Synthesis of 2-aryl(hetaryl)-1-hydroxyimidazoles by the reaction of aliphatic 1,2-hydroxylamino oximes with aromatic and heteroaromatic aldehydes

*B. A. Selivanov and A. Ya. Tikhonov**

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383) 330 9752. E-mail: alyatikh@nioch.nsc.ru

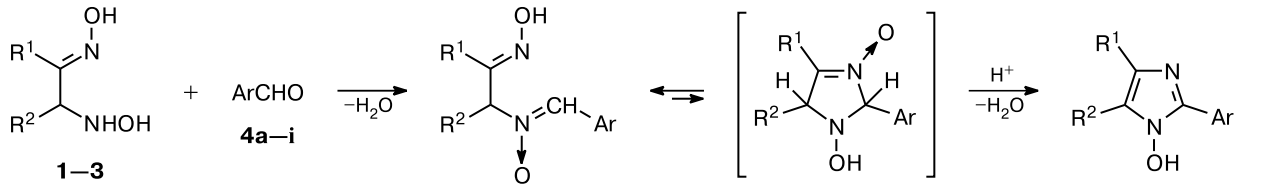
A reaction of aliphatic 1,2-hydroxylamino oximes bearing the hydroxylamino group at the secondary carbon atom with aromatic and heteroaromatic aldehydes in acetic acid leads to the corresponding 1-hydroxy-2-aryl(hetaryl)-4,5-dialkylimidazoles in high yields. α-Aryl(hetaryl)-nitrones initially formed by the condensation of 1,2-hydroxylamino oximes with aldehydes are quantitatively converted to the corresponding imidazoles.

Key words: 1-hydroxy-2-aryl(hetaryl)-4,5-dialkylimidazoles, hydroxylamino oximes, aromatic aldehydes, α-aryl(hetaryl)nitrones.

Imidazole derivatives are one of the important groups of heterocyclic compounds possessing a wide range of biological activity.[1—3] Among these compounds, 1-hydroxyimidazoles are of interest due to a possibility of their use in the synthesis of medicines,[3—5] since the presence of the 1-hydroxy group in the imidazole ring significantly broadens the possibilities of synthetic modification of imidazole molecule.[6—11] 1-Hydroxyimidazoles are commonly synthesized either by the reaction of 1,2-diketone monooximes with aldehydes and ammonia or ammonium acetate[5—7,9,12,13], or by the reduction of 2-substituted 1-hydroxyimidazole 3-oxides.[8,9,11,14,15] 1-Hydroxy-4,5-dialkylimidazoles (or tautomeric imidazole *N*-oxides) are formed by the oxidation of the imidazole ring, as a rule, in very low yields.[1,5,16] 1-Hydroxyimidazoles obtained by treatment of 1-hydroxy-3-imidazoline 3-oxides with dry HCl in ethanol are isomeric to 1-hydroxyimidazoles formed upon heating *in vacuo* of their acyl derivatives.[17] Besides, 1-hydroxy-5-methyl-2,4-diphenylimidazole was obtained by standing of the corresponding α-phenylnitrone, obtained by the condensation of alkylaromatic 1,2-hydroxylamino oxime (*syn*- or *anti*-isomers) with benzaldehyde, in ethyl alcohol saturated with HCl.[18] There were no literature data on the heterocyclization of α-arylnitrones obtained by the reaction of aliphatic 1,2-hydroxylamino oximes or their acetates with aromatic aldehydes.[5,19—22]

In the present work, we studied a possibility of the preparation of 1-hydroxy-2-arylimidazoles (or tautomeric imidazole *N*-oxides) by the reaction of aliphatic 1,2-hydroxylamino oximes **1**—**3** bearing the hydroxylamino groups at the secondary carbon atom with aromatic and heteroaromatic aldehydes **4** (Scheme 1). A suggestion on the possibility of this transformation was based on the fact that

Scheme 1



1, **5a—i**, **9a—i:** $R^1 = R^2 = Me$; **2**, **6a—i**, **10a—i:** $R^1—R^2 = (CH_2)_4$; **3**, **7d,h**, **11d,h**: $R^1—R^2 = (CH_2)_5$

Ar = Ph (**a**); 4-$MeOC_6H_4$ (**b**); 4-ClC_6H_4 (**c**); 4-$NO_2C_6H_4$ (**d**); 3-$NO_2C_6H_4$ (**e**); 2-$NO_2C_6H_4$ (**f**); pyridin-4-yl (**g**); pyridin-2-yl (**h**); 4-OH-3-$MeOC_6H_3$ (**i**)

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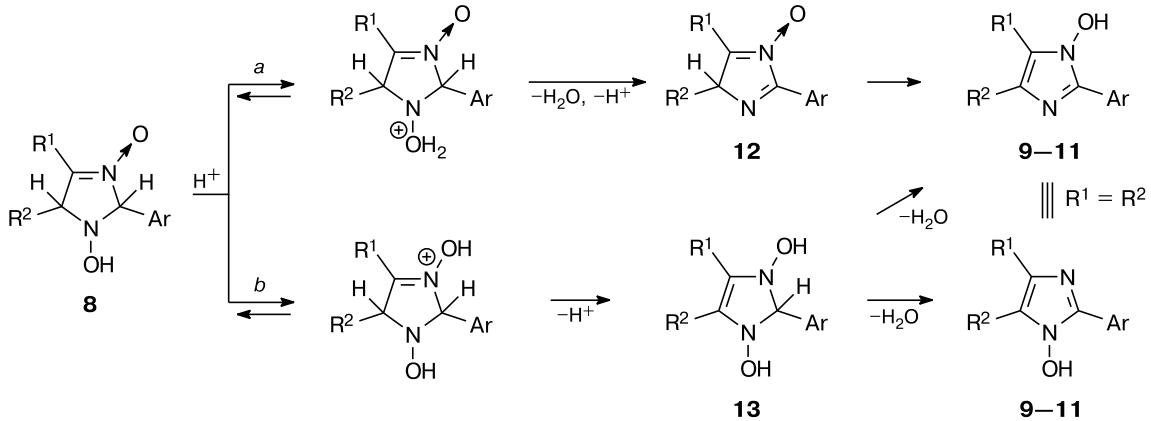
the reaction of aliphatic 1,2-hydroxylamino oximes with arylglyoxals under rather mild conditions led to 2-aroyl-1-hydroxyimidazoles through the formation of the intermediate 6-aroylnitrones.[20]

We synthesized α-arylnitrones **5c** and **6c** based on compounds **1** and **2** and *p*-chlorobenzaldehyde **4c** and studied a possibility of their cyclization to the corresponding 2-(4-chlorophenyl)-1-hydroxy-4,5-dialkylimidazoles **9c** and **10c**. The solvents differing in chemical and solvation properties, but having close boiling points such as pyridine, *n*-butanol, toluene, acetic acid (b.p. 115.5, 117, 110.6, and 118 °C, respectively[23]) were used to carry out the cyclization. The solutions of nitrones **5c** and **6c** were refluxed in the listed solvents for 3 h, then the solvent was evaporated *in vacuo* of a water-jet pump, the residue was analyzed by ^{1}H NMR spectroscopy. Both nitrones appeared to undergo no any transformations upon reflux in pyridine and *n*-butanol. Nitrone **5c** after heating in toluene did not change, either, whereas heating of nitrone **6c** in toluene for 3 h resulted in obtaining a complex mixture of products, out of which only the starting nitrone **6c**, *p*-chlorobenzaldehyde and cyclohexen-3-one oximes were identified by ^{1}H NMR spectroscopy and GLC-MS spectrometry. The reaction mixtures obtained by reflux of both nitrones **5c** and **6c** in acetic acid contained, according to the ^{1}H NMR spectroscopic data, the starting compounds (~30%) and the corresponding 2-(4-chlorophenyl)-1-hydroxy-4,5-dialkylimidazoles **9c** and **10c** (~70%). When the solutions of nitrones **5c** and **6c** in acetic acid were reflux for a longer time (8 h), they were virtually completely converted to the corresponding imidazole derivatives. Nitrones obtained from compound **1** and benzaldehyde **4a**, *p*-nitrobenzaldehyde **4d** and vanillin **4i** were refluxed in acetic acid for 8—20 h to be virtually completely converted to the corresponding 1-hydroxy-2-arylimidazoles **9a**,**d**,**i**. Reflux of nitrone **5c** in formic or trifluoroacetic acid led to the resinification of the starting nitrone. The experiments performed have shown that the use of acetic acid for the cyclization of nitrones to imidazole derivatives gave the best results.

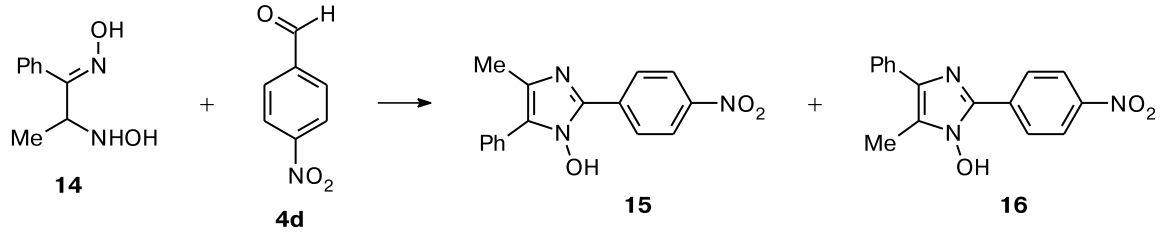
In this connection, we studied the reaction of hydroxylamino oximes **1**—**3** with aromatic and heteroaromatic aldehydes in acetic acid in order to prepare the corresponding imidazoles without isolation of α-aryl(heteroaryl)nitrones **5**—**7** (see Scheme 1). Reflux of the equimolar amounts of the starting 1,2-hydroxylamino oximes **1**—**3** and aldehydes **4a**—**i** in acetic acid was carried out until the starting aldehyde and/or nitrone were completely consumed (TLC monitoring). The yields of 2-aryl(heteroaryl)-1-hydroxy-4,5-dialkylimidazoles **9a**—**i**, **10a**—**i**, and **11d**,**h** were 55—92%. The reaction of 1,2-hydroxylamino oximes **1** and **2** with aldehydes containing electron-donating substituents was slower and accompanied by the formation of the resin-like compounds.

2-Aryl(hetaryl)-1-hydroxyimidazoles **9**—**11** were formed in the reaction of 1,2-hydroxylamino oximes **1**—**3** with aromatic or heteroaromatic aldehydes **4** in acetic acid as a result of the intramolecular cyclization of nitrones **5**—**7** and subsequent dehydration of the intermediately formed 1-hydroxy-3-imidazoline 3-oxides **8** (see Ref. 20). Since imidazoles **9**—**11** formed in the dehydration reaction of the intermediate 1-hydroxy-3-imidazoline 3-oxides **8** are symmetrically substituted, it is impossible to determine, which pathway follows the dehydration: the pathway *a* or the pathway *b* (Scheme 2). The pathway *a* seems the most probable when the aryl substituent contains a rather strong electron-withdrawing group. Its presence leads to the increase in the acidity of the hydrogen atom at the second carbon atom of the imidazoline ring and, therefore, to the easy dehydration of 3-imidazoline 3-oxide protonated at 1-hydroxy group with the formation of 4*H*-imidazole 1-oxide **12**, which rapidly isomerizes to 1-hydroxyimidazole **9**—**11**. The pathway *b* cannot be excluded, either:

Scheme 2



Scheme 3

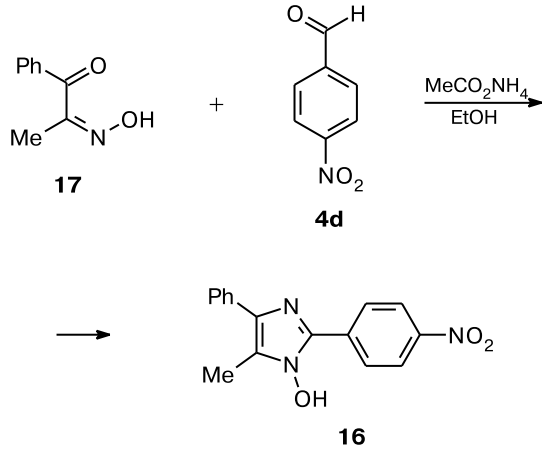


initially the *N*-oxide oxygen atom of imidazoline **8** is protonated, followed by the isomerization to 1,3-dihydroxy-4-imidazoline **13**, whose dehydration can occur with involvement of one of the two hydroxy groups with the formation of isomeric imidazoles in the case if $R^1 \neq R^2$.

In our opinion, the question which pathway follows the dehydration of imidazoline **8** can be answered by carrying out the reaction of unsymmetric derivatives, in particular, alkylaromatic 1,2-hydroxylamino oxime **14** (*anti*-isomer) with benzaldehyde derivative under the selected conditions. The ^{1}H NMR spectroscopic data showed that the reaction of 1,2-hydroxylamino oxime **14** with 4-nitrobenzaldehyde **4d** in refluxing acetic acid for 6 h gave a mixture of isomeric products: 1-hydroxy-4-methyl-2-(4-nitrophenyl)-5-phenylimidazole (**15**) and 1-hydroxy-5-methyl-2-(4-nitrophenyl)-4-phenylimidazole (**16**) in the ratio 1 : 2.3 (Scheme 3).

Compound **16** was obtained by the reaction of 2-hydroxyimino-1-phenylpropan-1-one (**17**) with aldehyde **4d** and ammonium acetate in ethanol[12] (Scheme 4).

Scheme 4



The formation in the reaction of a mixture of 1-hydroxyimidazoles **15** and **16** (see Scheme 3), in our opinion, can indicate a predominant formation of the intermediate 1,3-dihydroxy-4-imidazoline **13** (pathway *b*), whose rate of dehydration involving one of the hydroxy groups is influenced by the substituents at positions 4 and 5 of the imidazoline ring.

In conclusion, was showed that α-aryl- and α-hetarylnitrones formed in the reaction of aliphatic 1,2-hydroxylamino oximes bearing the hydroxylamino group at the secondary carbon atom with aromatic and heteroaromatic aldehydes underwent cyclization upon heating in acetic acid with the formation of the corresponding 1-hydroxy-2-aryl- and 1-hydroxy-2-hetaryl-4,5-dialkylimidazoles. The synthesis of 1-hydroxy-2-aryl- and 1-hydroxy-2-hetaryl-4,5-dialkylimidazoles can be accomplished by the reaction of the same 1,2-hydroxylamino oximes with aromatic or heteroaromatic aldehydes under conditions indicated above and without isolation of α-aryl(hetaryl)nitrones.

Experimental

IR spectra of compounds in KBr pellets (concentration 0.25%) were recorded on a Bruker Vector 22 FT-IR spectrometer. GLC-MS spectra were recorded on a Hewlett Pakard G1800A instrument consisting of an HP 5890 series II chromatograph and an HP 5971 mass selective detector. ^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer (400.136 MHz), using signals of residual protons of the solvent (DMSO-d_6 at δ 2.50, CD_3OD at δ 3.34, respectively) as references. Elemental analysis was performed on a Euro EA3000 automatic elemental CHNS-analyzer. Melting points were determined on a Mettler Toledo apparatus and were not corrected. The reaction progress and the purity of obtained compounds were monitored by TLC on Silufol UV-254 plates, eluent chloroform—methanol (10 : 1), visualization under UV light. All the solvents were purified according to the standard procedures.

Acetates of the starting 1,2-hydroxylamino oximes 1—3 were obtained according to the known procedure.[24]

***N*-(Benzylidene)-*N*-(2-hydroxyimino-1-methylpropyl)amine *N*-oxide (5a)** was obtained according to the procedure described earlier.[21] The yield was 53%, m.p. 107 °C (see Ref. 21: m.p. 108—110 °C).

***N*-(2-Hydroxyimino-1-methylpropyl)-*N*-(4-nitrobenzylidene)amine *N*-oxide (5d)** was obtained according to the procedure described earlier.[21] The yield was 95%, m.p. 160 °C (see Ref. 21: m.p. 157—158 °C).

***E*-isomer of 2-hydroxyamino-1-phenylpropanone oxime 14** was obtained according to the procedure given in the literature.[25]

2-Hydroxyimino-1-phenylpropane-1-one 17 was obtained according to the procedure given in the literature.[26]

Synthesis of *N*-(2-hydroxyiminoalkyl)-α-arylnitrones (5c,i, 6c) (general procedure). A solution of aromatic aldehyde (10 mmol) in minimum methanol was added to a solution of hydroxylamino oxime acetate (**1** or **2**) (11 mmol) in methanol (15 mL) with stirring. The mixture obtained was stirred for 4 h at ~20 °C (a precipitate began to form after 10—15 min) and kept for 16 h without stirring. A precipitate of α-arylnitrone **5a—i**, **6a—i** was filtered off, washed with minimum cold methanol, dried in air until the weight was constant.

***N*-(4-Chlorobenzylidene)-*N*-(2-hydroxyimino-1-methylpropyl)amine *N*-oxide (5c).** The yield was 86%, white crystals, m.p. 153 °C. Found (%): C, 54.36; H, 5.39; N, 11.98. $C_{11}H_{13}ClN_2O_2$. Calculated (%): C, 54.89; H, 5.44; N, 11.64. IR, ν/cm^{-1}: 3171, 3114, 3069, 2999, 1590, 1488, 1446, 1300, 1143, 1087, 987, 952. ^{1}H NMR (DMSO-d_6), δ: 1.51 (d, 3 H, CH—C<u>H</u>$_3$, J = 6.8 Hz); 1.77 (s, 3 H, N=C—C<u>H</u>$_3$); 4.91 (q, 1 H, C<u>H</u>—CH$_3$, J = 6.8 Hz); 7.50 (d, 2 H, H_{Ar}(3), H_{Ar}(5), J = 8.7 Hz); 8.04 (s, 1 H, Ar—C<u>H</u>=N); 8.30 (d, 2 H, H_{Ar}(2), H_{Ar}(6), J = 8.7 Hz); 11.04 (s, 1 H, N—O<u>H</u>).

***N*-(4-Hydroxy-3-methoxybenzylidene)-*N*-(2-hydroxyimino-1-methylpropyl)amine *N*-oxide (5i).** The yield was 87%, white crystals, m.p. 158 °C. Found (%): C, 52.79; H, 6.62; N, 10.89. $C_{12}H_{16}N_2O_4 \cdot H_2O$. Calculated (%): C, 53.33; H, 6.71; N, 10.36. IR, ν/cm^{-1}: 3519, 2844, 2785, 1601, 1587, 1516, 1407, 1287, 1169, 1142, 1034, 945. ^{1}H NMR (DMSO-d_6), δ: 1.49 (d, 3 H, CH—C<u>H</u>$_3$, J = 6.6 Hz); 1.77 (s, 3 H, N=C—C<u>H</u>$_3$); 3.77 (s, 3 H, OC<u>H</u>$_3$); 4.80 (q, 1 H, C<u>H</u>—CH$_3$, J = 6.6 Hz); 6.82 (d, 1 H, H_{Ar}(5), J = 8.3 Hz); 7.56 (dd, 1 H, H_{Ar}(6), J = 1.9 Hz, J = 8.3 Hz); 7.79 (s, 1 H, Ar—C<u>H</u>=N); 8.19 (d, 1 H, H_{Ar}(2), J = 1.9 Hz); 9.61 (s, 1 H, Ar—O<u>H</u>); 10.97 (s, 1 H, N—O<u>H</u>).

***N*-(4-Chlorobenzylidene)-*N*-(2-hydroxyiminocyclohexyl)-amine *N*-oxide (6c).** The yield was 75%, fluffy white crystals, m.p. 158 °C. Found (%): C, 58.39; H, 5.55; N, 10.64. $C_{13}H_{15}ClN_2O_2$. Calculated (%): C, 58.54; H, 5.67; N, 10.50. IR, ν/cm^{-1}: 3254, 2948, 2865, 1588, 1576, 1485, 1454, 1158, 1089, 943. ^{1}H NMR (DMSO-d_6), δ: 1.56, 1.93, 2.28, 2.44, 2.72 (all m, 8 H, cyclohexane ring); 4.80 (dd, 1 H, NC<u>H</u>—CH$_2$, J = 5.0 Hz, J = 7.5 Hz); 7.48 (d, 2 H, H_{Ar}(3), H_{Ar}(5), J = 8.8 Hz); 7.88 (s, 1 H, Ar—C<u>H</u>=N); 8.29 (d, 2 H, H_{Ar}(2), H_{Ar}(6), J = 8.8 Hz); 11.00 (s, 1 H, N—O<u>H</u>).

Selection of solvents for cyclization of α-arylnitrones. A solution of compound **6c** (0.5 mmol) in toluene (10 mL) was refluxed for 3 h. The solvent was evaporated *in vacuo* of a water-jet pump. According to the ^{1}H NMR spectroscopic and GLC-MS spectrometric data, the residue contained 45% of the starting nitrone, 15% of *para*-chlorobenzaldehyde oxime, 22% of cyclohexen-3-one oxime, and a number of unidentified compounds.

A solution of compound **6c** (0.5 mmol) in acetic acid (10 mL) was refluxed for 3 h. The solvent was evaporated *in vacuo* of a water-jet pump. According to the ^{1}H NMR spectroscopic data, the residue contained 32% of the starting nitrone and 66% of 2-(4-chlorophenyl)-1-hydroxy-4,5,6,7-tetrahydrobenzimidazole (**10c**).

A solution of compound **5c** (0.5 mmol) in toluene (10 mL) (pyridine, *n*-butanol) was refluxed for 3 h. The solvent was evaporated *in vacuo* of a water-jet pump. According to the ^{1}H NMR spectroscopic data, the residue was the starting nitrone **5c**.

A solution of compound **5c** (0.5 mmol) in acetic acid (10 mL) was refluxed for 3 h. The solvent was evaporated *in vacuo* of a water-jet pump. According to the ^{1}H NMR spectroscopic data, the residue contained 36% of the starting nitrone, 60% of 2-(4-chlorophenyl)-1-hydroxy-4,5-dimethylimidazole **9c**, and 3% of *p*-chlorobenzaldehyde.

Cyclization of α-arylnitrones (general procedure A). A solution of α-arylnitrone (**5a,c,d,i**, **6c**) (10 mmol) in acetic acid (25 mL) was refluxed until the starting compound was completely consumed (8—20 h), TLC monitoring. The solvent was evaporated *in vacuo* of a water-jet pump. The residue was dissolved in 5% aqueous hydrochloric acid (50 mL). The solution obtained was stirred for 2 h at ~20 °C with activated charcoal (2 g), filtered through a paper filter, and washed with water (2×10 mL). Aqueous ammonia (concentration ~25%) was added to the filtrate cooled with icy water to pH ~8. A precipitate formed was filtered off, washed with water (4×10 mL), diethyl ether (2×5 mL), and dried in air until the weight was constant. This procedure was used to obtain compounds **9a,c,d,i** and **10c**.

1-Hydroxy-4,5-dimethyl-2-phenylimidazole (9a). The reaction time was 8 h, the yield was 89%, white crystals, m.p. 115 °C (see Ref. 12: m.p. 115 °C).

2-(4-Chlorophenyl)-1-hydroxy-4,5-dimethylimidazole (9c). The reaction time was 8 h, the yield was 92%, white crystals, m.p. 138 °C (see Ref. 13: m.p. 201—202 °C). Found (%): C, 59.59; H, 4.96; N, 12.54. $C_{11}H_{11}ClN_2O$. Calculated (%): C, 59.33; H, 4.98; N, 12.58. IR, ν/cm^{-1}: 3095, 2926, 2850, 1650, 1540, 1493, 1387, 1296, 1094, 832, 751. ^{1}H NMR (CD_3OD), δ: 2.21 (s, 3 H, C<u>H</u>$_3$); 2.27 (s, 3 H, C<u>H</u>$_3$); 7.52 (m, 2 H, H_{Ar}(3), H_{Ar}(5)); 8.18 (m, 2 H, H_{Ar}(2), H_{Ar}(6)).

1-Hydroxy-4,5-dimethyl-2-(4-nitrophenyl)imidazole (9d). The reaction time was 8 h, the yield was 79%, bright yellow crystals, m.p. 220 °C (with decomp.) (see Ref. 13: m.p. 221—223 °C). Found (%): C, 56.58; H, 4.62; N, 17.95. $C_{11}H_{11}N_3O_3$. Calculated (%): C, 56.65; H, 4.75; N, 18.02. IR, ν/cm^{-1}: 3432, 1640, 1595, 1515, 1462, 1344, 1327, 1286, 1091, 855, 752. ^{1}H NMR (DMSO-d_6), δ: 2.09 (s, 3 H, C<u>H</u>$_3$); 2.11 (s, 3 H, C<u>H</u>$_3$); 8.26 (m, 4 H, Ar—H); 12.32 (br.s, 1 H, N—O<u>H</u>).

1-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4,5-dimethylimidazole (9i). The reaction time was 20 h, the yield was 77%, white crystals, m.p. 245 °C (with decomp.) (see Ref. 13: m.p. 258—259 °C). Found (%): C, 61.22; H, 6.13; N, 12.04. $C_{12}H_{14}N_2O_3$. Calculated (%): C, 61.53; H, 6.02; N, 11.96. IR, ν/cm^{-1}: 3427, 2962, 2924, 1649, 1551, 1506, 1462, 1440, 1280, 1225, 1095, 1038, 820, 735. ^{1}H NMR (DMSO-d_6), δ: 2.03 (s, 3 H, C<u>H</u>$_3$); 2.07 (s, 3 H, C<u>H</u>$_3$); 3.77 (s, 3 H, OC<u>H</u>$_3$); 6.79 (d, 1 H, H_{Ar}(5), J = 8.4 Hz); 7.53 (br.s, 1 H, H_{Ar}(6)); 7.68 (br.s, 1 H, H_{Ar}(2)); 9.27 (br.s, 1 H, Ar—O<u>H</u>); 11.80 (br.s, 1 H, N—O<u>H</u>).

2-(4-Chlorophenyl)-1-hydroxy-4,5,6,7-tetrahydrobenzimidazole (10c). The reaction time was 10 h, the yield was 89%, white crystals, m.p. 221 °C. Found (%): C, 62.05; H, 5.26; N, 11.15. $C_{13}H_{13}ClN_2O$. Calculated (%): C, 62.78; H, 5.27; N, 11.26. IR, ν/cm^{-1}: 2938, 2854, 1651, 1540, 1496, 1391, 1359, 1298, 1093, 1013, 830, 796, 750. ^{1}H NMR (DMSO-d_6), δ: 1.73 (br.s, 4 H, C<u>H</u>$_2$—C<u>H</u>$_2$); 2.45 (br.s, 4 H, C=C—C<u>H</u>$_2$); 7.46 (d, 2 H, H_{Ar}(3), H_{Ar}(5), J = 8.7 Hz); 8.03 (br.s, 2 H, H_{Ar}(2), H_{Ar}(6)); 11.86 (br.s, 1 H, N—O<u>H</u>).

Reaction of 1,2-hydroxyamino oxime acetates 1—3 with aromatic (heteroaromatic) aldehydes (general procedure B). A solution of 1,2-hydroxylamino oxime **1—3** (10 mmol) and aromatic (heteroaromatic) (10 mmol) aldehyde **4a—i** in acetic acid (25 mL) was refluxed until the starting compounds were completely consumed (8—20 h), TLC monitoring. The solvent was evaporated *in vacuo* of a water-jet pump. The residue was dis-

solved in 5% aq. hydrochloric acid (50 mL) with slight heating (below 50 °C). The solution obtained was stirred for 2 h at ~20 °C with activated charcoal (3 g). The charcoal was filtered off through a paper filter, washed with water on the filter (2×10 mL). Aqueous ammonia (concentration ~25%) was added to the filtrate cooled with icy water to pH ~8. A precipitate formed was filtered off, washed with water (4×10 mL), diethyl ether (2×5 mL), and dried in air until the weight was constant.

This procedure was used to obtain 1-hydroxyimidazole derivatives **9a—i**, **10a—i**, **11d**,**h**.

1-Hydroxy-4,5-dimethyl-2-phenylimidazole (9a). The reaction time was 8 h, the yield was 86%.

1-Hydroxy-2-(4-methoxyphenyl)-4,5-dimethylimidazole (9b). The reaction time was 20 h, the yield was 55%, white crystals, m.p. 114 °C. Found (%): C, 60.89; H, 6.94; N, 11.76. $C_{12}H_{14}N_2O_2 \cdot H_2O$. Calculated (%): C, 61.00; H, 6.83; N, 11.86. IR, ν/cm^{-1}: 3066, 2922, 2840, 1653, 1614, 1554, 1504, 1464, 1302, 1255, 1180, 1034, 832, 750. ^{1}H NMR (CD_3OD), δ: 2.21 (s, 3 H, C$\underline{H}_3$); 2.25 (s, 3 H, C$\underline{H}_3$); 3.88 (s, 3 H, O—CH_3); 7.07 (d, 2 H, H_{Ar}(3), H_{Ar}(5), J = 8.9 Hz); 8.14 (d, 2 H, H_{Ar}(2), H_{Ar}(6)), J = 8.9 Hz).

2-(4-Chlorophenyl)-1-hydroxy-4,5-dimethylimidazole (9c). The reaction time was 12 h, the yield was 88%.

1-Hydroxy-4,5-dimethyl-2-(4-nitrophenyl)imidazole (9d). The reaction time was 10 h, the yield was 90%.

1-Hydroxy-4,5-dimethyl-2-(3-nitrophenyl)imidazole (9e). The reaction time was 10 h, the yield was 78%, yellow crystals, m.p. 189 °C. Found (%): C, 52.11; H, 5.13; N, 16.58. $C_{11}H_{11}N_3O_3 \cdot H_2O$. Calculated (%): C, 52.59; H, 5.22; N, 16.72. IR, ν/cm^{-1}: 3421, 1646, 1546, 1525, 1348, 1306. ^{1}H NMR (DMSO-d_6), δ: 2.08 (s, 3 H, C$\underline{H}_3$); 2.10 (s, 3 H, C$\underline{H}_3$); 7.69 (t, 1 H, H_{Ar}(5), J = 8.2 Hz); 8.14 (dd, 1 H, H_{Ar}(4), J = 1.9 Hz, J = 8.2 Hz); 8.38 (br.s, 1 H, H_{Ar}(6), H_{Ar}(2)); 8.72 (br.s, 1 H, H_{Ar}(2), H_{Ar}(6)); 12.33 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-4,5-dimethyl-2-(2-nitrophenyl)imidazole (9f). The reaction time was 12 h, the yield was 69%, light yellow crystals, m.p. 234 °C (see Ref. 13: m.p. 243—245 °C). Found (%): C, 56.96; H, 4.88; N, 18.11. $C_{11}H_{11}N_3O_3$. Calculated (%): C, 56.65; H, 4.75; N, 18.02. IR, ν/cm^{-1}: 3435, 3085, 2926, 2886, 1613, 1530, 1353, 857, 788, 711. ^{1}H NMR (DMSO-d_6), δ: 2.03 (s, 3 H, C$\underline{H}_3$); 2.06 (s, 3 H, C$\underline{H}_3$); 7.63 (t, 1 H, H_{Ar}(4), J = 7.9 Hz); 7.70 (br.s, 1 H, H_{Ar}(6), J = 7.3 Hz); 7.77 (dd, 1 H, H_{Ar}(5), J = 7.3 Hz, J = 7.9 Hz); 7.96 (d, 1 H, H_{Ar}(3), J = 7.9 Hz); 11.67 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-4,5-dimethyl-2-(pyridin-4-yl)imidazole (9g). The reaction time was 10 h, the yield was 61%, white crystals, m.p. 150 °C (see Ref. 13: m.p. 187—190 °C). Found (%): C, 63.36; H, 5.82; N, 22.26. $C_{10}H_{11}N_3O$. Calculated (%): C, 63.48; H, 5.86; N, 22.21. IR, ν/cm^{-1}: 1648, 1604, 1552, 1542, 1410, 1295, 1228, 1001, 825, 816, 757. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, C$\underline{H}_3$); 2.09 (s, 3 H, C$\underline{H}_3$); 7.95 (d, 2 H, H_{Py}(2), H_{Py}(6), J = 5.3 Hz); 8.56 (d, 2 H, H_{Py}(3), H_{Py}(5), J = 5.3 Hz); 12.01 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-4,5-dimethyl-2-(pyridin-2-yl)imidazole (9h). The reaction time was 18 h, the yield was 90%, white crystals, m.p. 164 °C. Found (%): C, 62.00; H, 5.90; N, 21.38. $C_{10}H_{11}N_3O \cdot 0.25H_2O$. Calculated (%): C, 62.00; H, 5.98; N, 21.69. IR, ν/cm^{-1}: 3377, 3046, 2921, 2857, 1639, 1589, 1525, 1492, 1447, 1310, 1231, 1154, 1116, 991, 815, 795, 744. ^{1}H NMR (DMSO-d_6), δ: 2.06 (s, 3 H, C$\underline{H}_3$); 2.15 (s, 3 H, C$\underline{H}_3$); 7.32 (ddd, 1 H, H_{Py}(5), J = 1.4 Hz, J = 4.8 Hz, J = 7.8 Hz); 7.88 (dt, 1 H, H_{Py}(4), J = 7.8 Hz, J = 1.4 Hz); 8.57 (d, 1 H, H_{Py}(6), J = 4.8 Hz); 9.05 (br.s, 1 H, H_{Py}(3)); 12.62 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4,5-dimethylimidazole (9i). The reaction time was 20 h, the yield was 78%.

1-Hydroxy-2-phenyl-4,5,6,7-tetrahydrobenzimidazole (10a). The reaction time was 10 h, the yield was 73%, white crystals, m.p. 119 °C. Found (%): C, 72.56; H, 6.36; N, 13.33. $C_{13}H_{14}N_2O$. Calculated (%): C, 72.87; H, 6.59; N, 13.07. IR, ν/cm^{-1}: 3070, 2942, 2856, 2767, 2686, 1652, 1602, 1540, 1500, 1442, 1359, 1298, 1213, 794, 760, 749, 687. ^{1}H NMR (CD_3OD), δ: 1.91 (br.s, 4 H, C$\underline{H}_2$—C$\underline{H}_2$); 2.65 (br.s, 4 H, C=C—C$\underline{H}_2$); 7.52 (m, 3 H, H_{Ar}(3), H_{Ar}(4), H_{Ar}(5)); 8.20 (d, 2 H, H_{Ar}(2), H_{Ar}(6), J = 7.0 Hz).

1-Hydroxy-2-(4-methoxyphenyl)-4,5,6,7-tetrahydrobenzimidazole (10b). The reaction time was 18 h, the yield was 55%, white crystals, m.p. 186 °C. Found (%): C, 64.19; H, 6.80; N, 10.64. $C_{14}H_{16}N_2O_2 \cdot H_2O$. Calculated (%): C, 64.10; H, 6.92; N, 10.68. IR, ν/cm^{-1}: 2934, 2852, 2835, 1655, 1611, 1552, 1506, 1464, 1440, 1300, 1256, 1186, 1042, 830, 746. ^{1}H NMR (CD_3OD), δ: 1.89 (br.s, 4 H, C$\underline{H}_2$—C$\underline{H}_2$); 2.62 (br.s, 4 H, C=C—C$\underline{H}_2$); 3.88 (s, 3 H, O—CH_3); 7.07 (d, 2 H, H_{Ar}(3), H_{Ar}(5), J = 8.7 Hz); 8.14 (d, 2 H, H_{Ar}(2), H_{Ar}(6), J = 8.7 Hz).

2-(4-Chlorophenyl)-1-hydroxy-4,5,6,7-tetrahydrobenzimidazole (10c). The reaction time was 12 h, the yield was 87%.

1-Hydroxy-2-(4-nitrophenyl)-4,5,6,7-tetrahydrobenzimidazole (10d). The reaction time was 6 h, the yield was 79%, bright yellow crystals, m.p. 244 °C. Found (%): C, 60.28; H, 5.08; N, 16.20. $C_{13}H_{13}N_3O_3$. Calculated (%): C, 60.22; H, 5.05; N, 16.21. IR, ν/cm^{-1}: 2944, 1645, 1598, 1519, 1437, 1337, 856. ^{1}H NMR (DMSO-d_6), δ: 1.75 (br.s, 4 H, C$\underline{H}_2$—C$\underline{H}_2$); 2.46 (br.s, 4 H, C=C—C$\underline{H}_2$); 8.26 (m, 4 H, Ar—H); 12.33 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-2-(3-nitrophenyl)-4,5,6,7-tetrahydrobenzimidazole (10e). The reaction time was 6 h, the yield was 93%, light yellow crystals, m.p. 230 °C. Found (%): C, 59.78; H, 5.03; N, 16.28. $C_{13}H_{13}N_3O_3$. Calculated (%): C, 60.22; H, 5.05; N, 16.21. IR, ν/cm^{-1}: 3110, 2949, 1691, 1649, 1538, 1349, 1303, 743. ^{1}H NMR (DMSO-d_6), δ: 1.72 (br.s, 4 H, C$\underline{H}_2$—C$\underline{H}_2$); 2.46 (m, 4 H, C=C—C$\underline{H}_2$); 7.65 (t, 1 H, H_{Ar}(5), J = 8.0 Hz); 8.04 (dd, 1 H, H_{Ar}(4), J = 1.6 Hz, J = 8.0 Hz); 8.30 (d, 1 H, H_{Ar}(6), J = 8.0 Hz); 8.68 (br.s, 1 H, H_{Ar}(2)); 12.67 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-2-(2-nitrophenyl)-4,5,6,7-tetrahydrobenzimidazole (10f). The reaction time was 10 h, the yield was 60%, bright yellow crystals, m.p. 263 °C. Found (%): C, 60.45; H, 5.07; N, 16.29. $C_{13}H_{13}N_3O_3$. Calculated (%): C, 60.22; H, 5.05; N, 16.21. IR, ν/cm^{-1}: 3435, 2940, 2856, 1611, 1574, 1530, 1356, 1304, 859, 785, 714. ^{1}H NMR (DMSO-d_6), δ: 1.73 (br.s, 4 H, C$\underline{H}_2$—C$\underline{H}_2$); 2.46 (br.s, 4 H, C=C—C$\underline{H}_2$); 7.62 (dd, 1 H, H_{Ar}(4), J = 7.7 Hz, J = 8.1 Hz); 7.75 (m, 2 H, H_{Ar}(5), H_{Ar}(6); 7.96 (d, 1 H, H_{Ar}(3), J = 8.1 Hz); 11.63 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-2-(pyridin-4-yl)-4,5,6,7-tetrahydrobenzimidazole (10g). The reaction time was 24 h, the yield was 90%, white crystals, m.p. 203 °C. Found (%): C, 64.48; H, 6.08; N, 18.34. $C_{12}H_{13}N_3O \cdot 0.5H_2O$. Calculated (%): C, 64.27; H, 6.29; N, 18.74. IR, ν/cm^{-1}: 2936, 2847, 1598, 1550, 1440, 1406, 1354, 1208, 829, 798, 755. ^{1}H NMR (CD_3OD), δ: 1.91 (br.s, 4 H, C$\underline{H}_2$—C$\underline{H}_2$); 2.65 (br.s, 4 H, C=C—C$\underline{H}_2$); 8.20 (d, 2 H, H_{Py}(2), H_{Py}(6), J = 6.0 Hz); 8.65 (d, 2 H, H_{Py}(3), H_{Py}(5), J = 6.0 Hz).

1-Hydroxy-2-(pyridin-2-yl)-4,5,6,7-tetrahydrobenzimidazole (10h). The reaction time was 18 h, the yield was 79%, white crystals, m.p. 170 °C. Found (%): C, 67.14; H, 6.29; N, 19.54. $C_{12}H_{13}N_3O$. Calculated (%): C, 66.96; H, 6.09; N, 19.52. IR, ν/cm^{-1}: 3051, 2940, 2924, 2852, 1631, 1588, 1517, 1488, 1441,

1298, 1101, 791, 733, 660. ^{1}H NMR (CD_3OD), δ: 1.90 (br.s, 4 H, $C\underline{H}_2$—$C\underline{H}_2$); 2.67 (br.s, 4 H, C=C—$C\underline{H}_2$); 7.38 (ddd, 1 H, $H_{Py}(5)$, J = 1.1 Hz, J = 4.8 Hz, J = 7.8 Hz); 7.93 (dt, 1 H, $H_{Py}(4)$, J = 7.8 Hz, J = 1.1 Hz); 8.64 (d, 1 H, $H_{Py}(6)$, J = 4.8 Hz); 8.88 (d, 1 H, $H_{Py}(3)$, J = 7.8 Hz).

1-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-4,5,6,7-tetrahydrobenzimidazole (10i). The reaction time was 24 h, the yield was 85%, white crystals, m.p. 241 °C. Found (%): C, 64.45; H, 6.29; N, 10.54. $C_{14}H_{16}N_2O_3$. Calculated (%): C, 64.60; H, 6.20; N, 10.76. IR, ν/cm^{-1}: 2944, 2856, 1651, 1547, 1508, 1280, 1227, 1141, 1041, 764. ^{1}H NMR (DMSO-d_6), δ: 1.70 (br.s, 4 H, $C\underline{H}_2$—$C\underline{H}_2$); 2.42 (br.s, 4 H, C=C—$C\underline{H}_2$); 3.76 (s, 3 H, $OC\underline{H}_3$); 6.78 (d, 1 H, $H_{Ar}(5)$, J = 8.0 Hz); 7.50 (br.s, 1 H, $H_{Ar}(2)$, $H_{Ar}(6)$); 7.62 (br.s, 1 H, $H_{Ar}(2)$, $H_{Ar}(6)$); 9.34 (br.s, 1 H, Ar—O$\underline{H}$); 11.94 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-2-(4-nitrophenyl)-4,5-pentamethyleneimidazole (11d). The reaction time was 8 h, the yield was 89%, dark yellow crystals, m.p. 218 °C. Found (%): C, 61.06; H, 5.45; N, 14.86. $C_{14}H_{15}N_3O_3$. Calculated (%): C, 61.53; H, 5.53; N, 15.38. IR, ν/cm^{-1}: 2929, 2853, 1635, 1597, 1518, 1449, 1340, 1109, 853. ^{1}H NMR (DMSO-d_6), δ: 1.66 (br.s, 4 H, $C\underline{H}_2$—$C\underline{H}_2$); 1.77 (br.s, 2 H, $C\underline{H}_2$), 2.65 (m, 4 H, C=C—$C\underline{H}_2$); 8.26 (m, 4 H, Ar—H); 12.10 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-2-(pyridin-2-yl)-4,5-pentamethyleneimidazole (11h). The reaction time was 16 h, the yield was 63%, white crystals, m.p. 171 °C. Found (%): C, 62.82; H, 6.81; N, 16.98. $C_{13}H_{15}N_3O \cdot H_2O$. Calculated (%): C, 63.14; H, 6.93; N, 16.99. IR, ν/cm^{-1}: 3050, 2919, 2846, 1626, 1588, 1521, 1486, 1437, 1248, 1051, 790. ^{1}H NMR (DMSO-d_6), δ: 1.62 (m, 4 H, $C\underline{H}_2$—$C\underline{H}_2$); 1.74 (m, 2 H, $C\underline{H}_2$); 2.67 (m, 4 H, C=C—$C\underline{H}_2$); 7.31 (ddd, 1 H, $H_{Py}(5)$, J = 1.5 Hz, J = 4.6 Hz, J = 7.7 Hz); 7.87 (dt, 1 H, $H_{Py}(4)$, J = 7.7 Hz, J = 1.5 Hz); 8.55 (d, 1 H, $H_{Py}(6)$, J = 4.6 Hz); 8.99 (br.s, 1 H, $H_{Py}(3)$); 12.73 (br.s, 1 H, N—O$\underline{H}$).

1-Hydroxy-4-methyl-2-(4-nitrophenyl)-5-phenylimidazole (15) and 1-hydroxy-5-methyl-2-(4-nitrophenyl)-4-phenylimidazole (16) were obtained as a mixture of isomers (ratio **15** : **16** = = 1 : 2.3 according to the ^{1}H NMR spectroscopic data) by the reaction of compound **14** with aldehyde **4d** according to the procedure given above. The yield of the mixture of compounds **15** and **16** was 70%. The ^{1}H NMR spectrum of the predominant isomer **16** is given below. ^{1}H NMR spectrum of the minor isomer of imidazole **15** (DMSO-d_6), δ: 2.27 (s, 3 H, $C\underline{H}_3$); 7.51 (t, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 7.6 Hz); 7.61 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$), J = 7.6 Hz); other signals are overlapped with the strong signals of the predominant isomer.

1-Hydroxy-5-methyl-2-(4-nitrophenyl)-4-phenylimidazole (16). A mixture of compound **17** (1.63 g, 10 mmol), aldehyde **4d** (1.51 g, 10 mmol), and ammonium acetate (1.54 g, 20 mmol) was refluxed for 2 h in ethanol (40 mL). The solvent was evaporated *in vacuo*, the residue was triturated with water (50 mL). A precipitate was filtered off, washed with water (3×10 mL), dried in air until the weight was constant. The yield was 2.06 g (70%). Yellow crystals, m.p. 211 °C. Found (%): C, 61.71; H, 4.90; N, 13.04. $C_{16}H_{13}N_3O_3 \cdot H_2O$. Calculated (%): C, 61.34; H, 4.83; N, 13.41. IR, ν/cm^{-1}: 1595, 1526, 1348, 1333, 1209, 853. ^{1}H NMR (DMSO-d_6), δ: 2.44 (s, 3 H, $C\underline{H}_3$); 7.28 (t, 1 H, $H_{Ar}(4)$, J = 7.6 Hz); 7.43 (t, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 7.6 Hz); 7.73 (d, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$, J = 7.6 Hz); 8.31 (m, 2 H, $H_{Ar}(2)$, $H_{Ar}(6)$); 8.38 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$); 12.30 (br.s, 1 H, N—O$\underline{H}$).

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