A new simple approach to the preparation of imidazo[4,5-*e*]-1,2,4-triazine derivatives

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A simple method for the preparation of imidazo[4,5-*e*]-1,2,4-triazine derivatives has been developed by the interaction of 4,5-dihydroxyimidazolidin-2-ones with thiosemicarbazide under acidic catalysis.

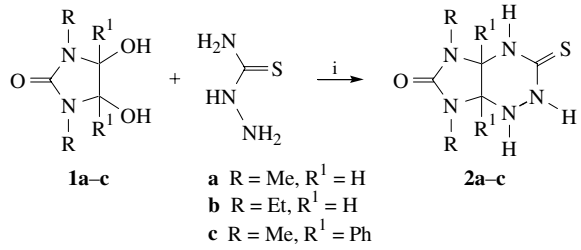
The synthesis of bicyclic bisureas (BBU) has been studied intensively.[1–6] This class of compounds is of considerable interest because they exhibit psychotropic activity.[7,8]

One of the most common methods for the preparation of bicyclic bisureas consists in the cyclocondensation of 4,5-dihydroxyimidazolidin-2-ones with both of the NH_2(NHR) groups of ureas under conditions of acid catalysis in water[1,3,4,9] or aqueous methanol.[10] It would be expected that an analogous cyclocondensation of 4,5-dihydroxyimidazolidin-2-ones with other *N*,*N*′-bisnucleophiles (*e.g.*, thiosemicarbazide) leads to imidazo[4,5-*e*]-1,2,4-triazine derivatives. Recently,[11] the synthesis of imidazo[4,5-*e*]-1,2,4-triazine derivatives **2** was published, which was based on an opposite approach – the annelation of an imidazole ring to a 1,2,4-triazine ring. This reaction is performed by the interaction of 5-methoxy-3-phenyl-1,2,4-triazine with different ureas in Ac_2O or $(CF_3CO)_2O$.

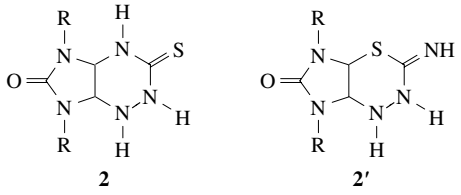
We studied the interaction of 4,5-dihydroxyimidazolidin-2-ones **1a–c** with thiosemicarbazide in order to find a new alternative approach to the preparation of imidazo[4,5-*e*]-1,2,4-triazine derivatives.

The optimal conditions leading to imidazo[4,5-*e*]-1,2,4-triazine derivatives **2a–c** were the following: methanol as a solvent; the addition of an equimolar amount of thiosemicarbazide in portions and the refluxing of the reaction mixture for 30 min in the presence of a catalytic amount of concentrated hydrochloric acid (Scheme 1). The yields of bicycles **2** were 90–96%.†

The resulting products were structurally characterised by elemental analysis, NMR spectroscopy and mass spectrometry. However, the possibility of formation of alternative structures **2′** (Scheme 2) cannot be excluded. With the use of compound **2a**‡ as an example, we found by X-ray diffraction analysis that the obtained bicyclic compounds exhibit structure **2**.



Scheme 1 *Reagents and conditions*: i, MeOH, conc. HCl, 60 °C, 30 min.



Scheme 2

These compounds are chiral (asymmetric 4a,7a-atoms). Compound **2a** crystallises as a racemate in centrosymmetric space group $P2_1/c$, $Z = 4$. In this compound, five- and six-membered rings are *cis* coupled at the C(4)–C(5) bond, and the H(4)–C(4)–C(5)–H(5) torsion angle is equal to 11° (Figure 1). The main geometry parameters of the five-membered ring are similar

† All new compounds 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 MHz for ^{1}H and 75.47 MHz for ^{13}C NMR spectra). Chemical shifts were measured with reference to the residual protons of a [$^2H_6$]DMSO solvent (δ 2.50 ppm). Mass spectra were measured on an MS 30 spectrometer.

*(4*aR*,7*aS*)-5,7-Dimethyl-3-thioxooctahydroimidazo[4,5-*e*]-1,2,4-triazin-6-one* **2a**: yield 93–94%, mp 234–235 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.59 (s, 3H, Me), 2.61 (s, 3H, Me), 4.61 (d, 1H, CH, ^3J 8.5 Hz), 4.79 (d, 1H, CH, ^3J 8.5 Hz), 5.66 (br. s, 1H, CH–N*H*–C=S), 8.77 (br. s, 1H, CH–N*H*–NH), 9.41 (br. s, 1H, NH–N*H*–C=S). ^{13}C NMR ([$^2H_6$]DMSO) δ: 27.1 (Me), 27.4 (Me), 63.7 (CH), 69.0 (CH), 158.0 (C=O), 184.0 (C=S). MS, *m*/*z* (*I*, %): 201 (38) [M$^+$], 184 (4), 170 (30), 144 (13), 126 (7), 112 (100), 97 (4), 89 (12), 83 (11), 69 (11), 58 (31). ^{13}C NMR ([$^2H_6$]DMSO) δ: 27.1 (Me), 27.4 (Me), 63.7 (CH), 69.0 (CH), 158.0 (C=O), 184.0 (C=S). MS, *m*/*z* (*I*, %): 201 (38) [M$^+$], 184 (4), 170 (30), 144 (13), 126 (7), 112 (100), 97 (4), 89 (12), 83 (11), 69 (11), 58 (31).

*5,7-Diethyl-3-thioxooctahydroimidazo[4,5-*e*]-1,2,4-triazin-6-one* **2b**: yield 86–87%, mp 216–218 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.99 (t, 3H, Me, ^3J 7.3 Hz), 1.01 (t, 3H, Me, ^3J 7.3 Hz), 3.05 (m, 2H, CH_2), 3.14 (m, 2H, CH_2), 4.73 (dd, 1H, CH, ^3J 8.6 Hz, ^3J 1.8 Hz), 4.91 (dd, 1H, CH, ^3J 8.8 Hz, ^3J 2.4 Hz), 5.59 (d, 1H, CH–N*H*–C=S, ^3J 2.4 Hz), 8.67 (d, 1H, CH–N*H*–NH, ^3J 1.8 Hz), 9.38 (br. s, 1H, NH–N*H*–C=S).

*5,7-Dimethyl-4*a*,7*a*-diphenyl-3-thioxooctahydroimidazo[4,5-*e*]-1,2,4-triazin-6-one* **2c**: yield 95–96%, mp 252–253 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.55 (s, 3H, Me), 2.63 (s, 3H, Me), 6.67 (s, 1H, NH CH–NH–C=S), 6.82–6.91 (m, 2H, 2CH_{Ph}), 6.92–7.07 (m, 8H, 8CH_{Ph}), 9.03 (s, 1H, NH–CH–N*H*-NH), 9.89 (s, 1H, NH–N*H*–C=S).

‡ *Crystallographic data for* **2a**: the crystals of $C_6H_{16}N_2SO_4$ are monoclinic at 110 K, space group $P2_1/c$, $a = 7.3242(9)$, $b = 14.073(2)$ and $c = 9.083(1)$ Å, $\beta = 97.843(2)°$, $V = 957.5(2)$ Å^3, $Z = 4$, $M = 201.26$, $d_{calc} = 1.441$ g cm^{-3}, μ(MoKα) = 3.18 cm^{-1}, $F(000) = 424$. Intensities of 7113 reflections were measured with a Smart 1000 CCD diffractometer at 110 K [λ(MoKα) = 0.71072 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, $2\theta < 60°$], and 2663 independent reflections (R_{int} = = 0.0205) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to $wR_2 = 0.1196$ and GOF = = 1.043 for all independent reflections [$R_1 = 0.0447$ was calculated against F for 2218 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0 on IBM PC AT.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 217810. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

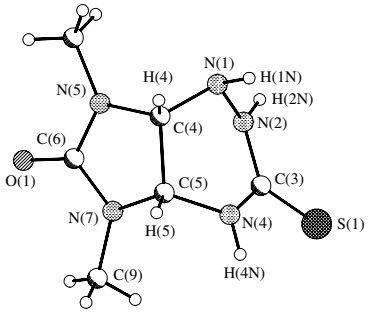


Figure 1 Molecular structure of compound **2a**. Selected bond lengths (Å): S(1)–C(3) 1.681(1), O(1)–C(6) 1.231(2), N(1)–N(2) 1.429(2), N(1)–C(4) 1.454(2), N(2)–C(3) 1.350(2), C(3)–N(4) 1.352(2), N(4)–C(5) 1.457(2), C(5)–N(7) 1.457(2), C(5)–C(4) 1.555(2), C(4)–N(5) 1.440(2), N(7)–C(6) 1.360(2), C(6)–N(5) 1.358(2); bond angles (°): N(2)–N(1)–C(4) 111.4(1), C(3)–N(2)–N(1) 119.9(1), N(2)–C(3)–N(4) 114.1(1), N(2)–C(3)–S(1) 122.2(1), N(4)–C(3)–S(1) 123.7(1), C(3)–N(4)–C(5) 120.6(1), N(7)–C(5)–N(4) 112.8(1), N(7)–C(5)–C(4) 102.7(1), N(4)–C(5)–C(4) 111.0(1), N(5)–C(4)–N(1) 112.4(1), N(5)–C(4)–C(5) 102.8(1), N(1)–C(4)–C(5) 113.3(1), C(6)–N(7)–C(9) 123.5(1), C(6)–N(7)–C(5) 111.8(1), C(9)–N(7)–C(5) 123.8(1), O(1)–C(6)–N(5) 125.6(1), O(1)–C(6)–N(7) 125.7(1), N(5)–C(6)–N(7) 108.7(1), C(6)–N(5)–C(4) 112.9(1), C(6)–N(5)–C(8) 124.1(1), C(4)–N(5)–C(8) 122.9(1).

to those of the 2,6-dialkyl derivatives of glycolurils.[12,13] The configuration of N(5) and N(7) atoms is planar; the sums of valence angles are 359.2 and 359.8°, respectively. The conformation of the five-membered ring represents an envelope with the deviation of the C(4) atom by 0.16 Å, whereas the conformation of the six-membered ring is a twist with the C(4) and C(5) atoms deviated from the N(1)–N(2)–C(3)–N(4) plane by 0.20 and –0.19 Å, respectively. The configuration of N(2) and N(4) atoms is flat; the sum of the angles is ~352.0°, whereas the configuration of the N(1) atom is pyramidal with the deviation from the H(1N)C(4)N(2) plane by 0.38 Å. Although the N(1) atom is a constituent of the hydrazine group, the N(2)–C(3) and C(3)–N(4) bond lengths are almost equal (Figure 1). The other bond lengths in the six-membered ring are close to expected values for this class of compounds. An analysis of crystal packing demonstrated that the intermolecular H-bonds N(1)–H(1N)···O(1) [N(1)···O(1) 2.845(2) Å] and N(2)–H(2N)···N(1) [N(2)···N(1) 2.997(2) Å], as well as the C(5)–H(5)···O(1) [C(5)···O(1) 3.135(2) Å] contact, join molecules into layers parallel to the plane *bc*. In turn, the intermolecular H-bonds with the C=S group {N(4)–H(4N)···S(1) [N(4)···S(1) 3.467(2) Å]} join the layers into a three-dimensional framework.

Thus, the study of the interaction of 4,5-dihydroxyimidazolidin-2-ones **1a**–**c** with thiosemicarbazide allowed us to find a new reaction, the annelation of a hexahydro-1,2,4-triazine ring to an imidazolidin-2-one ring to result in 5,7-disubstituted (as well as 5,7,4a,7a tetrasubstituted) 3-thioxooctahydroimidazo-[4,5-*e*]-1,2,4-triazin-6-ones **2**. This reaction is a new simple approach to the preparation of imidazo[4,5-*e*]-1,2,4-triazine derivatives.

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