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Single-stage synthesis of 3-hydroxy- and 3-alkoxy-5-arylimidazolidine-2,4-diones by reaction of arylglyoxal hydrates with *N*-hydroxy- and *N*-alkoxyureas

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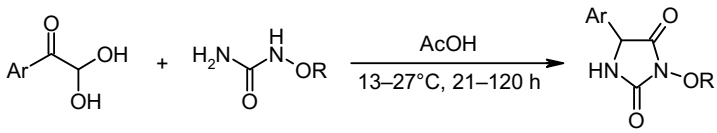


Ar = Ph, 4-XC_6H_4 (X = Cl, Br, F, Me, OMe), 2-thienyl; R = H, Me, Et, Bu

Arylglyoxal hydrates interact with *N*-alkoxyureas and *N*-hydroxyurea in acetic acid with selective formation of 3-alkoxy-5-aryl-imidazolidine-2,4-diones and 5-aryl-3-hydroxyimidazolidine-2,4-diones, respectively. The structures of 3-methoxy-5-phenyl-imidazolidine-2,4-dione, 3-ethoxy-5-phenylimidazolidine-2,4-dione, and 3-butoxy-5-(4-chlorophenyl)imidazolidine-2,4-dione were studied by X-ray structural analysis.

Keywords: 3-alkoxy-5-arylimidazolidine-2,4-diones, *N*-alkoxyureas, arylglyoxals, 5-aryl-3-hydroxyimidazolidine-2,4-diones, *N*-hydroxy-urea, cyclization, X-ray structural analysis.

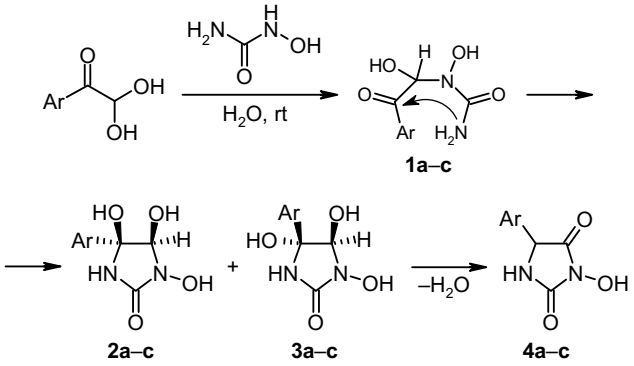
The reactions of arylglyoxals with binucleophilic reagents are well known methods for the preparation of nitrogen heterocycles. Condensation of glyoxals with ureas can, depending on the conditions, lead either to substituted hydantoins,[1,2] or to 2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones,[3] while 4,5-dihydroxyimidazolidine-2-thiones are formed in reactions with thioureas.[4]

The goal of this work was to study the possibilities for a selective single-stage synthesis of 5-aryl-3-hydroxyimid-azolidine-2,4-diones and 3-alkoxy-5-arylimidazolidine-2,4-di-ones from arylglyoxals, as well as to study the structure of 3-alkoxy-5-arylimidazolidine-2,4-diones.

We have previously shown that interaction of arylglyoxal hydrates with *N*-hydroxyurea in aqueous medium at room temperature involves the formation of substituted *N*-hydroxyureas **1a**–**c**, followed by cyclization to 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones **2**, **3** **a**–**c**, which then undergo elimination of water molecule, forming 5-aryl-3-hydroxyimidazolidine-2,4-diones (5-aryl-3-hydroxyhydantoins) **4a**–**c** (Scheme 1).[5]

However, performing the reaction at 20–23°C, depending on the nature of arylglyoxal, may in some cases produce either a mixture of substituted *N*-hydroxyureas **1** and 5-aryl-3-hydroxyhydantoins **4** (X = Me,[5] OMe), i.e., products of the first and third step of the mechanism, or a diastereomeric mixture of 5-aryl-3,4,5-trihydroxyimid-azolidin-2-ones, for example, compounds **2**, **3** (X = Cl)[5] or their mixture with products of the third step, 5-aryl-

Scheme 1



3-hydroxyhydantoins **4** (X = H).

In the latter case, performing the reaction with gentle heating or removal of water from the reaction mixture by distillation at elevated temperature under vacuum facilitated the complete conversion of 3,4,5-trihydroxy-5-phenylimidazolidin-2-one diastereomers **2a** and **3a** to 3-hydroxy-5-phenylimidazolidine-2,4-dione **4a**.[5]

The major product of reaction between (4-chlorophenyl)-glyoxal hydrate and *N*-hydroxyurea in aqueous medium at 15–23°C was 5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidin-2-one diastereomer with *cis* orientation of hydroxy groups at C-4,5 carbon atom, compound **2b**, which was characterized by X-ray structural analysis.[5] The ratio of diastereomers **2b** and **3b** was determined by the intensity ratio of the C<u>H</u>OH proton doublets in the ^{1}H NMR spectra, which was equal to 97:3. Compounds **2b**, **3b** were converted quantitatively to 5-(4-chlorophenyl)-3-hydroxyimidazolidine-2,4-dione (**4b**) by refluxing in MeCN solution.

The reaction of arylglyoxals with *N*-alkoxyureas could be expected to produce the respective 3-alkoxyhydantoins. Indeed, the reaction of anhydrous phenylglyoxal with *N*'-ethoxy-*N*-phenylurea in CH_2Cl_2 at 20°C gave 1,5-bis-(phenyl)-3-ethoxyimidazolidine-2,4-dione in moderate yield (46%).[6] Thus, the reaction of arylglyoxals with *N*-hydroxy- and *N*-alkoxyureas could be generally applicable to the preparation of 3-hydroxy- and 3-alkoxy-5-arylimidazolidine-2,4-diones, and could compete with the very few known methods for the preparation of 3-hydroxy- and 3-alkoxyhydantoins and their derivatives.[7–13] The practical challenges were associated with the difficult removal of impurities formed in the first and second stages of this synthesis.

We found that performing the reaction of *N*-hydroxyurea with arylglyoxal hydrates in acetic acid at 15–20°C produced 5-aryl-3-hydroxyimidazolidine-2,4-diones **4a**–**g**

Scheme 2

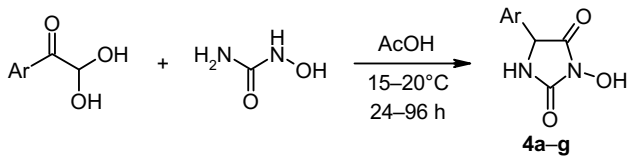


Table 1. Yields of 5-aryl-3-hydroxyimidazolidine-2,4-dione monohydrates **4a**–**g**

Compound	Ar	Temperature, °C	Time, h	Yield, %
4a	Ph	18–19	24	76
4b	4-ClC_6H_4	18–19	24	69
4c	4-MeC_6H_4	19–20	24	63
4d	4-$MeOC_6H_4$	19–20	96	95
4e	4-BrC_6H_4	17–18	26	77
4f	4-FC_6H_4	16–17	24	63
4g	2-Thienyl	15–16	24	40

as the only products, formed in the third step of Scheme 1 (Scheme 2, Table 1). Products of the first and second steps were absent in the reaction mixture.

A complete conversion of arylglyoxal hydrate is typically observed after maintaining the reaction mixture for 1 day at room temperature. Longer time was required in the case of (4-methoxyphenyl)glyoxal hydrate (Table 1), that probably could be explained by deactivation of β-carbonyl group in glyoxal by the *p*-methoxyphenyl substituent, creating an obstacle to cyclization in the second stage of the reaction (Scheme 1).

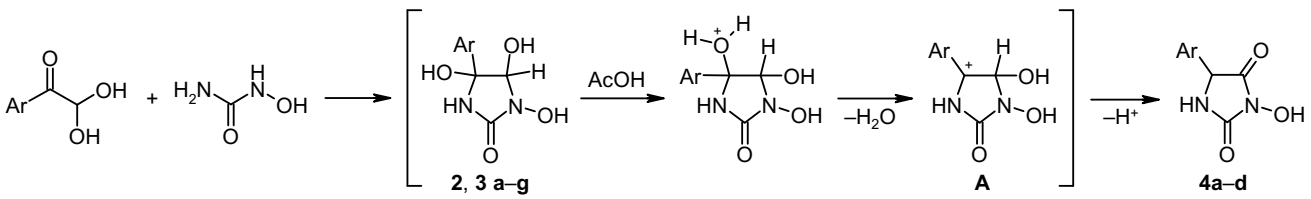
The conversion of intermediates **2**, **3** **a**–**g** to 5-aryl-3-hydroxyimidazolidine-2,4-diones **4a**–**g**, i.e., the third stage of the mechanism (Scheme 1), could be facilitated by acidic catalysis (AcOH) and may involve the formation of intermediate "benzyl" cation **A** in acidic medium followed by 1,2-hydride shift (Scheme 3).

The interaction of arylglyoxal hydrates with *N*-alkoxyureas in acetic acid at room temperature for several days led to a selective formation of 3-alkoxy-5-arylimidazolidine-2,4-diones **5a**–**j** (Scheme 4, Table 2), probably according to the mechanism shown in Schemes 1 and 3.

The structure of 3-hydroxy- and 3-alkoxy-5-aryl-imidazolidine-2,4-diones was confirmed by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and in the case of compounds **5a**,**b**,**f** also by X-ray structural analysis (Fig. 1, 3, Table 3).

Compounds **5a**,**b**,**f** had related structures (Fig. 1). The five-membered ring in all three structures was planar, the

Scheme 3



Scheme 4

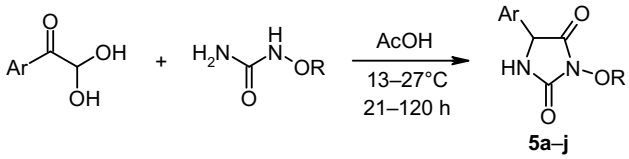


Table 2. Yields of 3-alkoxy-5-arylimidazolidine-2,4-diones **5a**–**j**

Compound	Ar	R	Temperature, °C	Time, h	Yield, %
5a	Ph	Me	14–15	74	69
5b	Ph	Et	17–18	118	99
5c	Ph	*n*-Bu	13–14	45	63
5d	4-ClC_6H_4	Me	26–27	92	78
5e	4-ClC_6H_4	Et	26–27	98	78
5f	4-ClC_6H_4	*n*-Bu	25–26	95	88
5g	4-FC_6H_4	Me	26–27	21	78
5h	4-FC_6H_4	Et	26–27	91	99
5i	4-BrC_6H_4	Et	15–16	68	85
5j	2-Thienyl	Et	20–21	120	64

endocyclic torsion angles did not exceed 4°. The alkyl substituent at the O(2) atom was oriented orthogonally to the five-membered ring plane (the torsion angle C(10)–O(2)–N(1)–C(2) was –87.6(4)°, –83.2(2)°, and –87.3(2)° for compounds **5a**,**b**,**f**, respectively). At the same time, the butyl substituent in compound **5f** was disordered over the two positions A and B with the relative occupancy 0.59(1):0.41(1) due to a rotation around O(2)–C(10) bond, with slightly different conformations at positions A and B. The respective torsion angles N(1)–O(2)–C(10)–C(11) (158.6(4)° and –166.1(5)° at positions A and B) and C(10)–C(11)–C(12)–C(13) (–91.3(9)° and 85.3(17)°) have opposite signs, while the torsion angles O(2)–C(10)–C(11)–C(12) are practically equal (–175.7(5)° and 178.7(7)°).

We should note that the configuration of the N(1) nitrogen atom in 3-methoxy-5-phenylimidazolidine-2,4-dione (**5a**) was planar, while in compounds **5b**,**f** it was slightly pyramidal. The Winkler–Dunitz pyramidality parameters χ,[14] representing angles between the planes drawn through the nitrogen atom and two adjacent atoms, were 0.3(7)°, 17.7(3)°, and 9.2(4)° for compounds **5a**,**b**,**f**, respectively. Thus, the pyramidality of the N(1) atom increased in the series of substituents Me→Bu→Et. The higher pyramidality in the case of ethyl substituent, compared to butyl, apparently could be explained by the differences in C(10)–C(11) bond orientation relative to the N(1)–O(2) bond: it was *syn*-clinal in *N*-ethoxyhydantoin **5b** and *anti*-periplanar in *N*-butoxyhydantoin **5f** (the values of the respective torsion angles were 65.1(3)° for compound **5b** and 158.6(4)°; –166.1(5)° for the two disordered positions of compound **5f**). The connection between rotation angle along the O(2)–C(10) bond and the degree of nitrogen atom pyramidality was confirmed by quantum-chemical calculations using the the B97-D3/def2-SVP density functional method. Scanning of

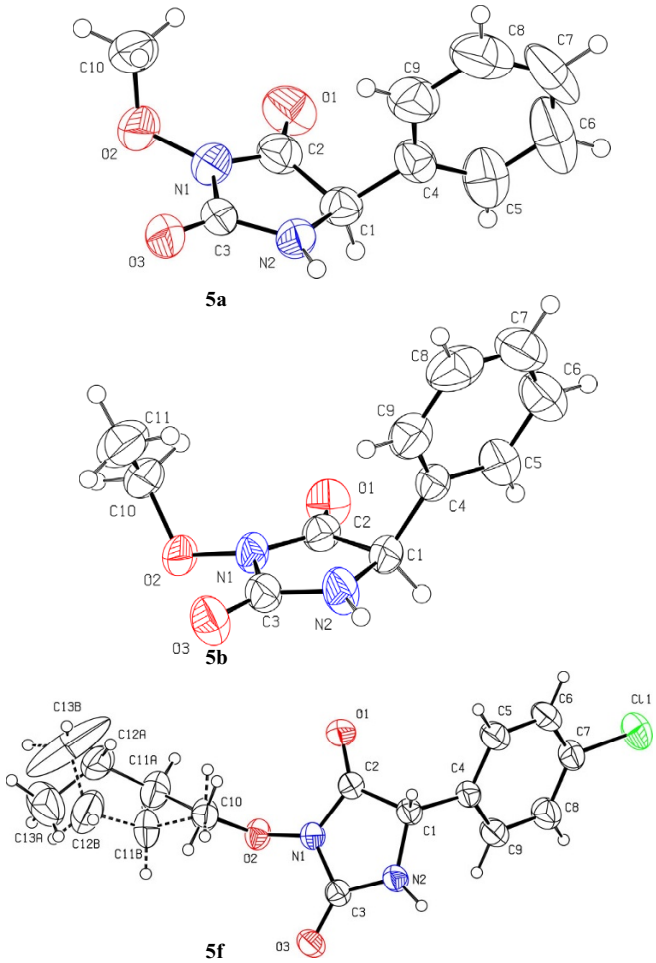


Figure 1. Molecular structure of compounds **5a**,**b**,**f** with non-hydrogen atoms represented by thermal vibration ellipsoids of 50% (compounds **5a**,**b**) and 30% (compound **5f**) probability.

the relaxed potential energy surface during variation of the torsion angle N–O–C–C in molecule of 3-ethoxy-5-phenylimidazolidine-2,4-dione **5b** (Fig. 2) showed that the nitrogen atom was most pyramidal when the C–C bond had *syn*-clinal orientation relative to the C–O bond, and least pyramidal when the orientation was *syn*- and *anti*-periplanar. This dependence could probably be explained by interaction between the nitrogen lone electron pair and a methyl group hydrogen atom, which is attractive precisely at *syn*-clinal orientation. According to X-ray structural data, the N···H distance in 3-ethoxy-5-phenylimidazolidine-2,4-dione (**5b**) was equal to 2.65 Å, corresponding to the sum of van der Waals radii of the atoms.[15] The graph of energy *vs.* torsion angle also showed two minima at *syn*-clinal and *anti*-periplanar areas, corresponding to the conformations of molecules **5b**,**f** observed in the crystalline state.

The crystals of 3-alkoxy-5-arylimidazolidine-2,4-diones contained molecules linked by intermolecular N(2)–H···O(3) hydrogen bonds. More specifically, molecular chains along the screw axis 2_1 were observed in 3-alkoxy-5-phenylimidazolidine-2,4-diones **5a**,**b**, while the molecules were arranged in 3-butoxy-5-(4-chlorophenyl)imidazolidine-2,4-dione (**5f**) in centrally symmetric dimers (Fig. 3).

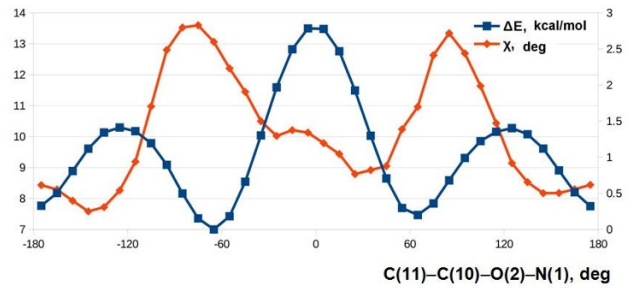


Figure 2. The dependence of N(1) (χ) atom pyramidality and energy (Δ*E*) of 3-ethoxy-5-phenylimidazolidine-2,4-dione (**5b**) molecule on the torsion angle C(11)–C(10)–O(2)–N(1), calculated by the B97-D3/def2-SVP method.

The N(1)–C(2) amide bond in all three compounds was much shorter than the N(1)–C(3) bond. This was probably caused by the greater conjugation between lone electron pair of the N(1) atom and the C(2)=O(1) carbonyl bond compared to the C(3)=O(3) carbonyl bond (Table 3). ^{1}H NMR signals of N(1)–H and C(1)–H protons in 3-alkoxy-5-arylimidazolidine-2,4-diones **5a**,**b**,**f** were singlets, similarly as in the case of other 3-alkoxyhydantoins and 3-hydroxyhydantoins. This was in good agreement with the planar conformation of the N(1) atom observed in the crystal structure.

The proposed single-stage synthesis of 3-hydroxy-5-arylimidazolidine-2,4-diones and 3-alkoxy-5-arylimidazolidine-2,4-diones by reactions of aryl glyoxals with *N*-hydroxyurea and *N*-alkoxyureas in acetic acid at room temperature can be considered to be quite promising. Structural features of 3-alkoxy-5-arylimidazolidine-2,4-diones were studied, in particular the planarity of five-membered ring was established, and the non-equivalence of amide N–C bonds in the ring system was observed.

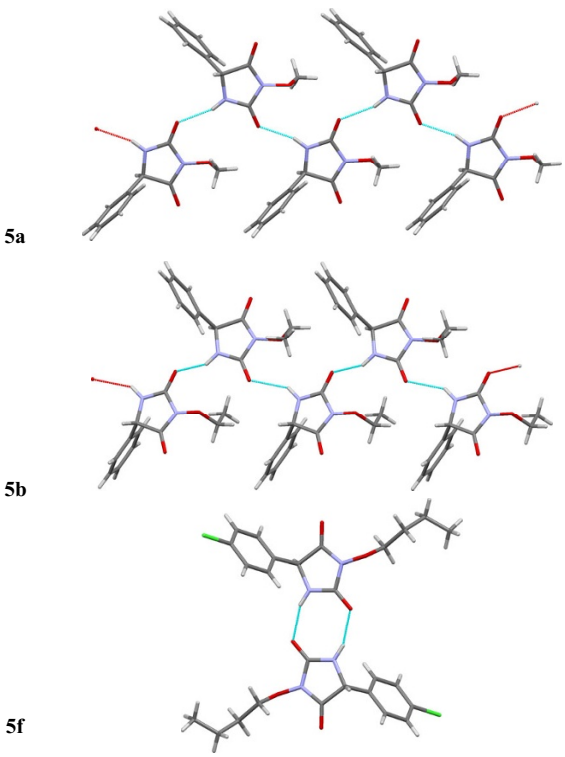


Figure 3. Hydrogen bonds in the crystal structures of 3-alkoxy-5-arylimidazolidine-2,4-diones **5a**,**b**,**f**.

Table 3. The characteristic bond lengths in 3-alkoxy-5-arylimidazolidine-2,4-diones **5a**,**b**,**f**

Compound	Bond lengths, Å			
	N(1)–O(2)	N(2)–C(3)	N(1)–C(3)	N(1)–C(2)
5a	1.386(4)	1.330(4)	1.403(4)	1.354(5)
5b	1.379(2)	1.323(3)	1.412(2)	1.368(3)
5f	1.374(2)	1.341(2)	1.400(3)	1.362(3)

Experimental

IR spectra were recorded on a UR-20 spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Varian VXP-300 spectrometer (300 and 75 MHz, respectively). The solvents were DMSO-d_6 (compounds **1d**, **2b**, **3b**, **4a**–**g**, **5a**,**g**; ^{1}H NMR spectra of compounds **5h**–**j**) and $CDCl_3$ (compounds **5b**–**e**; ^{13}C NMR spectra of compounds **5h**–**j**), with TMS as internal standard. ^{13}C NMR spectra of compounds **2b**, **4e**,**g**, **5b**,**c** were recorded in APT mode. Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode. Elemental analysis for C, H, and N was performed on a Carlo Erba analyzer. Melting points were determined in a capillary with a PTOP sulfuric acid apparatus.

N-Hydroxyurea[16] (stored at –26°C), *N*-methoxyurea,[17] *N*-ethoxyurea,[18] and *N*-*n*-butoxyurea[18] were obtained according to published procedures. 2-Thienylglyoxal hydrate was obtained by a published procedure,[19] then purified by vacuum distillation, converted to hydrate, and recrystallized from benzene. Phenylglyoxal hydrate was obtained according to a published procedure,[20] then purified by vacuum distillation and conversion to hydrate. The rest of the arylglyoxal hydrates were obtained analogously. The solvents were purified according to standard procedures.

Preparation of *cis*- and *trans*-5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidin-2-ones 2b, 3b. A solution of *N*-hydroxyurea (90 mg, 1.180 mmol) in H_2O (20 ml) was stirred with (4-chlorophenyl)glyoxal hydrate (220 mg, 1.180 mmol) at 20–25°C for 27 h (the precipitate of glyoxal hydrate dissolved nearly completely). Then additional *N*-hydroxyurea (80 mg, 1.052 mmol) was added, and the mixture was stirred for 30 min until precipitate formed. The obtained white precipitate was maintained for 24 h at 20°C, then filtered off and dried under vacuum (3 mmHg), yeilding a mixture of diastereomers **2b** and **3b** (218 mg, 66%) in 97:3 ratio (according to ^{1}H NMR data).

The aqueous filtrate was evaporated under vacuum (3 mmHg) at 20°C to one half volume, the precipitate that formed was filtered off and dried under vacuum (3 mmHg), giving additional crop of diastereomers **2b**, **3b** (38 mg, 11%) as 97:3 mixture. The obtained diastereomers **2b**, **3b** were combined and recrystallized from 1:1 THF–hexane mixture. The *cis*-diastereomer **2b** was finally isolated, as identified by ^{1}H NMR spectroscopy and mass spectrometry.[5]

***cis*-Diastereomer 2b**. Yield 167 mg (53%), colorless crystals, mp 104–106°C (decomp.) (mp 103–106°C (THF–hexane)).[5] ^{13}C NMR spectrum, δ, ppm: 82.1 (C(OH)Ar); 89.7 (CHOH); 128.0, 128.1 (CH Ar); 132.8, 141.7 (C Ar); 159.6 (C=O).

***trans*-Diastereomer 3b**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.84 (1H, d, CHOH, *J* = 5.7); 6.41 (1H, d, *J* = 5.7, CHOH); 6.60 (1H, s, 5-OH); 7.34–7.51 (4H, m, H Ar); 8.01 (1H, s, NH); 9.07 (1H, s, NOH).

The reaction of phenylglyoxal hydrate with *N*-hydroxyurea in water at 20°C gave a mixture of diastereomers **2a** and **3a** (4:1−9:1) and hydantoin **4a**, which were difficult to separate due to the similar solubility of these compounds in water. Compounds **2a** and **3a** could be readily and selectively converted upon gentle heating to hydantoin **4a**.

Preparation of 5-aryl-3-hydroxyimidazolidine-2,4-diones 4a–g (General method). A mixture of *N*-hydroxyurea (118 mg, 1.546 mmol) and arylglyoxal hydrate (1.546 mmol) with AcOH (10 ml) was stirred until complete dissolution, the obtained solution was maintained at 15–20°C for 24–96 h (Table 1). The solvent was evaporated under vacuum (3 mmHg) at 20°C, the residue was washed with cold water (5 ml) and dried under vacuum (3 mmHg). For additional purification, compounds **4a**–**g** were recrystallized from 1:2 mixture of THF and hexane.

3-Hydroxy-5-phenylimidazolidine-2,4-dione (4a). Colorless crystals, mp 170–172°C (decomp.), after second recrystallization 175–176°C (decomp.) (mp 175–176°C (decomp., THF–hexane)).[5] ^{13}C NMR spectrum, δ, ppm: 57.7 (C-5); 126.9, 128.6, 128.8, 135.5 (C Ph); 154.4 (C=O); 167.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 193 $[M+H]^+$ (100), 175 $[M+H-H_2O]^+$ (10).

5-(4-Chlorophenyl)-3-hydroxyimidazolidine-2,4-dione (4b). Colorless crystals, mp 167–169°C (decomp.) (mp 132–134°C (decomp.)).[5] ^{13}C NMR spectrum, δ, ppm: 57.0 (C-5); 128.7, 128.8, 133.2, 134.3 (C Ar); 154.4 (C=O); 167.5 (C=O).

Also the hydrate of 5-(4-chlorophenyl)-3-hydroxyimidazolidine-2,4-dione **4b** was formed in 100% yield after refluxing a solution of 5-(4-chlorophenyl)-3,4,5-trihydroxyimidazolidine-2-one (**2b**) in MeCN for 2 h, followed by removing the solvent under vacuum (10 mmHg).

3-Hydroxy-5-(4-methylphenyl)imidazolidine-2,4-dione (4c). Colorless crystals, mp 141–143°C (decomp.) (mp 136–139°C (decomp.)).[5] ^{13}C NMR spectrum, δ, ppm: 20.6 (CH_3); 57.4 (C-5); 126.8, 129.4, 132.4, 137.9 (C Ar); 154.5 (C=O); 167.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 207 $[M+H]^+$ (49), 119 (100), 91 (36).

3-Hydroxy-5-(4-methoxyphenyl)imidazolidine-2,4-dione (4d). Pinkish-white crystals, mp 158–159°C (decomp.). IR spectrum, ν, cm^{-1}: 1715 (C=O), 1770 (C=O), 3260 (N–H), 3580 (O–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.77 (3H, s, OCH_3); 5.17 (1H, s, 5-CH); 6.99 (2H, d, *J* = 8.7, H Ar); 7.25 (2H, d, *J* = 8.7, H Ar); 8.69 (1H, s, NH); 10.59 (1H, s, NOH). ^{13}C NMR spectrum, δ, ppm: 55.2 (OCH_3); 57.2 (C-5); 114.2, 127.3, 128.1 (C Ar); 154.4 (C=O); 159.4 (C-4 Ar); 168.1 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 223 $[M+H]^+$ (100), 205 $[M+H-H_2O]^+$ (34). Found, %: C 49.74; H 5.28; N 11.57. $C_{10}H_{10}N_2O_4 \cdot H_2O$. Calculated, %: C 50.00; H 5.04; N 11.66.

Synthesis of compound 4d in neutral aqueous medium. A solution of (4-methoxyphenyl)glyoxal hydrate (911 mg, 5.00 mmol) in H_2O (50 ml) was heated to 45°C and treated with a solution of *N*-hydroxyurea (380 mg, 5.00 mmol) in H_2O (7 ml). The reaction mixture was stirred for 2 h at 27–30°C, then maintained without stirring for 40 h at 27–30°C, and the obtained precipitate of ***N*-hydroxy-*N*-[hydroxy(4-methoxybenzoyl)]methylurea (1d)** was filtered off. The remaining aqueous filtrate was maintained for another 24 h at 27–30°C, then cooled to 0°C and maintained for 5 days. The crystalline precipitate that formed was filtered off and dried under vacuum, giving 3-hydroxy-5-(4-methoxyphenyl)imidazolidine-2,4-dione hydrate (**4d**) (211 mg, 18%), which was identified by ^{1}H NMR spectroscopy and mass spectrometry.

Compound 1d. Yield 489 mg (41%), white crystals, mp 145–147°C (decomp.). IR spectrum, ν, cm^{-1}: 1660 (C=O), 1680 (C=O), 3295 (NH_2), 3346 (OH), 3450 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 5.88 (1H, d, *J* = 8.4, CHOH); 6.53 (1H, d, *J* = 8.4, CHOH); 6.54 (2H, br. s, NH_2); 7.06 (2H, d, *J* = 9.0, H); 7.99 (2H, d, *J* = 9.0, H Ar); 9.24 (1H, s, NOH). Mass spectrum, *m*/*z* (I_{rel}, %): 241 $[M+H]^+$ (50), 223 (18), 180 (76), 176 (46), 165 (57), 120 (48), 107 (31), 105 (44), 89 (86), 77 (100). Found, %: C 49.85; H 5.16; N 11.49. $C_{10}H_{12}N_2O_5$. Calculated, %: C 50.00; H 5.04; N 11.66.

5-(4-Bromophenyl)-3-hydroxyimidazolidine-2,4-dione (4e). Colorless crystals, mp 175–177°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.28 (1H, s, 5-CH); 7.32 (2H, d, *J* = 8.4, H Ar); 7.64 (2H, d, *J* = 8.4, H Ar); 8.78 (1H, s, NH); 10.70 (1H, br. s, NOH). ^{13}C NMR spectrum, δ, ppm: 56.9 (C-5); 121.6 (C Ar); 128.8 (CH Ar); 131.5 (CH Ar); 134.7 (C Ar); 154.1 (C=O); 167.1 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 273 $[M(^{81}Br)+H]^+$ (100), 271 $[M(^{79}Br)+H]^+$ (92). Found, %: C 37.14; H 3.45; N 9.55. $C_9H_7BrN_2O_3 \cdot H_2O$. Calculated, %: C 37.39; H 3.14; N 9.69.

5-(4-Fluorophenyl)-3-hydroxyimidazolidine-2,4-dione (4f). Colorless crystals, mp 198–199°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.27 (1H, s, 5-CH); 7.26 (2H, dd, *J* = 8.4, *J* = 10.3, H Ar); 7.34 (2H, dd, *J* = 8.4, *J* = 5.8, H Ar); 8.74 (1H, s, NH); 10.60 (1H, br. s, NOH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 56.9 (C-5); 115.6 (d, J_{CF} = 21.8, C-3,5 Ar); 128.9 (d, J_{CF} = 9.0, C-2,6 Ar); 131.6 (C-1 Ar); 154.3 (C=O); 162.2 (d, J_{CF} = 250.5, C-4 Ar); 167.7 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 211 $[M+H]^+$ (100), 193 $[M+H-H_2O]^+$ (11). Found, %: C 47.41; H 4.07; N 12.13. $C_9H_7FN_2O_3 \cdot H_2O$. Calculated, %: C 47.37; H 3.98; N 12.28.

3-Hydroxy-5-(2-thienyl)imidazolidine-2,4-dione (4g). Yellowish crystals, unstable at room temperature, mp 98–103°C (decomposition at 176–178°C, with loss of water) (mp 107–108°C (decomp.)).[5] ^{13}C NMR spectrum, δ, ppm: 54.1 (C-5); 126.5, 126.6, 127.3 (C-3,4,5 thiophene); 138.0 (C-2 thiophene); 154.1 (C=O); 167.0 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 199 $[M+H]^+$ (100), 181 $[M+H-H_2O]^+$ (9). Found, %: C 38.70; H 3.95; N 12.73. $C_7H_6N_2O_3S \cdot H_2O$. Calculated, %: C 38.89; H 3.73; N 12.96.

Preparation of 3-alkoxy-5-arylimidazolidine-2,4-diones 5a–j (General method). A mixture of *N*-alkoxyurea

(0.965 mmol), arylglyoxal hydrate (0.965 mmol), and AcOH (10 ml) was stirred until complete dissolution, the obtained solution was maintained at 13–27°C for 21–120 h (Table 2), then AcOH was removed by evaporation under vacuum (3 mmHg) at 20°C, the residue was washed with cold (5°C) water (10 ml) and dried under vacuum (3 mmHg). For additional purification, the obtained compounds were recrystallized from CH_2Cl_2 (compound **5g**), CCl_4 (compounds **5e**,**j**), or 1:2 mixture of CH_2Cl_2–hexane (the rest of the compounds).

3-Methoxy-5-phenylimidazolidine-2,4-dione (5a). Colorless crystals, mp 161–162°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 5.25 (1H, s, 5-CH); 7.35–7.45 (5H, m, H Ph); 8.90 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 57.8 (C-5); 64.7 (OCH_3); 126.9, 128.6, 128.8, 134.8 (C Ph); 152.6 (C=O); 166.7 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 207 $[M+H]^+$ (100). Found, %: C 58.02; H 4.98; N 13.37. $C_{10}H_{10}N_2O_3$. Calculated %: C 58.25; H 4.89; N 13.59.

3-Ethoxy-5-phenylimidazolidine-2,4-dione (5b). Colorless crystals, mp 130–131°C. IR spectrum, ν, cm^{-1}: 1740 (C=O), 1770 (C=O), 3320 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.19 (2H, dq, *J* = 1.8, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.03 (1H, s, 5-CH); 6.54 (1H, br. s, NH); 7.34–7.48 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 13.3 ($OCH_2\underline{C}H_3$); 58.7 (C-5); 73.7 ($O\underline{C}H_2CH_3$); 126.4, 129.0, 129.1 (CH Ph); 133.3 (C-1 Ph); 154.2 (C=O); 166.8 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 221 $[M+H]^+$ (100). Found, %: C 60.14; H 5.02; N 12.43. $C_{11}H_{12}N_2O_3$. Calculated %: C 59.99; H 5.49; N 12.72.

3-*n*-Butoxy-5-phenylimidazolidine-2,4-dione (5c). Colorless crystals, mp 78–80°C. IR spectrum, ν, cm^{-1}: 1730 (C=O), 1775 (C=O), 3240 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.2, $O(CH_2)_3\underline{Me}$); 1.44 (2H, sextet, *J* = 7.2, $O(CH_2)_2C\underline{H}_2Me$); 1.68 (2H, quin, *J* = 7.2, $OCH_2C\underline{H}_2Et$); 4.04–4.15 (2H, m, $NOCH_2$); 5.02 (1H, s, 5-CH); 7.03 (1H, s, NH); 7.34–7.44 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 13.5 ($O(CH_2)_3\underline{C}H_3$); 18.5 ($O(CH_2)_2\underline{C}H_2Me$); 29.7 ($OCH_2\underline{C}H_2Et$); 58.6 (C-5); 77.4 ($OCH_2$); 126.4, 129.1, 129.2 (CH Ph); 133.4 (C-1 Ph); 154.1 (C=O); 166.7 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 249 $[M+H]^+$ (100). Found %: C 63.12; H 6.67; N 11.14. $C_{13}H_{16}N_2O_3$. Calculated %: C 62.89; H 6.50; N 11.28.

5-(4-Chlorophenyl)-3-methoxyimidazolidine-2,4-dione (5d). Colorless crystals, mp 142–145°C (decomp.) ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.00 (3H, s, OCH_3); 5.06 (1H, s, 5-CH); 6.28 (1H, s, NH); 7.35 (2H, d, *J* = 8.4, H Ar); 7.43 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 58.2 (C-5); 65.3 (OCH_3); 127.8, 129.4, 131.6, 135.6 (C); 153.1 (C=O); 165.6 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 243 $[M(^{37}Cl)+H]^+$ (35), 241 $[M(^{35}Cl)+H]^+$ (100). Found, %: C 49.84; H 3.95; N 11.55. $C_{10}H_9ClN_2O_3$. Calculated %: C 49.91; H 3.77; N 11.64.

5-(4-Chlorophenyl)-3-ethoxyimidazolidine-2,4-dione (5e). Colorless crystals, mp 115–118°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.5, $OCH_2C\underline{H}_3$); 4.19 (2H, dq, *J* = 1.2, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.04 (1H, s, 5-CH); 6.66 (1H, s, NH); 7.32 (2H, d, *J* = 8.4, H Ar); 7.40 (2H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.3 ($OCH_2\underline{C}H_3$); 58.1 (C-5); 73.9 ($O\underline{C}H_2CH_3$); 127.8, 129.4, 131.8, 135.8 (C Ar); 154.2 (C=O); 166.5 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 257 $[M(^{37}Cl)+H]^+$ (32), 255 $[M(^{35}Cl)+H]^+$ (100). Found, %: C 51.75; H 4.58; N 10.85. $C_{11}H_{11}ClN_2O_3$. Calculated %: C 51.88; H 4.35; N 11.00.

3-*n*-Butoxy-5-(4-chlorophenyl)imidazolidine-2,4-dione (5f). Colorless crystals, mp 151–152°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.93 (3H, t, *J* =7.4, $O(CH_2)_3C\underline{H}_3$); 1.45 (2H, sextet, *J* = 7.4, $O(CH_2)_2C\underline{H}_2Me$); 1.69 (2H, quin, *J* = 7.4, $OCH_2C\underline{H}_2Et$); 4.12 (2H, td, *J* = 7.4, *J* = 2.4, $NOCH_2$); 5.03 (1H, s, 5-CH); 6.61 (1H, br. s, NH); 7.32 (2H, d, *J* = 8.4, H Ar); 7.40 (2H, d, *J* = 8.4, H Ar). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.89 (3H, t, *J* = 7.4, $O(CH_2)_3C\underline{H}_3$); 1.40 (2H, sextet, *J* = 7.4, $O(CH_2)_2C\underline{H}_2Me$); 1.59 (2H, quin, *J* = 7.2, $OCH_2C\underline{H}_2Et$); 4.03 (2H, td, *J* = 7.4, *J* = 2.1, $NOCH_2$); 5.29 (1H, s, 5-CH); 7.39 (2H, d, *J* = 8.4, H Ar); 7.50 (2H, d, *J* = 8.4, H Ar); 8.89 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 13.6 ($O(CH_2)_3\underline{C}H_3$); 18.7 ($O(CH_2)_2\underline{C}H_2Me$); 29.8 ($OCH_2\underline{C}H_2Et$); 58.1 (C-5); 78.0 ($NOCH_2$); 127.8, 129.4, 131.8, 135.4 (C Ar); 154.0 (C=O); 166.3 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 283 $[M(^{35}Cl)+H]^+$ (100). Mass spectrum (FAB, KI), *m/z* (I_{rel}, %): 321 $[M(^{35}Cl)+K]^+$ (33), 283 $[M(^{35}Cl)+H]^+$ (41), 134 (100). Found, %: C 55.01; H 5.36; N 9.85. $C_{13}H_{15}ClN_2O_3$. Calculated, %: C 55.23; H.35; N 9.91.

5-(4-Fluorophenyl)-3-methoxyimidazolidine-2,4-dione (5g). Colorless crystals, mp 163–164°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.88 (3H, s, OCH_3); 5.29 (1H, s, 5-CH); 7.28 (2H, t, *J* = 8.7, H Ar); 7.43 (2H, dd, *J* = 8.7, *J* = 5.7, H Ar); 8.94 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 57.2 (C-5); 64.9 (OCH_3); 115.8 (d, J_{CF} = 21.8, C-3,5 Ar); 129.2 (d, J_{CF} = 8.8, C-2,6 Ar); 131.1 (C-1 Ar); 152.7 (C=O); 162.3 (d, J_{CF} = 243.4, C-4 Ar); 166.8 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 225 $[M+H]^+$ (100). Found, %: C 53.39; H 4.22; N 12.32. $C_{10}H_9FN_2O_3$. Calculated %: C 53.57; H 4.05; N 12.50.

3-Ethoxy-5-(4-fluorophenyl)imidazolidine-2,4-dione (5h). Colorless crystals, mp 126–129°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 4.09 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.29 (1H, s, 5-CH); 7.26 (2H, t, *J* = 8.7, H Ar); 7.43 (2H, dd, *J* = 8.1, *J* =5.7, H Ar); 8.89 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 13.4 ($OCH_2\underline{C}H_3$); 58.1 (C-5); 73.8 ($O\underline{C}H_2CH_3$); 116.2 (d, J_{CF} = 21.8, C-3,5 Ar); 128.3 (d, J_{CF} = 8.5, C-2,6 Ar); 129.0 (C-1 Ar); 153.8 (C=O); 163.1 (d, J_{CF} = 247.1, C-4 Ar); 166.5 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 239 $[M+H]^+$ (100). Found, %: C 55.25; H 4.82; N 11.63. $C_{11}H_{11}FN_2O_3$. Calculated %: C 55.46; H 4.65; N 11.76.

5-(4-Bromophenyl)-3-ethoxyimidazolidine-2,4-dione (5i). Colorless crystals, mp 140–142°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.21 (3H, t, *J* = 6.9, $OCH_2C\underline{H}_3$); 4.08 (2H, q, *J* = 6.9, $OC\underline{H}_2CH_3$); 5.29 (1H, s, 5-CH); 7.33 (2H, d, *J* = 8.1, H Ar); 7.62 (2H, d, *J* = 8.1, H Ar); 8.92 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.4 ($OCH_2\underline{C}H_3$); 58.2 (C-5); 73.9 ($O\underline{C}H_2CH_3$); 123.5, 128.1, 132.2, 132.4 (C); 154.1 (C=O); 166.3 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 301 $[M(^{81}Br)+H]^+$ (100), 299 $[M(^{79}Br)+H]^+$ (99), 255 $[M(^{81}Br)+H–EtOH]^+$ (14), 253 $[M(^{79}Br)+H–EtOH]^+$ (15). Found, %: C 44.02; H 3.98; N 9.16. $C_{11}H_{11}BrN_2O_3$. Calculated %: C 44.17; H 3.71; N 9.37.

3-Ethoxy-5-(2-thienyl)imidazolidine-2,4-dione (5j). Yellowish crystals, mp 100–102°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 4.09 (3H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.58 (1H, s, 5-CH); 7.07 (1H, t, *J* = 4.2, H thiophene); 7.14 (1H, d, *J* = 3.3, H thiophene); 7.58 (1H, d, *J* = 4.2, H thiophene); 9.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.2 ($OCH_2\underline{C}H_3$); 55.0 (C-5); 73.7 ($O\underline{C}H_2CH_3$); 126.5, 126.6, 127.4, 135.9 (C thiophene); 153.5 (C=O); 165.7 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 227 $[M+H]^+$ (100), 225 $[M–H]^+$ (68). Found, %: C 47.52; H 4.31; N 12.53. $C_9H_{10}N_2O_3S$. Calculated, %: C 47.78; H 4.46; N 12.38.

X-ray structural study of compounds 5a,b,f. Crystals suitable for X-ray structural analysis were grown from a solution in CH_2Cl_2–hexane mixture. The studied crystal of compound **5a** was a non-merohedral twin, with components rotated by 180° along the *c** axis, the relative contributions of components were 0.6826(14) : 0.3174(14). X-ray structural study of compounds **5a**,**b**,**f** was performed on a Xcalibur 3 automatic four-circle diffractometer (MoKα-radiation, graphite monochromator, Sapphire-3 CCD detector, ω-scanning). The structure was solved by conjugate gradient technique with the SHELXD[21] software (for compound **5a** – by non-overlapping reflections) and refined by full matrix method of least squares in anisotropic approximation for non-hydrogen atoms, using the SHELXL[21] software (for compound **5a** – by reflections from the two twinned components). The atomic coordinates, molecular geometry parameters, and crystallographic data of compounds **5a**,**b**,**f** were deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1051542, CCDC 617197, and CCDC 1051543, respectively).

Quantum-chemical calculations for a molecule of compound 5b were performed by the B97-D3/def2-SVP method.[22–26] Scanning of potential energy surface was accomplished by a sequence of geometry optimizations with the N–O–C–C torsion angle fixed at various values between 0 and 360°, with a 10° step. The calculations were performed with the ORCA 3.0.3 software.[27]

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