-1} and those of CH bonds at 3044, 2976 and 2918 cm^{-1}. The stretching vibrations of the C=N and C=S bonds manifest themselves as bands at 1573 and 1527 cm^{-1}. The mass spectrum contains peaks with *m*/*z* 233.06 $[M+H]^+$ and 255.05 $[M+Na]^+$. Assignment of the signals of protons and nitrogen atoms was based on the cross peaks in the HSQC and HMBC {^{1}H-^{15}N} spectra.

† All new compounds **1c–e**, **2c**,**d** and **7a**,**b** gave satisfactory elemental analysis data. Their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz). Chemical shifts were measured with reference to the residual protons of the DMSO-d_6 solvent (δ 2.50 ppm). The high resolution mass spectrum (HRMS) of compound **7a** was measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI).[16] The mass spectrum of compound **7a** was measured on an MS 30 spectrometer.

1,3-Dimethyl-4,5-bis(4-methylthiosemicarbazido)imidazolidin-2-one **1c**: yield 69%, mp 247–249 °C (decomp.). ^{1}H NMR, δ: 2.66 (s, 6H, NMe), 2.93 (d, 6H, NMe, *J* 4.2 Hz), 3.89 (s, 2H, CH), 5.82 (s, 2H, NH), 8.07 (q, 2H, NH, *J* 4.2 Hz), 8.66 (s, 2H, NH). ^{13}C NMR, δ: 28.47 (NMe), 30.52 (NMe), 73.71 (CH), 158.47 (C=O), 182.80 (C=S).

1,3-Diethyl-4,5-bis(4-methylthiosemicarbazido)imidazolidin-2-one **1d**: yield 81%, mp 252–254 °C (decomp.). ^{1}H NMR, δ: 0.92 (t, 6H, Me, *J* 6.7 Hz), 2.94 (d, 6H, NMe, *J* 4.2 Hz), 2.97–3.09 (m, 2H, NCH_2), 3.28–3.40 (m, 2H, NCH_2), 4.10 (s, 2H, CH), 5.77 (s, 2H, NH), 8.00 (q, 2H, NH, *J* 4.2 Hz), 8.53 (s, 2H, NH). ^{13}C NMR, δ: 12.10 (Me), 30.47 (NMe), 34.48 (NCH_2), 70.24 (CH), 157.47 (C=O), 182.89 (C=S).

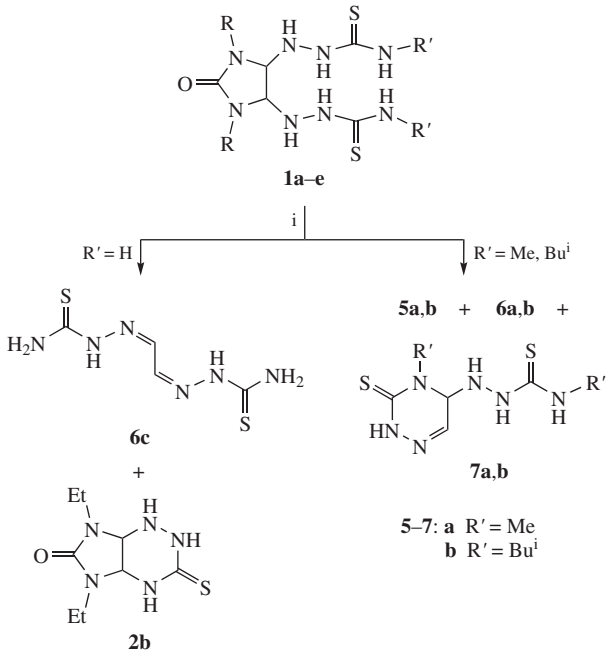
1,3-Dimethyl-4,5-bis(4-isobutylthiosemicarbazido)imidazolidin-2-one **1e**: yield 71%, mp 264–266 °C (decomp.). ^{1}H NMR, δ: 0.85 (d, 12H, Me, *J* 6.6 Hz), 1.88–1.93 (m, 2H, CH), 2.66 (s, 6H, NMe), 3.29–3.37 (m, 4H, CH_2), 4.00 (s, 2H, CH), 5.84 (s, 2H, NH), 7.95 (t, 2H, NH, *J* 4.9 Hz), 8.66 (s, 2H, NH). ^{13}C NMR, δ: 20.04 (Me), 27.84 (CH), 28.35 (NMe), 50.28, 50.44 (CH_2), 73.88 (CH), 158.36 (C=O), 182.29 (C=S).

4,5,7-Trimethyl-3-thioxoperhydroimidazo[4,5-e][1,2,4]triazin-6-one **2c**: yield 35%, mp 269–271 °C (decomp.). ^{1}H NMR, δ: 2.62 (s, 3H, NMe), 2.75 (s, 3H, NMe), 3.23 (s, 3H, NMe), 4.98 (d, 1H, CH, *J* 8.6 Hz), 5.05 (d, 1H, CH, *J* 8.6 Hz), 5.65 (br. s, 1H, NH), 9.40 (s, 1H, NH). ^{13}C NMR, δ: 26.99 (NMe), 30.01 (NMe), 39.70 (NMe), 70.93 (CH), 72.40 (CH), 158.29 (C=O), 188.00 (C=S).

5,7-Diethyl-4-methyl-3-thioxoperhydroimidazo[4,5-e][1,2,4]triazin-6-one **2d**: yield 21%, mp 184–186 °C (decomp.). ^{1}H NMR, δ: 1.01 (t, 6H, Me, *J* 7.1 Hz), 3.00–3.10 (m, 2H, NCH_2), 3.17–3.26 (m, 2H, NCH_2), 3.23 (s, 3H, NMe), 5.09 (d, 1H, CH, *J* 8.8 Hz), 5.16 (d, 1H, CH, *J* 8.8 Hz), 5.59 (s, 1H, NH), 9.42 (s, 1H, NH). ^{13}C NMR, δ: 12.84 (Me), 13.23 (Me), 30.87 (NCH_2), 34.05 (NCH_2), 36.68 (NMe), 71.18 (CH), 75.63 (CH), 161.85 (C=O), 189.71 (C=S).

4-Methyl-5-(4-methylthiosemicarbazido)-4,5-dihydro-1,2,4-triazine-3(2H)-thione **7a**: yield 42% (from **1c**), mp 221–223 °C (decomp.). IR (ν/cm^{-1}): 3309, 3261, 3168 (NH), 3044, 2976, 2918 (CH), 1573 (C=N), 1527 (C=S), 1449, 1407, 1296, 1279, 1145, 1048, 1031, 878, 831, 811, 751. ^{1}H NMR, δ: 2.87 (d, 3H, NMe, *J* 4.4 Hz), 3.25 (s, 3H, NMe_{cycle}), 4.80 (t, 1H, 5-H, *J* 3.1 Hz), 6.08 (d, 1H, 1′-H, *J* 3.1 Hz), 6.92 (d, 1H, 6-H, *J* 2.9 Hz), 7.95 (q, 1H, 4′-H, *J* 4.4 Hz), 8.68 (s, 1H, 2′-H), 11.23 (s, 1H, 2-H). ^{13}C NMR, δ: 30.50 (NMe), 37.34 (NMe_{cycle}), 67.01 (5-C), 135.38 (6-C), 173.31 (C=S), 183.20 (C=S). MS, *m*/*z* (%): 128 (86) [M–HNHNC(S)NHMe]$^+$. HRMS, *m*/*z*: 233.0644 $[M+H]^+$ ($C_6H_{12}N_6S_2$, Δ = 2.5 ppm), 255.0459 $[M+Na]^+$ ($C_6H_{12}N_6S_2$, Δ = 0.7 ppm). Found (%): C, 31.09; H, 5.20; N, 36.12; S, 27.49. Calc. for $C_6H_{12}N_6S_2$ (%): C, 31.02; H, 5.21; N, 36.17; S, 27.60.

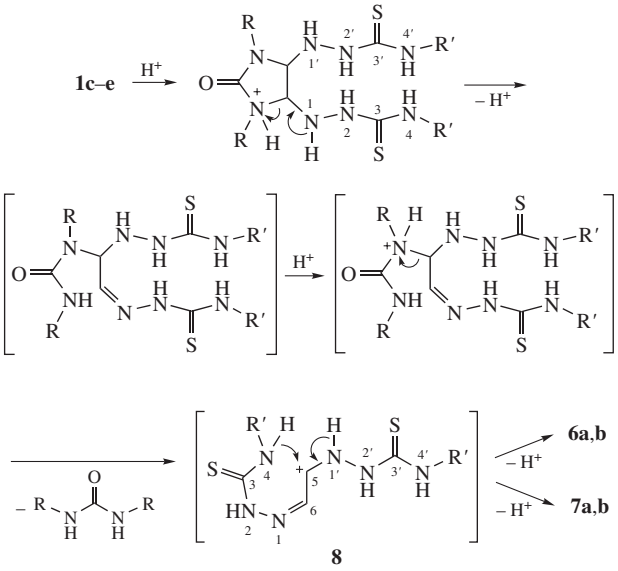
4-Isobutyl-5-(4-isobutylthiosemicarbazido)-4,5-dihydro-1,2,4-triazine-3(2H)-thione **7b**: yield 31%, mp 235–237 °C (decomp.). ^{1}H NMR, δ: 0.82 (d, 6H, Me, *J* 6.6 Hz), 0.85 (d, 6H, Me, *J* 6.6 Hz), 1.89–2.04 (m, 2H, CH), 3.06–3.13 (m, 2H, CH_2), 4.34–4.41 (m, 2H, CH_2), 4.74 (t, 1H, 5-H, *J* 3.1 Hz), 6.07 (d, 1H, 1′-H, *J* 3.0 Hz), 7.04 (d, 1H, 6-H, *J* 3.1 Hz), 7.79 (t, 1H, 4′-H, *J* 5.8 Hz), 8.62 (s, 1H, 2′-H), 11.35 (s, 1H, 2-H).



Scheme 3 *Reagents and conditions*: i, EtOH, H_2O, conc. HCl (10 : 1 : 0.1), reflux, 1–2 h.

Compounds **6a** and **7a** are likely to be products of hydrolysis of imidazolidinones **1c**,**d**. This result was an additional stimulus to study the conversion of derivatives **1a–e** on treatment with an acid (Scheme 3).

Compound **1a** remains unchanged under the conditions specified in Scheme 3. An increase in the amount of the acid (EtOH–conc. HCl, 10 : 1 or 5 : 1) results in the formation of glyoxal thiosemicarbazone **6c**, 1,3-dimethylurea, 1,3-dimethylhydantoin, thiosemicarbazide and other unidentified decomposition products. Compound **1b** is converted upon reflux for 1 h to give imidazotriazine **2b** in 80% yield and glyoxal thiosemicarbazone **6c** (up to 15%). Heating a suspension of derivatives **1c–e** for 2 h affords thiosemicarbazides **5a**,**b** (yield 7–11%), thiosemicarbazones **6a**,**b** (8–15%) and triazines **7a**,**b** (31–42%) (see Scheme 3). The reaction is likely to start in protonation of nitrogen atoms of the thiosemicarbazide moiety or ring nitrogen atoms in compounds **1c–e**. Protonation at the N(1) or N(1′) atom in the thiosemicarbazide moiety leads to elimination of a molecule of thiosemi-



Scheme 4

carbazide **5**. Protonation at nitrogen atoms of the imidazolidine ring results in the evolution of a 1,3-dialkylurea molecule to give carbocation **8** (Scheme 4). Deprotonation of the latter may involve the formation of a new bond between the C(5) and N(1′) or N(4) atoms to produce thiosemicarbazone **6** or triazine **7**, respectively.

In conclusion, a study of the effect of HCl on 1,3-dialkyl-4,5-bis(thiosemicarbazido)imidazolidin-2-ones allowed us to obtain hitherto unknown compounds, 4-alkyl-5-(4-alkylthiosemicarbazido)-4,5-dihydro-1,2,4-triazine-3(2*H*)-thiones **7a**,**b**. Furthermore, another method for synthesizing 5,7-diethyl-3-thioxoperhydroimidazo[4,5-*e*][1,2,4]triazin-6-one **2b** from 1,3-diethyl-4,5-bis(thiosemicarbazido)imidazolidin-2-one **1b** in acidic medium was found.

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