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Cyclization of 1,3-dialkyl-4,5-bis(1-thiosemicarbazido)-imidazolidin-2-ones(thiones) with aromatic aldehydes

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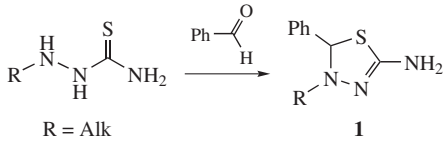
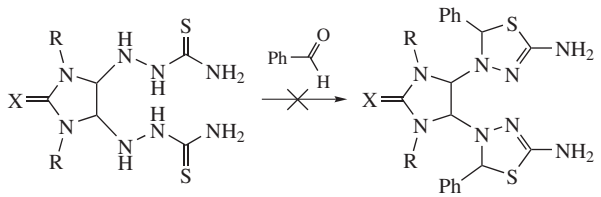
Cyclization of 1,3-dialkyl-4,5-bis(1-thiosemicarbazido)imidazolidin-2-ones(thiones) with aromatic aldehydes under acidic catalysis affords 1,3-dialkyl-4-(arylideneamino)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones and 5,7-dialkyltetrahydro-1*H*-imidazo[4,5-*e*]-1,2,4-triazine-3,6(2*H*,4*H*)-dithiones.

Thiosemicarbazide derivatives are intensively investigated both as ligands in complexation reactions[1–3] and as synthons for the preparation of N- and S-heterocycles.[4–6] According to literature data,[6] 1-alkylthiosemicarbazides react with benzaldehyde in the presence of hydrochloric acid giving thiadiazoline **1** derivatives (Scheme 1).



Scheme 1

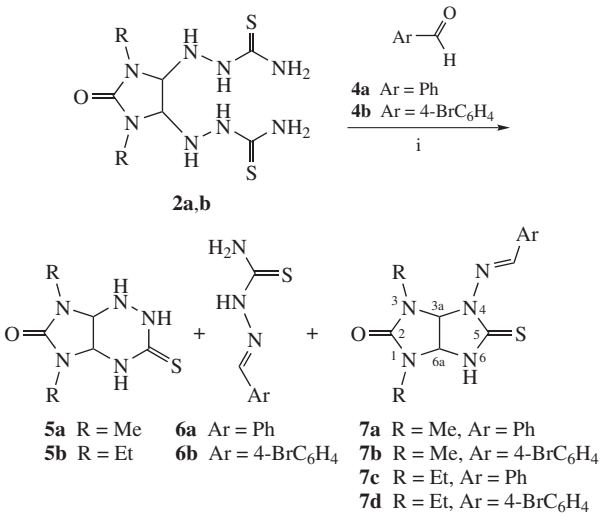
In the present study, we explored the reaction of 1,3-dialkyl-4,5-bis(1-thiosemicarbazido)imidazolidin-2-ones(thiones) **2a**,**b** (**3a**,**b**) with benzaldehydes and found that analogous thiadiazoline derivatives did not form (Scheme 2).



Scheme 2

In fact, treatment of compounds **2a**,**b** with the equimolar amount of benzaldehyde **4a** or *p*-bromobenzaldehyde **4b** in methanol in the presence of HCl furnished 5,7-dialkyl-3-thioxo-octahydro-6*H*-imidazo[4,5-*e*]-1,2,4-triazin-6-ones[7] **5a**,**b**, known aldehyde thiosemicarbazones **6a**,**b**, and previously unknown 1,3-dialkyl-4-(*E*-arylideneamino)-5-thioxohexahydroimidazo-[4,5-*d*]imidazol-2(1*H*)-ones (thioglycolurils of a new substitution type) **7a**–**d** (Scheme 3).

When 2 moles of benzaldehyde per 1 mole of starting **2a** or **2b** were used, yields of thiosemicarbazone **6a** and thioglycolurils **7a**,**c** increased (Scheme 4). Yield of thiosemicarbazone **6a** was 35–37% (theoretically, 2 moles of **6** can be obtained from 1 mole of starting **2**); yields of **7a**,**c** were 55–58%. 4-Bromo-



Scheme 3 *Reagents and conditions*: i, MeOH, conc. HCl, reflux, 1.5 h.

benzaldehyde **4b** caused removal of both thiosemicarbazide moeities from **2a**,**b** to give imidazolidinediones **8a**,**b** (Scheme 4).

In this case, the yield of **6b** increased to 70–73% (*cf.* the yield of **6a**) and the yields of **7b**,**d** decreased to 20–22% (*cf.* the yields of **7a**,**c**).

The structure of thioglycolurils **7a**–**d** was ascertained by elemental analysis, mass spectrometry and IR, ^{1}H and ^{13}C NMR spectroscopy data.† The IR spectra of **7a**,**c**,**d** showed the absorption bands of stretch vibrations of the NH bond in the 3210–3260 cm^{-1} region, those of alkyl groups at 2870–2970 cm^{-1}, and those of the carbonyl group in the region of 1670–1700 cm^{-1}. Less intensive absorption bands at 1560–1610 cm^{-1} may be ascribed to vibrations of the C=N bond as well as of the conjugated C=C bonds of the aromatic ring (see ref. 9).

Spectra of 2D proton–proton, proton–carbon, and proton–nitrogen correlations were recorded for compound **7a**. In the ^{1}H-{^{13}C} HSQC spectrum, a cross-peak of the proton signal with δ 9.13 ppm and the carbon atom signal with δ 151.5 ppm was observed. Judging from δ 151.5 ppm and ^1J 167.0 Hz, this carbon atom of CH group had sp^2-hybridization and was bound to the electron-acceptor atom (N). The ^{1}H-{^{13}C} HMBC spectrum displayed a cross-peak of the proton signal with δ 9.13 ppm and

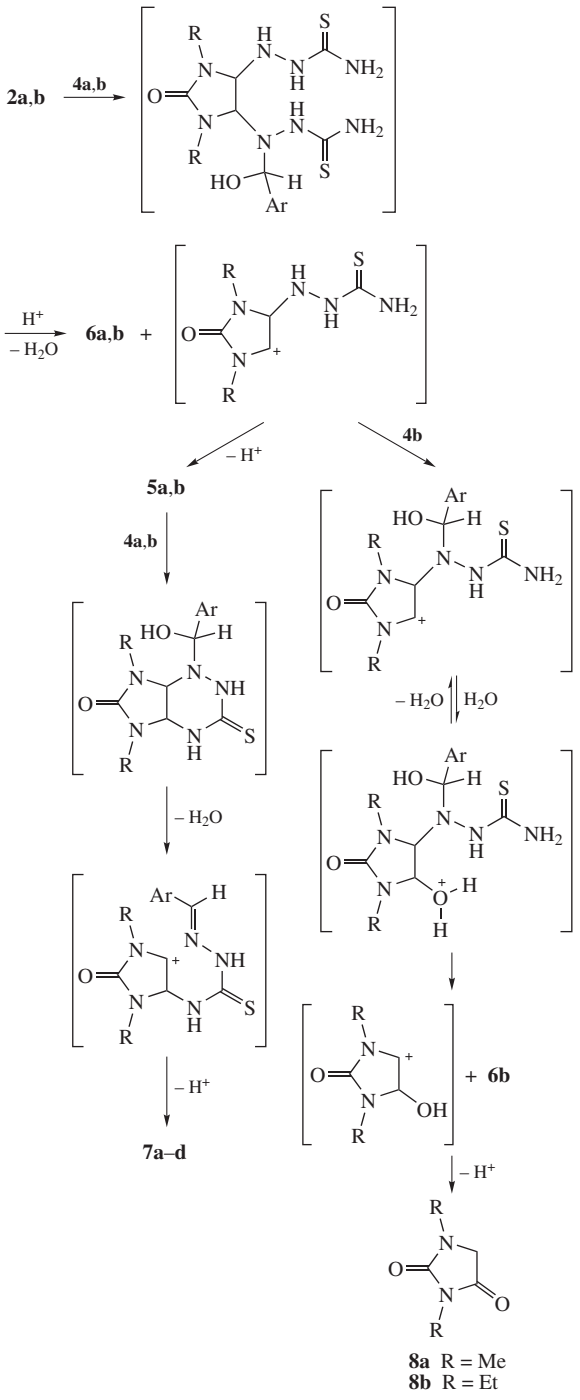
signals from *ipso* and *ortho* carbon atoms of the benzene ring, to which this CH group was directly bound.

The proton and nitrogen atom signals assignment was based on the cross-peaks in the HMBC ^{1}H-{^{15}N} spectrum.

Originating from the NOESY and TOCSY spectra of **7a**, protons for the methyl group at the N^1 atom had correlations with protons at the C^{6a} atom and N^6 atom only (for the numeration of atoms, see Scheme 3). The methyl group protons at N^3 had correlations with protons at C^{3a} and at the C=N group carbon atom as well as with the benzene ring protons. In the TOCSY spectrum, two isolated spin systems formed by the C^{3a}, C^{6a}, and N^6 protons as well as by the N=C group proton and benzene ring protons were detected.

Compounds **7a–d** can exist in the form of either *E* or *Z* isomers. According to literature data for aldoximes,[10–12] the spin–spin ^{15}N=CH interaction constant $J < 4$ Hz is only characteristic of *E* isomers and $^2J > 10$ Hz of *Z* isomers. Judging from the value of 2.62 Hz of the spin–spin ^{15}N=CH coupling constant for **7a**, we may conclude that this compound possesses the *E* configuration.

To expand the scope of the discovered reaction, thio analogues **3a**,**b** were tested. Boiling of **3a**,**b** with benzaldehyde in methanol with the catalytic amount of HCl gave derivatives of imidazo-



Scheme 4

[4,5-*e*]-1,2,4-triazine **9a**,**b**‡ and thiosemicarbazone of benzaldehyde **6a** (Scheme 5). In a similar manner, **3a**,**b** reacted with 4-bromobenzaldehyde resulting in bicyclic compounds **9a**,**b** and thiosemicarbazone **6b**. Yields of imidazotriazines **9a**,**b** were 55–63% and those of thiosemicarbazones **6a**,**b** were 85–93% (at the equimolar ratio of **3a**,**b** and aldehyde).

The reaction may be regarded as a new preparative method for the synthesis of **9a**,**b**. Previously,[13] such compounds were obtained in 5–15% yields as by-products in the synthesis of **3a**,**b** being the result of the aldehyde-assisted cyclization of vicinal dithiosemicarbazides.

The imidazotriazine structure of compound **9b** was proven by NMR spectroscopy‡ and supported by single crystal X-ray diffraction§ (Figure 1), The geometric parameters of the molecule of **9b** are within the values expected for the compounds of this type.[14,15] The conformation of the imidazole ring is a flat-

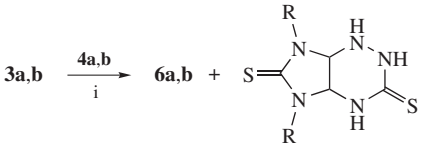
† All compounds **7a–d** gave satisfactory elemental analysis data. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C). Chemical shifts were measured with reference to the residual protons of a DMSO-d_6 solvent (δ 2.50 ppm). Mass spectra were measured on an MS 30 spectrometer. IR spectra were recorded on a Specord M80-2 instrument.

For **7a**: yield 55%, mp 239–241 °C (decomp.). ^{1}H NMR, δ: 2.75 (s, 3H, MeN^1), 2.86 (s, 3H, MeN^3), 5.41 (d, 1H, HC^{6a}, *J* 8.1 Hz), 5.98 (d, 1H, HC^{3a}, *J* 8.1 Hz), 7.47 (m, 3H, *m*-H$_{Ph}$, *p*-H$_{Ph}$), 7.77 (m, 2H, *o*-H$_{Ph}$), 9.13 (s, 1H, N=CH), 10.02 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 28.2 (MeN^1), 30.1 (MeN^3), 68.1 (HC^{6a}), 74.9 (HC^{3a}), 127.3 (*o*-C$_{Ph}$), 128.9 (*m*-C$_{Ph}$), 130.6 (*p*-C$_{Ph}$), 133.9 (*ipso*-C$_{Ph}$), 151.5 (N=CH), 157.5 (C=O), 179.0 (C=S). MS, *m*/*z* (%): 289 (M$^+$, 3), 230 (0.4), 186 (6), 153 (6), 127 (13), 112 (100), 111 (34), 104 (37), 103 (34), 98 (39), 89 (26), 88 (26), 83 (48), 77 (29). IR (ν/cm^{-1}): 3256 (NH), 2960 (Me), 1700, 1692 (CO), 1572, 1560 (C=N, C=C), 1508, 1488, 1404, 1272, 1248, 1228, 1208, 1056, 1032, 848.

For **7b**: yield 20%, mp 217–219 °C (decomp.). ^{1}H NMR, δ: 2.75 (s, 3H, MeN^1), 2.86 (s, 3H, MeN^3), 5.41 (d, 1H, HC^{6a}, *J* 8.2 Hz), 5.98 (d, 1H, HC^{3a}, *J* 8.2 Hz), 7.69 (m, 4H, *o*-H$_{Ph}$, *m*-H$_{Ph}$), 9.06 (s, 1H, N=CH), 10.07 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 28.2 (MeN^1), 30.2 (MeN^3), 68.1 (HC^{6a}), 74.6 (HC^{3a}), 123.8 (Ar), 129.1 (Ar), 131.9 (Ar), 133.3 (Ar), 149.0 (N=CH), 157.5 (C=O), 179.1 (C=S). MS, *m*/*z* (%): 369 (M$^+$ + 1, 8), 368 (M$^+$, 8), 310 (19), 186 (50), 183 (33), 153 (45), 144 (37), 127 (55), 125 (40), 112 (100), 102 (43), 104 (37), 98 (92), 82 (55).

For **7c**: yield 58%, mp 226–228 °C (decomp.). ^{1}H NMR, δ: 1.06 (m, 6H, Me), 3.10–3.43 (m, 4H, NCH$_2$), 5.51 (d, 1H, HC^{6a}, *J* 8.8 Hz), 5.99 (d, 1H, HCNN, *J* 8.8 Hz), 7.47 (m, 3H, *m*-H$_{Ph}$, *p*-H$_{Ph}$), 7.76 (m, 3H, *o*-H$_{Ph}$), 9.27 (s, 1H, N=CH), 9.96 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 12.9 (Me), 13.4 (Me), 35.9 (NCH$_2$), 37.1 (NCH$_2$), 66.2 (HC^{6a}), 74.7 (HC^{3a}), 127.4 (*o*-C$_{Ph}$), 128.9 (*m*-C$_{Ph}$), 130.8 (*p*-C$_{Ph}$), 133.7 (*ipso*-C$_{Ph}$), 153.8 (N=CH), 156.8 (C=O), 178.6 (C=S). MS, *m*/*z* (%): 317 (M$^+$, 50), 258 (40), 214 (18), 179 (19), 172 (35), 155 (13), 140 (81), 127 (21), 125 (47), 112 (57), 103 (42), 101 (80), 97 (32), 82 (54), 76 (37), 59 (100). IR (ν/cm^{-1}): 3212 (NH), 2972, 2932, 2876 (Et), 1692, 1684 (CO), 1608, 1572 (C=N, C=C), 1504, 1480, 1448, 1400, 1336, 1276, 1252, 1232, 1196, 1072, 1060, 916, 832, 804.

For **7d**: yield 22%, mp 232–234 °C (decomp.). ^{1}H NMR, δ: 1.05 (m, 6H, Me), 3.09–3.42 (m, 4H, NCH$_2$), 5.51 (d, 1H, HC^{6a}, *J* 8.4 Hz), 5.99 (d, 1H, HCNN, *J* 8.4 Hz), 7.70 (br. s, 4H, *o*-H$_{Ph}$, *m*-H$_{Ph}$), 9.24 (s, 1H, N=CH), 10.02 (s, 1H, NH). ^{13}C{^{1}H} NMR, δ: 12.9 (Me), 13.4 (Me), 35.9 (NCH$_2$), 37.2 (NCH$_2$), 66.2 (HC^{6a}), 74.4 (HC^{3a}), 124.1 (C$_{Ar}$), 129.1 (C$_{Ar}$), 132.0 (C$_{Ar}$), 133.1 (*ipso*-C$_{Ar}$), 151.6 (N=CH), 156.8 (C=O), 178.6 (C=S). MS, *m*/*z* (%): 397 (M$^+$ + 1, 14), 396 (M$^+$, 15), 338 (39), 336 (41), 214 (19), 184 (29), 181 (50), 172 (26), 156 (16), 154 (41), 140 (100), 125 (41), 112 (87), 102 (43), 82 (30). IR (ν/cm^{-1}): 3224 (NH), 2972, 2932, 2872 (Et), 1684, 1676 (CO), 1588 (C=N, C=C), 1504, 1480, 1452, 1400, 1336, 1272, 1252, 1236, 1196, 1072, 1008, 912, 828, 800.



9a R = Me, 63%
9b R = Et, 55%

Scheme 5 *Reagents and conditions*: i, MeOH, conc. HCl, reflux, 2 h.

tened envelope with the N(1) atom deviating by 0.05(1) Å, that of the triazine moiety is a boat with the C(1) and C(3) atoms deviating by 0.53(1) and 0.35(1) Å, respectively. The N(1), N(2), N(4), and N(5) atoms are planar, whereas the N(3) atom is piramidalized; the sums of the corresponding valence angles are 353.1(1)–359.6(1) and 328.2(1)°, respectively. As in the case of the phenyl analogue of **9b**,[15] N(4)H and N(5)H are in the equatorial plane of the triazine cycle, and the N(3)H is axial. This allows the molecules of **9b** to form the 3D-framework in a crystal through the N–H···S hydrogen bonds [N···S 3.3051(14)–3.3626(14) Å, ∠NHS 159(1)–175(1)°], which are complemented by weaker C–H···S contacts [the smallest C···S distance is 3.6501(14) Å].

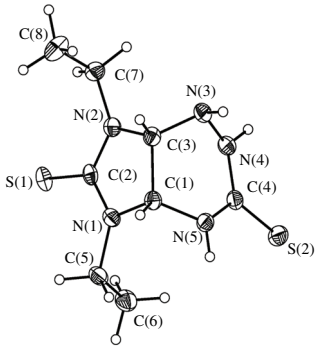


Figure 1 General view of the molecule of **9b** in representation of atoms *via* thermal ellipsoids at 50% probability level.

‡ *5,7-Dimethyltetrahydro-1*H-*imidazo[4,5-*e*]-1,2,4-triazine-3,6(2*H,*4*H)-*dithione* **9a**: yield 63% (lit.,[13] 10%), mp 206–208 °C (decomp.). ^{1}H and ^{13}C NMR spectra were described previously.[13]

*5,7-Diethyltetrahydro-1*H-*imidazo[4,5-*e*]-1,2,4-triazine-3,6(2*H,*4*H)-*dithione* **9b**: yield 55% (lit.,[13] 15%), mp 238–240 °C (decomp.). ^{1}H and ^{13}C NMR, and mass spectra were described previously.[13]

§ *Crystallographic data*. Crystals of **9b** ($C_8H_{15}N_5S_2$, M = 245.37) are orthorhombic, space group *Pbca*, at 120 K: a = 14.4098(8), b = 9.8694(6) and c = 16.3533(9) Å, V = 2325.7(2) Å^3, Z = 8 (Z' = 1), d_{calc} = 1.402 g cm^{-3}, μ(MoKα) = 4.35 cm^{-1}, F(000) = 1040. Intensities of 24006 reflections were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = = 0.71072 Å, ω-scans, $2\theta < 58°$] and 3087 independent reflections (R_{int} = = 0.0221) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms of NH groups were located from the Fourier synthesis of the electron density. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation in riding model with the U_{iso}(H) parameters equal to $1.2U_{eq}(C_i)$, for methyl groups equal to $1.5U_{eq}(C_{ii})$, where $U(C_i)$ and $U(C_{ii})$ are respectively the equivalent thermal parameters of the carbon atoms to which corresponding H atoms are bonded. The refinement converged to wR_2 = 0.1210 and GOF = 1.002 for all independent reflections [R_1 = 0.0437 was calculated against F for 2736 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[16]

CCDC 786199 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

In summary, we discovered a new route of the cyclization of 1,3-dialkyl-4,5-bis(1-thiosemicarbazido)imidazolidin-2-ones **2a**,**b** with aromatic aldehydes that led to 1,3-dialkyl-4-(*E*-arylideneamino)-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones **7a**–**d**. Interestingly, similar reaction of thio analogues **3** gives mostly their intramolecular cyclization products containing nothing of benzaldehyde moieties, the benzaldehydes serving here as cyclization promoters.

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