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A new approach to the synthesis of 1,3-dimethyl-4,5-disubstituted imidazolidin-2-ones

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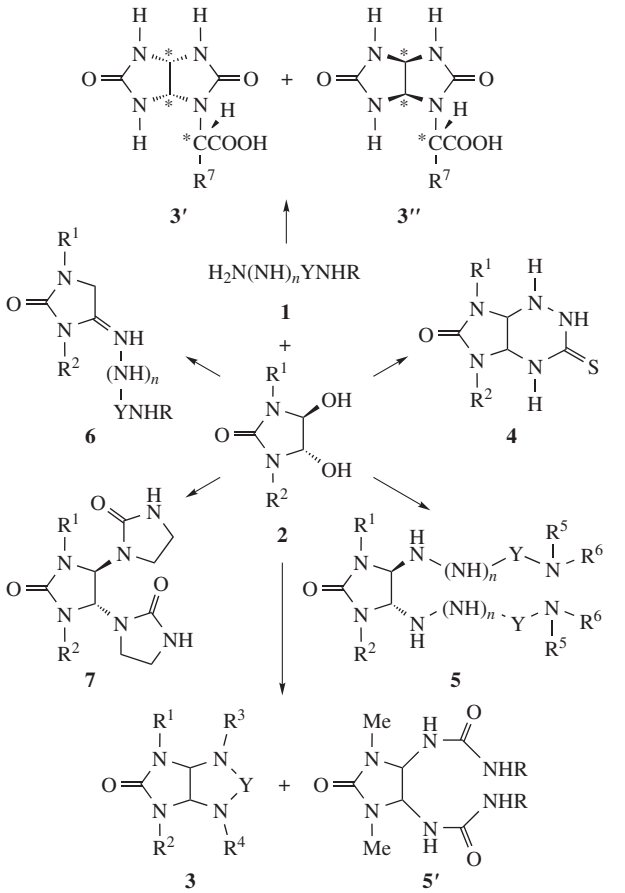
1,3-Dimethyl-4,5-di(ureido)-substituted imidazolidin-2-ones have been synthesised by the nitrosation of 1,3-dimethyl-4,5-di(3-ethylureido)imidazolidin-2-one followed by the reactions of amines with the resulting 1,3-dimethyl-4,5-di(3-nitroso-3-ethylureido)imidazolidin-2-one, and the structure of 1,3-dimethyl-4,5-di(3-ethylureido)imidazolidin-2-one has been confirmed by X-ray diffraction analysis.

The condensation of ureas and their analogues **1** [thioureas, sulfamides, guanidines, thiosemicarbazide and aminoguanidine hydrochloride, ureidoalcohols and ureidoacids, including (*S*) or (*R*)-*N*-α-carbamoylamino acids] with 4,5-dihydroxyimidazolidin-2-ones (DHI) **2** mostly results in glycolurils (2,4,6,8-tetraazabicyclo[3.3.0]octan-3,7-diones) and their analogues with predefined positions, number and type of substituents at the nitrogen atoms in compounds **3**,[1–17] including enantiomerically pure compounds **3′** and **3″**,[15–17] unknown representatives of imidazotriazine systems **4**,[18] 4,5-di[3-alkylureido(3-pyrimidinylureido-, 3,3-dialkylureido-, 3-aminoguanidino- or thiosemicarbazido)]imidazolidin-2-ones **5**[19] and compounds **6** with an imine bond (4-guanidinimino and 4,4′-sulfonyldiiminoimidazolidin-2-ones).[20] Similar reactions involving imidazolidin-2-one gave hitherto unknown ensembles of three imidazolidine rings **7**[21] (Scheme 1).

4,5-Disubstituted imidazolidin-2-ones **5** are obtained by the two-stage α-ureidoalkylation of various ureas, aminoguanidine hydrochloride and thiosemicarbazide using DHI **2** as ureidoalkylating reagents,[19] but the range of 4,5-di(3-alkylureido, 3,3-dialkylureido)imidazolidin-2-ones synthesised by this method is limited.[19(c)] However, the incorporation of two pharmacophoric moieties (namely, urea and imidazolidine moieties) into one molecule makes them potential biologically active compounds, since imidazolidin-2-one derivatives exhibit a directed effect on the central nervous system, as well as herbicidal and insecticidal activities.[22] Furthermore, compounds with conglomerate-forming properties were found among imidazolidin-2-one derivatives: DHI unsubstituted at nitrogen atoms,[2,19(a)] 4,5-dimethyl-4,5-di-(3-aminoguanidino)imidazolidin-2-one,[19(a)] 6-(5-methyl-2-oxa-4-imidazolidinyl)hexanoic acid[23] and *N*-(1,3-diethyl-5-hydroxy-2-oxo-4-imidazolidinyl)-*N*,*N*′-dimethylsulfamide;[24] hence the development of the synthesis of imidazolidin-2-one derivatives is of practical significance.

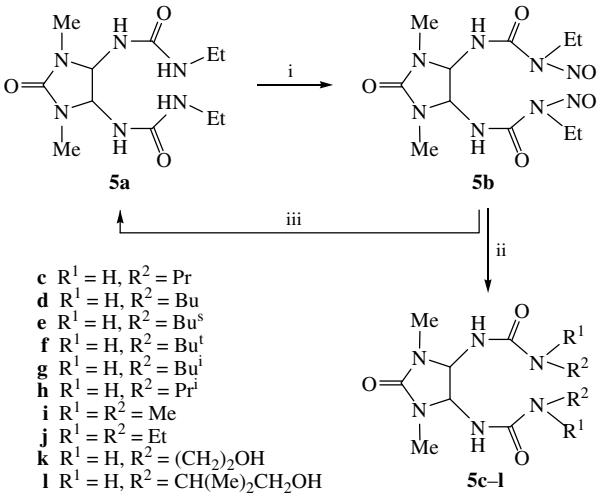
The aim of this study was to develop a new approach to the synthesis of a wide range of 4,5-di(3-alkylureido-3,3-dialkylureido)imidazolidin-2-ones.

Since known processes provide a limited number of 4,5-diureidoimidazolidin-2-one derivatives **5** and their yields are as low as 2–9%,[19(c)] another approach to their synthesis has been developed. The substituents in ureido moieties were modified in two stages: (i) nitrosylation of compound **5a** obtained by a reported procedure[19(c)] involving the α-ureidoalkylation of 1-ethylurea with 1,3-dimethyl-DHI **2a** followed by (ii) the reaction of resulting nitroso derivative **5b** with primary (propyl-, butyl-, *sec*-butyl-, *tert*-butyl-, isopropyl-, isobutyl-) and secondary (1,1-dimethyl- or 1,1-diethyl-) amines or aminoalcohols (2-hydroxyethyl- or 1,1-dimethyl-2-hydroxyethylamine). This approach



Scheme 1

allowed us to obtain compounds **5c–l** in 66–97% yields, including trisurea **5a** formed in the reaction of nitrosourea **5b** with ethylamine (Scheme 2). Compounds **5a–l** were characterised by their melting points and spectral parameters.†



Scheme 2 *Reagents and conditions*: i, H_2O, $NaNO_2$/[H^+], 0 °C, 15–20 min; ii, R^1NHR^2, H_2O, 10–15 °C, 40 min/room temperature, 3–12 h; iii, $EtNH_2$, H_2O, 10–15 °C, 40 min/room temperature, 3 h.

† All new compounds gave satisfactory elementary analyses. Their structures were confirmed by ^{1}H NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H NMR spectra). Chemical shifts were measured with reference to the residual protons of [$^2H_6$]DMSO as a solvent (δ 2.50 ppm). The mass spectra were measured on an MS 30 spectrometer.

Synthesis of 1,3-dimethyl-4,5-di(3-nitroso-3-ethylureido)imidazolidin-2-one **5b**. A mixture of concentrated H_2SO_4 (0.02 mol) with ice (6 g) was added with stirring to a cooled (0 °C) solution of 1,3-dimethyl-4,5-di-(3-ethylureido)imidazolidin-2-one **5a** (0.01 mol) and $NaNO_3$ (0.02 mol) in water (100 ml) at such a rate that the temperature of the reaction mixture did not exceed 0 °C. Once all the acid was added, the mixture was stirred for another 15–20 min. The precipitate of compound **5b** was filtered off, thoroughly washed with cold water (50 ml), dried and crystallised from MeOH.

General procedure for the synthesis of 1,3-dimethyl-4,5-di[3-alkyl-(hydroxyalkyl, 3,3'-dialkylureido)]imidazolidin-2-ones **5c–l**. An appropriate amine (ethyl-, propyl-, butyl-, *sec*-butyl-, *tert*-butyl-, isopropyl-, isobutyl-, 1,1-dimethyl-, 1,1-diethyl-, 2-hydroxyethyl- or 1,1-dimethyl-2-hydroxyethylamine) (0.12 mol) was slowly added dropwise to a suspension of nitroso derivative **5b** (0.04 mol) in water (100 ml) with stirring and cooling at 10–15 °C for 40 min. The mixture was kept at room temperature for 3–12 h until gas evolution ceased. The reaction mixtures were concentrated to dryness. The resulting precipitates of **5c–l** were recrystallised from MeOH.

1,3-Dimethyl-4,5-di(3-ethylureido)imidazolidin-2-one **5a**: yield 88% (6%[19(c)]), mp 215–217 °C. For ^{1}H NMR spectrum see ref. 19(c). MS, *m*/*z* (%): 199 (M^+ – 87, 20), 198 (66), 184 (10), 155 (35), 154 (71), 153 (66), 128 (57), 127 (100), 113 (70), 112 (45), 98 (43), 97 (52), 88 (32), 82 (36), 73 (37), 71 (57), 70 (88).

1,3-Dimethyl-4,5-di(3-nitroso-3-ethylureido)imidazolidin-2-one **5b**: yield 97%, mp 165–167 °C. ^{1}H NMR, δ: 0.99 (t, 6H, 2Me, *J* 7.2 Hz), 2.56 (s, 6H, 2N–Me), 3.03 (m, 4H, 2N–CH_2), 4.92 (d, 2H, 2CH, *J* 8.3 Hz), 6.66 (d, 2H, 2NH, *J* 8.3 Hz).

1,3-Dimethyl-4,5-di(3-propylureido)imidazolidin-2-one **5c**: yield 79% (4%[19(c)]), mp 198–200 °C. ^{1}H NMR, δ: 0.82 (t, 6H, 2Me, *J* 7.7 Hz), 1.36 (m, 4H, 2CH_2), 2.55 (s, 6H, 2N–Me), 2.95 (m, 4H, 2N–CH_2), 4.91 (d, 2H, 2CH, *J* 8.3 Hz), 6.00 (t, 2H, 2NH, *J* 5.5 Hz), 6.62 (d, 2H, 2NH, *J* 8.3 Hz).

1,3-Dimethyl-4,5-di(3-butylureido)imidazolidin-2-one **5d**: yield 78% (9%[19(c)]), mp 203–204 °C. ^{1}H NMR, δ: 0.87 (t, 6H, 2Me, *J* 7.4 Hz), 1.32 (m, 8H, 4CH_2), 2.56 (s, 6H, 2N–Me), 3.01 (m, 4H, 2N–CH_2), 4.91 (d, 2H, 2CH, *J* 8.8 Hz), 5.97 (t, 2H, 2NH, *J* 5.9 Hz), 6.62 (d, 2H, 2NH, *J* 8.8 Hz).

The crystallization of monocyclic trisureas **5a–l** from H_2O, MeOH, EtOH, Pr^iOH, $CHCl_3$ and various mixtures of these solvents showed that these compounds formed fine powders. A crystal for XRD could only be obtained for compound **5a** from EtOH. XRD showed that compound **5a** crystallised in *Pbca* centrosymmetric space group and was a racemate (Figure 1).‡

According to XRD of compound **5a**, the urea fragments in molecules are characterised by a transoid arrangement with the torsion angle N(3)C(1)C(2)N(5) equal to 110.7°. The bond lengths in the imidazolium ring and its conformation are governed mainly by the conjugation of the nitrogen lone electron pairs with the C=O group. Indeed, the ring has a flattened envelope conformation with the C(1) atom deviated by only 0.06 Å from the plane of the rest of the atoms. The configuration of the N(1) and N(2) atoms is almost planar with the sum of bond angles equal to 359.4°.

Although the molecule of compound **5a** is chiral due to a transoid arrangement of the substituents at the C(1) and C(2) atoms, it crystallises in a centrosymmetric group. The molecules in the crystal are assembled into double H-bonded chains with a hydrophobic coating (ethyl groups).

1,3-Dimethyl-4,5-di(3-sec-butylureido)imidazolidin-2-one **5e**: yield 81% (2%[19(c)]), mp 208–210 °C. ^{1}H NMR, δ: 0.80 (m, 6H, 2Me), 1.13 (m, 6H, 2Me), 1.45 (m, 4H, 2CH_2), 2.57 (s, 6H, 2NMe), 3.59 (m, 2H, 2CH), 4.87 (d, 2H, 2CH, *J* 8.6 Hz), 5.97 (m, 2H, 2NH), 6.64 (d, 2H, 2NH, *J* 8.6 Hz).

1,3-Dimethyl-4,5-di(3-tert-butylureido)imidazolidin-2-one **5f**: yield 95% (9%[19(c)]), mp 210–212 °C. ^{1}H NMR, δ: 1.21 (s, 18H, 2CMe_3), 2.48 (s, 6H, 2N–Me), 4.30 (d, 2H, 2CH, *J* 8.5 Hz), 5.75 (s, 2H, 2NH), 6.87 (d, 2H, 2NH, *J* 8.5 Hz).

1,3-Dimethyl-4,5-di(3-isobutylureido)imidazolidin-2-one **5g**: yield 84%, mp 237–238 °C. ^{1}H NMR, δ: 0.98 (br. d, 6H, 2Me), 2.57 (s, 6H, 2N–Me), 3.13 (m, 2H, 2CH), 3.72 (m, 4H, 2CH_2), 4.92 (d, 2H, 2CH, *J* 8.3 Hz), 5.97 (t, 2H, 2NH, *J* 5.0 Hz), 6.66 (d, 2H, 2NH, *J* 8.3 Hz).

1,3-Dimethyl-4,5-di(3-isopropylureido)imidazolidin-2-one **5h**: yield 86%, mp 225–227 °C. ^{1}H NMR, δ: 1.09 (d, 6H, 2Me, *J* 7.2 Hz), 2.56 (s, 6H, 2N–Me), 3.70 (m, 2H, 2CH), 4.90 (d, 2H, 2CH, *J* 8.3 Hz), 5.85 (d, 2H, 2NH, *J* 8.1 Hz), 6.50 (d, 2H, 2NH, *J* 8.3 Hz).

1,3-Dimethyl-4,5-di(3,3-dimethylureido)imidazolidin-2-one **5i**: yield 77% (20%[19(c)]), mp 220–221 °C. For ^{1}H NMR spectrum see ref. 19(*c*).

1,3-Dimethyl-4,5-di(3,3-diethylureido)imidazolidin-2-one **5j**: yield 69% (52%[19(c)]), mp 198–199 °C. For ^{1}H NMR spectrum see ref. 19(*c*). MS, *m*/*z* (%): 227 (M^+ – 115, 40), 226 (75), 155 (50), 154 (100), 153 (87), 128 (28), 127 (46), 113 (81), 112 (78), 100 (68), 97 (47), 82 (26), 73 (40), 72 (81), 70 (55).

1,3-Dimethyl-4,5-di[3-(2-hydroxyethyl)ureido]imidazolidin-2-one **5k**: yield 76%, mp 210–211 °C. ^{1}H NMR, δ: 2.56 (s, 6H, 2NMe), 3.10 [m, 8H, 2$(CH_2)_2$], 4.92 (d, 2H, 2CH, *J* 8.3 Hz), 6.07 (t, 2H, 2OH, *J* 5.0 Hz), 6.66 (d, 2H, 2NH, *J* 8.3 Hz).

1,3-Dimethyl-4,5-di[3-(1,1-dimethyl-2-hydroxyethylureido)]imidazolidin-2-one **5l**: yield 66%, mp 295–296 °C. ^{1}H NMR, δ: 1.19 (s, 6H, 2CMe), 2.56 (s, 6H, 2NMe), 3.35 (m, 2H, CH_2), 4.31 (br. d, 2H, 2NH), 4.97 (t, 2H, 2OH, *J* 5.0 Hz), 5.72 (s, 2H, CHCH), 6.70 (br. d, 2H, 2NH).

‡ *Crystallographic data*. Crystals of **5a** ($C_{11}H_{22}N_6O_3$, M = 286.35) are orthorhombic, space group *Pbca*, at 298 K: a = 11.946(2), b = 9.235(2) and c = 27.111(6) Å, V = 2990.9(10) Å^3, Z = 8 (Z' = 1), d_{calc} = 1.272 g cm^{-3}, μ(MoKα) = 0.95 cm^{-1}, F(000) = 1232. The intensities of 12406 reflections were measured with a SMART 1000 CCD diffractometer [λ(MoKα) = = 0.71072 Å, ω-scans, $2\theta < 56°$] and 3525 independent reflections (R_{int} = = 0.0316) were used in the further refinement. The hydrogen atoms of amino groups were located from the Fourier density synthesis, while the positions of all the other atoms were calculated geometrically. The structure was solved by the direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. For compound **1**, the refinement converged to wR_2 = 0.0936 and GOF = 1.066 for all independent reflections [R_1 = 0.0492 was calculated against F for 1722 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

CCDC 671212 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, 2008.

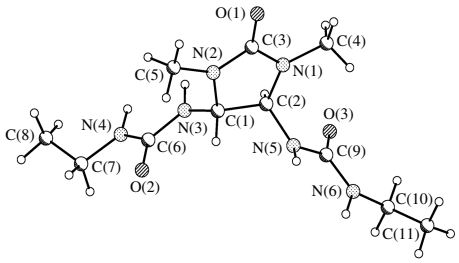


Figure 1 General view of molecule **5a**. Selected bond lengths (Å): O(1)–C(3) 1.234(2), N(1)–C(3) 1.356(3), N(1)–C(4) 1.448(3), N(1)–C(2) 1.456(3), C(1)–N(3) 1.432(2), C(1)–N(2) 1.456(3), O(3)–C(9) 1.233(2), N(3)–C(6) 1.366(2), N(4)–C(6) 1.339(3), N(4)–C(7) 1.461(3), N(5)–C(9) 1.381(2), N(6)–C(9) 1.341(3), N(6)–C(10) 1.450(3); bond angles (°): C(3)–N(1)–C(4) 123.57(18), C(3)–N(1)–C(2) 113.23(16), C(4)–N(1)–C(2) 122.60(17), N(3)–C(1)–N(2) 114.21(16), C(3)–N(2)–C(5) 124.48(19), C(3)–N(2)–C(1) 113.29(17), C(5)–N(2)–C(1) 121.62(18), C(6)–N(3)–C(1) 123.48(15), C(6)–N(4)–C(7) 122.8(2), C(9)–N(5)–C(2) 119.95(15), C(9)–N(6)–C(10) 121.58(17).

Thus, a new approach to the synthesis of 1,3-dimethyl-4,5-di[3-alkylureido-, 3,3-dialkylureido-, 3-(2-hydroxyethyl)-ureido- or (1,1-dimethyl-2-hydroxyethyl)ureido]imidazolidin-2-ones has been elaborated based on the nitrosation of 1,3-dimethyl-4,5-di(3-ethylureido)imidazolidin-2-one followed by reactions of 1,3-dimethyl-4,5-di(3-nitroso-3-ethylureido)imidazolidin-2-one with amines. The structures of the target 4,5-disubstituted imidazolidin-2-ones were confirmed by ^{1}H NMR and mass-spectrometric data, as well as by X-ray diffraction analysis in the case of compound **5a**.

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