



## Regioselective synthesis of 2,8-disubstituted 1,5-diphenylglycolurils

Vladimir V. Baranov,<sup>a</sup> Maria M. Antonova,<sup>a</sup> Yulia V. Nelyubina,<sup>b</sup> Natal'ya G. Kolotyrkina,<sup>a</sup> Igor E. Zanin,<sup>c</sup> Angelina N. Kravchenko<sup>\*a</sup> and Nina N. Makhova<sup>a</sup>

<sup>a</sup> 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

<sup>b</sup> 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

<sup>c</sup> Voronezh State University, 394000 Voronezh, Russian Federation. Fax: +7 473 220 8755; e-mail: iezan@mail.ru

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A new synthetic approach to 2,8-disubstituted 1,5-diphenylglycolurils is based on condensation of 1-(hydroxyalkyl)ureas (ureido alcohols) with tetrahydroimidazooxazolone and tetrahydroimidazooxazinone derivatives which were unexpectedly obtained by acidcatalyzed reaction of ureido alcohols with benzil. An X-ray diffraction study of the supramolecular organization of the obtained compounds revealed the chirality of the crystals of achiral glycoluril molecules.

Glycolurils are used as psychotropic agents,<sup>1–3</sup> anion-binding receptors<sup>4</sup> and molecular capsules.<sup>5</sup> In recent years, 2,8-disubstituted glycolurils attract attention as molecular templates for intramolecular Claisen-type condensations<sup>6</sup> and promising substrates in combinatorial<sup>7</sup> and supramolecular<sup>8</sup> chemistry. The fact of chirality generation from achiral glycoluril molecules was revealed in the study of supramolecular organization in the solid state of three representatives of 2,8-disubstituted 1,5-diarylglycol-urils.<sup>9</sup> Self-organization of molecules is of great importance for the understanding of biological processes.<sup>10</sup>

Condensation of monosubstituted ureas with benzil is the principal access to 2,8-disubstituted 1,5-diphenylglycolurils,<sup>11–13</sup> however, only 1-methyl- and 1-benzylureas<sup>11,13</sup> and *N*-carbamoylglycine benzyl ester<sup>12</sup> were previously used. These reactions occur regioselectively giving along with the major 2,8-disubstituted glycolurils **1** minor 2,6-disubstituted glycolurils. Here *N*-hydroxy-alkylureas (ureido alcohols) have not been tested. It seems reasonable to attach hydroxyalkyl groups at the glycoluril nitrogen atoms since this may facilitate intermolecular hydrogen bonding and thus affect ordering of the molecules in the crystal.

To prepare 2,8-di(hydroxyalkyl)-1,5-diphenylglycolurils, we performed the reaction between benzil **2** and ureido alcohols **3a–c**. First, the previously known<sup>11–13</sup> conditions were tested, but reaction did not occur upon refluxing for 12 h in benzene with trifluoroacetic acid.

Carrying out the process in alcohols led to unexpected results. Condensation of compounds **3a**–c with benzil in MeOH proceeded selectively to predominantly give hitherto unknown methyl ethers of tetrahydroimidazooxazolone **4** and tetrahydroimidazooxazinones **5**,**6** in 38, 66 and 61% yields, respectively (Scheme 1).<sup>†</sup> The expected glycolurils **1a**,**b** were obtained in low yields (14 and 5%, respectively).

The synthesis of compounds **4–6** by one-step procedure seems to be a new easy method totally different from published data.<sup>14–17</sup>



Scheme 1 Reagents and conditions: i, MeOH, HCl, reflux, 2 h; ii, Pr<sup>i</sup>OH, HCl, reflux, 2 h; iii, DMSO, heating to a boil, 5 min.

<sup>1</sup>H and <sup>13</sup>C NMR spectra of each structure **4–6** exhibit only one set of signals which means that the reaction is highly diastereoselective. According to X-ray diffraction (XRD) data, the phenyl groups in compounds **4–6** are *trans*-oriented to the imidazolidine ring, while the asymmetric carbon atoms have  $7R^*,7aR^*$  or  $8R^*,8aR^*$ -configuration in bicyclic compounds **4,5**, or  $3R^*,8R^*$ ,  $8aR^*$ -configuration in compound **6**. The homogeneity of compounds **4,5** was confirmed by powder XRD.

The condensation of ureido alcohol **3a** with benzil in Pr<sup>i</sup>OH under the same conditions proceeded regioselectivly to afford glycoluril **1a** in 68% yield, whereas the reaction of compounds **3b,c** gave only hitherto unreported tetrahydroimidazooxazinones **7b,c** in 63 and 65% yields, respectively. <sup>1</sup>H and <sup>13</sup>C NMR study showed that compound **7b** is formed as a single diastereomer similar to methyl ether **5**. XRD studies of crystals **7b** confirm that the phenyl groups have *trans* orientation with respect to the imidazoline ring. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **7c** with three chiral centers contain doubled signals of NH protons (two singlets at  $\delta$  8.19 and 8.26 ppm) and broadened singlets of OH protons ( $\delta$  5.72 and 6.62 ppm), indicating that this compound is formed as two diastereomers.

<sup>&</sup>lt;sup>†</sup> Ureido alcohols **3a–c** were obtained by N-carbamoylation of amino alcohols as described;<sup>20,21</sup> compound **3c** was previously unknown.

For synthetic procedures and characteristics of compounds **1a–c**, **3a–c**, **4–6**, **7a–c**, **8b,c**, **9** and **10** as well as crystal data for compounds **1a,b**, **4–6**, **7b**, see Online Supplementary Materials.

CCDC 967848–967853 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.



When compounds **7b**,**c** are heated to the boiling point of DMSO- $d_6$  in NMR tubes, the signals of OH protons at C(7) at  $\delta$  5.89–5.97 ppm (**7b**) or at C(8) at  $\delta$  5.72–6.48 ppm (**7c**) and the signals of NH in **7b** (s,  $\delta$  8.05 ppm) and **7c** (2s from the diastereomers at  $\delta$  8.19 and 8.26 ppm) disappear and signals of dihydroimidazooxazinones **8b**,**c** (Scheme 1) appear. We failed to isolate compounds **8b**,**c** since they revert to the original **7b**,**c** at room temperature. Compounds **8b**,**c** were characterized by <sup>1</sup>H

and <sup>13</sup>C NMR spectra (see Online Supplementary Materials). The results obtained suggest the following key stages of the processes (Scheme 2). Evidently, benzil 2 and ureido alcohols 3 give first intermediates 10, which cyclize into bicyclic systems 7 being in equilibrium with their dehydration products 8. One can expect that in acid medium, intermediates 7 and 8 would generate carbonium ions which can then react both with methanol to give compounds 4–6 and with ureido alcohols to provide the desired glycolurils 1.

Oxazolone **7a** was synthesized from compound **9** under the action of HNO<sub>3</sub>. Oxazoline **9** was prepared by condensation of ureido alcohol **3a** with benzoin **11**.<sup>18</sup> Depending on the amount of HNO<sub>3</sub> used, compound **9** can transform into either product **10** (2 equiv. HNO<sub>3</sub>) or **7a** (diastereomeric mixture, 4 equiv. HNO<sub>3</sub>) (Scheme 3,<sup>†</sup> *cf.* ref. 19).

To accomplish synthesis of 2,8-di(hydroxyalkyl)-1,5-diphenylglycolurils, we performed reactions between compounds  $7\mathbf{a}-\mathbf{c}$  and  $3\mathbf{a},\mathbf{b}$  by refluxing in alcohols (Pr<sup>i</sup>OH for  $7\mathbf{a}$ , MeOH for  $7\mathbf{b}$ , or both in Pr<sup>i</sup>OH and MeOH for  $7\mathbf{c}$ ). Symmetric glycoluril  $1\mathbf{a}$  was obtained in the highest yield (93%) by refluxing the mixture of compounds  $3\mathbf{a}$  and  $7\mathbf{a}$  for 20 min. Nonsymmetric glycoluryl  $1\mathbf{c}$ was prepared from compounds  $3\mathbf{b}$  and  $7\mathbf{a}$  in 8 h (41% yield).



Scheme 3 Reagents and conditions: i, (CH<sub>2</sub>OH)<sub>2</sub>, 160 °C, 1 h; ii, MeCN, 2 equiv. HNO<sub>3</sub>, 5 min; iii, MeCN, 4 equiv. HNO<sub>3</sub>, 5 min.

Along with glycoluril **1c**, bicyclic product **7b** was unexpectedly isolated. Glycolurils **1b** (69% yield) and **1c** (90% yield) were also obtained in the condensation of compound **7b** with ureido alcohols **3b** and **3a**, respectively, by refluxing of suspensions of the reactants in methanol in the presence of hydrochloric acid (Scheme 4).

The chemistry herein performed is a new approach to previously inaccessible 2,8-di(hydroxyalkyl)glycoluril derivatives. Note that the reaction is fully regioselective giving no isomeric 2,6-derivatives.

The supramolecular organization in the solid state of glycolurils 1a,b is of intense interest. According to XRD, glycolurils 1a,b are severely twisted about the bridgehead dihedral angle, which is  $18.9(1)^{\circ}$  and  $25.0(1)^{\circ}$ , so the resulting crystal structure may be described as consisting of two chiral enantiomers (space groups  $P2_1/n$  and  $P\overline{1}$ ; Figure 1). Other geometric parameters are also similar, expect for those related to  $(CH_2)_nOH$  groups. They both are characterized by a cisoid arrangement of phenyl substituents [the angle C(5)C(1)C(3)C(11) equals to  $18.9(1)-25.3(1)^{\circ}$ ], an envelope conformation of imidazole moieties [with the atom C(3) deviated by 0.31(1)-0.39(1) Å and the angle between the mean planes being 107.8(1)-112.4(1)°], and a cisoid disposition of hydroxyalkyl groups [the respective pseudo-torsion angle CNNC is 7.9(1)-15.2(1)°]. However, the latter groups have significantly different conformations: they are both anti in 1a but gauche-anti and gauche-gauche in 1b. The gauche-gauche conformation of the second hydroxypropyl chain in 1b is stabilized by an intramolecular H-bond with one of the C=O groups [O-O 2.6912(12) Å, ∠OHO 170(1)°].



Scheme 4 Reagents and conditions: i (for 7a), 3a, Pr<sup>i</sup>OH, HCl, reflux, 20 min; ii (for 7a), 3b, Pr<sup>i</sup>OH, HCl, reflux, 8 h; iii (for 7b), 3b, MeOH, HCl, reflux, 8 h; iv (for 7b), 3a, MeOH, HCl, reflux, 8 h.



Figure 1 Molecular structures of compounds 1a,b in representation of atoms *via* thermal ellipsoids at 50% probability level.

As a result of these differences, the molecules of **1a** and **1b** pack differently in crystals. In **1a**, intermolecular N–H···O(hydroxyl) bonds [N···O 2.851(2) and 2.877(2) Å,  $\angle$ NHO 168(1)° and 175(1)°] assemble the glycoluril species into chiral tapes, which are held together by O–H···O=C bonds [O···O 2.659(2) and 2.771(2) Å,  $\angle$ OHO 159(1)° and 166(1)°] in such a manner as to form centrosymmetric dimers of neighboring molecules from different tapes. In **1b**, however, intermolecular N–H···O(hydroxyl) bonds [N···O 2.8359(14) and 2.9260(13) Å,  $\angle$ NHO 169(1)° and 165(1)°] results in double chains of centrosymmetrically bonded glycoluril species; these are assembled by O–H···O=C bond [O···O 2.7012(13) Å,  $\angle$ OHO 167(1)°] into corrugated layers. In both cases, the 3D framework is completed through numerous weaker interactions, which include, among others, C–H···O, C–H···π and H···H contacts.

The homogeneity of compounds **1a**,**b** was confirmed by powder XRD (see Table S1, Figures S1,S2, Online Supplementary Materials).

The other four bicycles X-rayed (**4–6** and **7b**) have molecular geometry with the expected differences governed by the nature of a substituent R and the value of *n* (see Scheme 1); the differences in their crystal packing mainly results from co-crystallization of **6** and **7b** with solvate molecules of acetonitrile and DMSO, respectively (Figure S5, Table S2). Note that in the crystal of **6** there are two symmetry independent species of the product having opposite configurations – *R*,*R*,*R* and *S*,*S*,*S*. Compounds **4**, **5** and **7b** also crystallize as all-*S*,*S* and all-*R*,*R* isomers, both present in the centrosymmetric space groups  $P\bar{1}$ ,  $P2_1/c$  and C2/c.

All having a diphenylimidazole fragment in common, they are characterized by a transoid arrangement of phenyl substituents [the angle C(6)C(4)C(5)C(12) is  $89.4(1)-96.0(1)^{\circ}$ ] and an envelope conformation of imidazole moieties [with the atom C(4) deviated by 0.34(1)-0.47(1) Å]. The conformations of the oxazole rings with n = 0 (4) and n = 1 (5, 6 and 7b) are envelope [with the atom C(4) deviated by 0.54(1) Å] and chair [with the atoms C(18) and N(3) deviated by 0.66(1)-0.68(1) and 0.55(1)-0.56(1) Å], respectively.

The major supramolecular motif in the crystals of these four bicycles is a centrosymmetric dimer formed by N–H···O bonds that is observed [N···O 2.8538(11)–2.903(2) Å,  $\angle$ NHO 173(1)°– 177(1)°] in **4**, **5** and **7b**. In the latter cases, these dimers are also supplemented by two solvate DMSO molecules through O–H···O bonds [O···O 2.6848(18) Å,  $\angle$ NHO 172(1)°]. In the crystal **6**, containing two symmetry independent bicycle species and a solvate acetonitrile molecule, the H-bonded associates are chiral chains formed by each independent bicycle molecule separately through N–H···O bonding [N···O 2.862(3) and 2.902(3) Å,  $\angle$ NHO 161(1)° and 174(1)°], which are then combined together to

form double chains through O–H···O bonds [O···O 2.719(2) and 2.725(2) Å,  $\angle$ NHO 167(1) and 171(1)°]. The overall centrosymmetric packing of **6** results from weak intermolecular interactions. The latter include, among others, C–H···O, C–H··· $\pi$  and S··· $\pi$  contacts. In the case of the bicycles **4** and **5** geometrical criteria allow distinguishing C–H···O, C–H··· $\pi$  and H···H contacts and additional contacts C–H···N with acetonitrile molecules in **6**.

In conclusion, the condensation of ureido alcohols **3a–c** with benzil **2** affords new tetrahydroimidazooxazolone **7a** and tetrahydroimidazooxazinones **7b,c**, whose reaction with ureido alcohols result in 2,8-bis(hydroxyalkyl)glycolurils. It has been found that chirality is generated in the crystals of non-chiral compounds **1a,b**.

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## **Online Supplementary Materials**

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2014.04.017.

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