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HNO_2-assisted triazine cycle contraction in 3-oxo-, 3-thioxo- and 3-imino-5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones

Angelina N. Kravchenko,*[a] Galina A. Gazieva,[a] Sergei V. Vasilevskii,[a] Pavel A. Belyakov[a] and Yulia V. Nelyubina[b]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: kani@server.ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5085; e-mail: unelya@xrlab.ineos.ac.ru*

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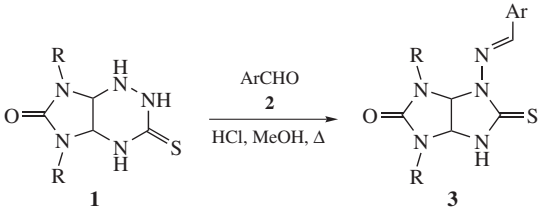
Treatment of 3-oxo-, 3-thioxo- and 3-imino-5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones with $NaNO_2$ in the presence of AcOH caused contraction of the perhydrotriazine cycle to the imidazolidine one. The products were transformed into glycolurils and their analogues.

A triazine cycle is known to reduce to an imidazolidine one on impact of benzaldehyde.[1] We have recently demonstrated that imidazotriazines **1** in reactions with aromatic aldehydes **2** transform to *N*-benzylidenamino-5-thioxohexahydroimidazo[4,5-*d*]-imidazol-2(1*H*)-ones (thioglycolurils) **3** (Scheme 1).[2,3]



1 **3**

Scheme 1

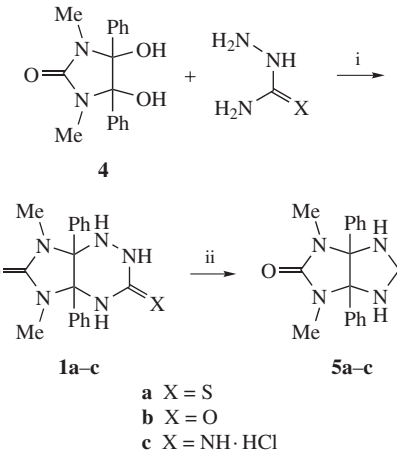
This research unexpectedly revealed a similar process while examining nitrosation of 3-thioxo-, 3-oxo- and 3-iminoimidazo-[4,5-*e*][1,2,4]trazin-6-ones **1a–c**, although initially we aimed to introduce a nitroso group at triazine nitrogen atoms.[4]

We examined a reaction between imidazotriazines **1a–c** and sodium nitrite in acids using the classic nitrosation procedure.[5] The starting compounds **1a–c** were synthesized by our original procedure through α-ureidoalkylation of thiosemicarbazide, semicarbazide and aminoguanidine hydrochloride, respectively, with 4,5-dihydroxy-1,3-dimethyl-4,5-diphenylimidazolidin-2-one (DHI) **4**[6] (Scheme 2).

The first tests were run for imidazotriazine **1a** using sodium nitrite, 10% hydrochloric acid or glacial AcOH. Instead of the anticipated *N*-nitroso derivative of imidazotriazine **1a**, the final product appeared to be unknown thioglycoluril **5a**, which apparently originated from the triazine cycle contraction to the imidazolidine one. The yields of thioglycoluril **5a** were 93% (AcOH) and 70% (aqueous HCl).

In order to expand the scope of the discovered reaction, we subjected 3-oxo- and 3-imino-5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*][1,2,4]triazin-6-ones **1b**,**c** to analogous transformations and obtained glycoluril **5b** (yield 89%) described in literature[7–9] (the yield was not reported) and new iminoglycoluril **5c** (yield 85%), respectively.

Based on the classic mechanism of N-nitrosation, we suggested a probable mechanism for **1** → **5** transformation (Scheme 3). First,



4

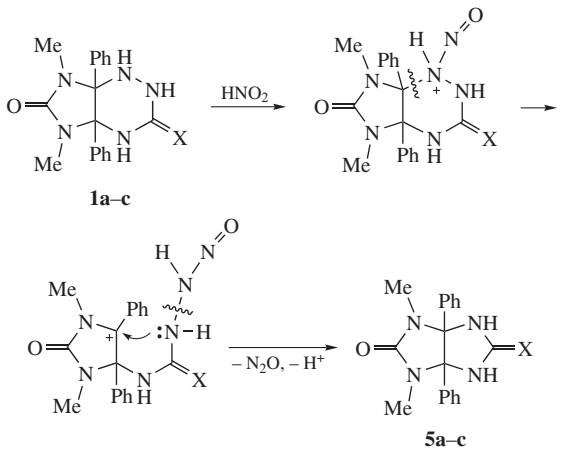
1a–c **5a–c**

a X = S
b X = O
c X = NH · HCl

Scheme 2 *Reagents and conditions*: i, MeOH, HCl, ii, $NaNO_2$, AcOH, room temperature, 2 h or $NaNO_2$, 10% HCl, room temperature, 2 h.

N(1)H nitrosation occurred, next, cleavage of N(1)–C(7a) bond took place, and finally, the new intermediate cyclized with the N_2O release.

To verify the structures of compounds **5** we attempted to performe their independent syntheses by DHI α-ureidoalkyla-



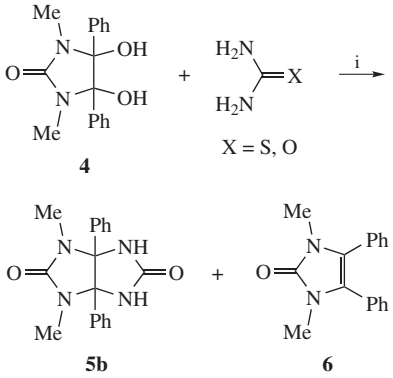
1a–c

5a–c

Scheme 3

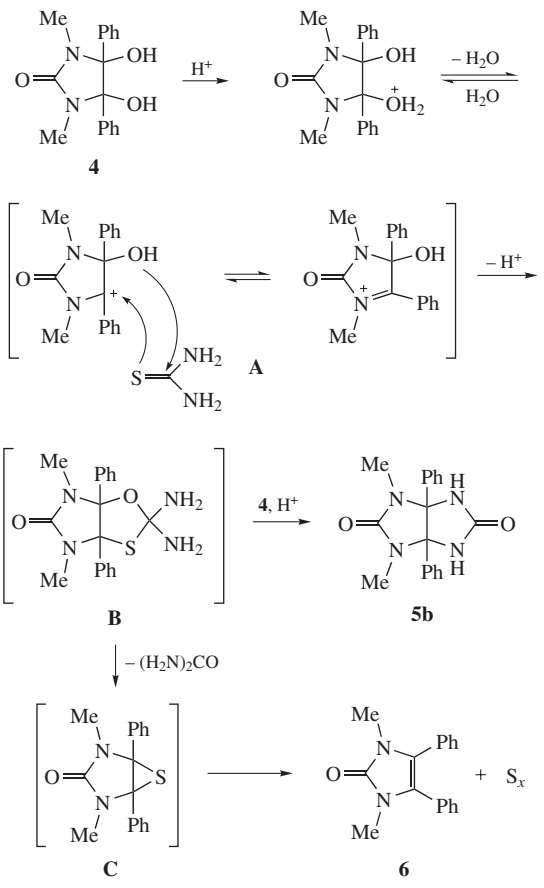
tion of the corresponding substrates under the acidic catalytic conditions, similarly to the known synthesis of compound **5b**.[7] As for compound **5c**, aminoguanidine hydrochloride did not react with DHI **4**.

Reactions of DHI **4** with either urea or thiourea in boiling MeOH for 30 min appeared to give the same product – glycoluril **5b** in 85% and 79% yields, respectively (Scheme 4). The yield of compound **5b** prepared by nitrosation was higher (93%). The second reaction product was 1,3-dimethyl-4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one **6**.[10] It was absolutely unpredictable that the DHI **4** reaction with thiourea would produce glycoluril **5b**. Furthermore, in the test experiment when thioglycoluril **5a** was subjected to the reaction conditions (see Scheme 4) no replacement of sulfur with oxygen occurred.



Scheme 4 *Reagents and conditions*: i, MeOH, HCl, reflux, 30 min.

On the basis of our experimental data and in terms of the classic understanding of the acid-catalyzed α-amidoalkylation mechanism,[11,12] the mechanism proposed by Butler,[13] and communications on processes of the thiirane building and destruction,[14,15] we suggest that acid-promoted condensation of DHI **4** with thiourea (Scheme 5) produces the carbenium-iminium ion **A** (shown as two resonance structures), which in turn traps thiourea molecule by the sulfur atom to form intermediate **B**. This intermediate can interact with the second molecule of DHI to afford a bicyclic product (**5b**) and intermediate (**C**) which on loss of elemental sulfur yields imidazolone **6**.



Scheme 5

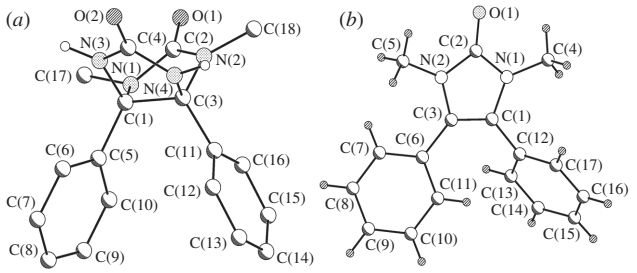


Figure 1 General views of compounds (*a*) **5b** and (*b*) **6**. The hydrogen atoms of the molecule **5b**, except for those of the NH groups, are omitted for clarity.

The structures of compounds **5a–c** and **6** were confirmed by elemental analysis and ^{1}H and ^{13}C NMR spectroscopy.† Structures of **5b** and **6** were ultimately established by X-ray diffraction.‡ As signals from NH group protons are not visible in the ^{1}H NMR

† 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). Melting points were determined with a GALLENKAMP instrument (Sanyo). Commercial compounds (benzil, 1,3-dimethylurea, and semicarbazide hydrochloride) supplied by ACROS and thiosemicarbazide, dihydrate of aminoguanidine hydrochloride (IREA) were used in the syntheses. The solvents were used as purchased. Starting DHI **4** was synthesized by analogy with the procedure for the benzil condensation with 1,3-dimethylurea.[16]

Compounds **5a–c** *(general procedure)*. Sodium nitrite (0.28 g, 4 mmol) was added portionwise to the suspension of 5,7-dimethyl-4a,7a-diphenylperhydroimidazo[4,5-*e*][1,2,4]triazine-3,6-dione **1a** (4 mmol) or its thio or imino analogue **1b**,**c** in glacial AcOH (30 ml) at room temperature, and the mixture was stirred for 2 h. The precipitate formed was filtered off, washed with AcOH and water to afford products **5a–c**.

All compounds **5a–c** gave satisfactory elemental analysis data.

For **5a**: yield 93%, mp 336–338 °C (AcOH). ^{1}H NMR, δ: 2.61 (s, 6H, MeN), 6.82–7.19 (m, 10H, 2Ph), 9.96 (s, 2H, NH). ^{13}C {^{1}H} NMR, δ: 26.8 (NMe), 87.5 (*C*Ph), 127.1 (Ph), 127.9 (Ph), 128.4 (Ph), 133.9 (Ph), 158.5 (C=O), 183.1 (C=S).

For **5b**: yield 89%, mp 324–326 °C (AcOH). ^{1}H NMR, δ: 2.56 (s, 6H, MeN), 6.91–7.21 (m, 10H, 2Ph), 8.31 (s, 2H, NH). ^{13}C {^{1}H} NMR, δ: 26.2 (NMe), 83.7 (*C*Ph), 127.3 (Ph), 127.7 (Ph), 128.2 (Ph), 135.3 (Ph), 159.0 (C=O), 160.1 (C=O).

For **5c**: yield 85%, mp 332–334 °C (AcOH). ^{1}H NMR, δ: 2.69 (s, 6H, MeN), 6.92–7.23 (m, 10H, 2Ph). ^{13}C {^{1}H} NMR, δ: 27.0 (NMe), 87.3 (*C*Ph), 127.2 (Ph), 128.1 (Ph), 128.7 (Ph), 133.6 (Ph), 158.3 (C=O), 159.1 (C=NH). LS/MS, *m*/*z*: 322.1 $[M+H]^+$ ($C_{36}H_{30}N_6O_3S$).

Parallel syntheses of 2,4-dimethyl-1,5-diphenylglycoluril **5b** *by α-ureidoalkylation of urea and thiourea using DHI* **4**. Procedure A: MeOH (10 ml) was poured to the mixture of DHI **4** (0.7 g, 2.34 mmol) and urea (0.14 g, 2.34 mmol). One drop of conc. HCl was added, and the mixture was boiled for 0.5 h. Precipitation started after 20 min of boiling, and the boiling was continued for more 10 min, and then cooled. The precipitate was filtered off and washed with methanol to produce 0.64 g (85%) of **5b**, white crystals, mp 324–326 °C (MeOH).

Procedure B: MeOH (25 ml) was poured to the mixture of DHI **4** (1.19 g, 4 mmol) and thiourea (0.3 g, 4 mmol). Two drops of conc. HCl were added, the mixture was boiled for 1 h, and then cooled. The precipitate was filtered off and washed with methanol. Yield of **5b**, 1.01 g (79%), white crystals, mp 324–326 °C (MeOH). The filtrate was kept for 2 days. The crystals that formed were filtered off to give 0.13 g (12%) of 1,3-dimethyl-4,5-diphenyl-1,3-dihydro-2*H*-imidazol-2-one **6**, mp 184–186 °C (MeOH) (lit.,[10] 185–187 °C).

spectrum of **5c** (Y = $^{+}NH_2Cl^{-}$), an LC/MS analysis was performed that confirmed a presence of the molecular ion with *m*/*z* 322.1.

According to the X-ray data, compound **5b** [Figure 1(*a*)] crystallizes in a centrosymmetric space group *Pbca*. The imidazolidine cycles in this bicyclic system have an envelope conformation with the atoms C(1) and C(3) deviated by 0.43(1) and 0.41(1) Å in dimethyl-substituted and NH containing fragments, respectively; the angle between their mean planes being 71.8(2)°. The pseudotorsion angle C(5)C(1)C(3)C(11) is equal to 26.3(2)°; the angle between the phenyl rings is 46.9(2)°.

In a crystal of **5b**, the molecules are held together by N(3)–H···O(2) and N(4)–H···O(1) hydrogen bonds of intermediate strength [N···O 2.804(2) and 2.867(2) Å, ∠NHO 176(1) and 160(1)°]. The resulting H-bonded chains are assembled in a 3D framework by various weak interactions of C–H···O and C–H···π types.

Compound **6** has already been described in literature;[10] however, no X-ray diffraction data for it were available to date. The imidazolone cycle in **6** [Figure 1(*b*)] is planar (within 0.01 Å). The torsion angle C(6)C(3)C(1)C(12) that characterizes the mutual disposition of phenyl substituents in **6** is 3.8(3)°, with the angle between their mean planes being 66.0(3)°. As the molecule lacks any convenient proton donors, in a crystal it forms weak C–H···O and C–H···π contacts only.

In summary, the herein discovered contraction of the perhydrotriazine cycle in 3-oxo-, 3-thioxo- and 3-iminoperhydroimidazo-[4,5-*e*][1,2,4]triazin-6-ones to the imidazolidine cycle may serve as a new synthetic pathway to prepare glycolurils and their analogues, which may promote their wider use in medicinal chemistry and related areas.

‡ *Crystallographic data*.

Crystals of **5b** ($C_{18}H_{18}N_4O_2$, M = 322.36) are orthorhombic, space group *Pbca*, at 120 K: a = 16.405(5), b = 11.891(4) and c = 16.595(5) Å, V = = 3237.2(17) Å^3, Z = 8 (Z' = 1), d_{calc} = 1.323 g cm^{-3}, μ(MoKα) = 0.89 cm^{-1}, F(000) = 1360.

Crystals of **6** ($C_{17}H_{16}N_2O$, M = 264.32) are monoclinic, space group $P2_1/n$, at 120 K: a = 5.9478(6), b = 16.7752(18) and c = 13.4216(14) Å, β = 90.408(2)°, V = 1339.1(2) Å^3, Z = 4 (Z' = 1), d_{calc} = 1.311 g cm^{-3}, μ(MoKα) = 0.83 cm^{-1}, F(000) = 560.

Intensities of 16375 and 14537 reflections for **5b** and **6**, respectively, were measured with a Bruker SMART 1000 CCD diffractometer [λ(MoKα) = = 0.71072 Å, ω-scans, $2\theta < 58°$]. Then 3873 and 3553 independent reflections [R_{int} = 0.0476 for **5b** and 0.0468 for **6**] were used in further refinement. The structures were solved by the direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms of NH groups in **5b** were located from the Fourier density synthesis. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation within riding model. For **5b**, the refinement converged to wR_2 = 0.1432 and GOF = 1.001 for all the independent reflections [R_1 = 0.0541 was calculated against F for 2101 observed reflections with $I > 2\sigma(I)$]. For **6**, the refinement converged to wR_2 = 0.1043 and GOF = 1.002 for all the independent reflections [R_1 = 0.0428 was calculated against F for 2203 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[17]

CCDC 907773 and 907774 contain 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, 2012.

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