The peculiarities of the 4-carboxyphenylglyoxal and N-alkoxy-N’-ary lureas interaction

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Keywords: N-alkoxy-N’-ary lureas, N-alkoxy-N’-alkylureas, aryglyoxals; synthesis; 3-alkoxy-1-aryl-5-(4-carboxypheny)l-4,5-dihydroxyimidazolidin-2-ones; 5-(4-carboxypheny)l-4,5-dihydroxy-1-methyl-3-propoxyimidazolidin-2-one; 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-ones.

It was found that 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones are the only products of interaction of N-alkoxyureas with aryglyoxals which have strong electronegative substituent in the forth position of the aryl moiety. The possibility of obtaining such products as 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones, 3-alkoxy-1-alkyl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones and 3-alkoxy-1-phenyl-4,5-dihydroxy-5-(4-nitrophenyl)-imidazolidin-2-ones has been verified in the experimental way. In most the cases 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones were produced as a mixture of diastereomers.

INTRODUCTION

As it was shown in our previous publications,[1-6] the aryglyoxals’ interaction with N-hydroxyurea and N-alkoxyureas is a very promising way to get valuable pharmaceutical materials. Three types of products can be produced by this reaction. As we have shown some of the products transform into others.

The following products can be obtained from this reaction: substituted ureas 1, diastereomers of 3,4,5-trihydroxy-5-arylimidazolidin-2-ones, 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones 2 and 3 respectively, or 3-hydroxy- or 3-alkoxyhydantoins 4.

![Diagram](https://via.placeholder.com/150)

Scheme 1. The products of interaction of aryglyoxals with N-hydroxyurea or N-alkoxyureas.

The mechanism of this interaction could not be completely established because of lack of experimental evidence. In any case the formation pattern of each product type is valuable. It is important to know this pattern not only in order to determine the reaction mechanism, but also to get further perspective synthones and materials in pharmacy, organic synthesis and bioorganic chemistry.

The relevance of the products which can be obtained by the interaction of aryglyoxals with N-hydroxyurea or N-alkoxyureas is significant because of the importance of imidazolidin-2-ones and imidazolidin-2,4-diones among pharmaceutical materials.[7-10] Aryglyoxals are widely used in synthesis of these biologically active nitrogen-containing heterocycles.[11]

Despite the differences between the products of the aryglyoxals interaction with N-hydroxyurea or N-alkoxyureas we have observed several patterns in their formation. In fact, the type of the product strongly depends on the glyoxal reagent. However, when we use aryglyoxals with electron-donating groups in aryl moiety, the substituted ureas 1 might be not the only products of this reaction.[1] As usual the first type products, substituted ureas 1, forms imidazolidin-2-ones 2 and 3, which further turns into hydantoins 4. Nevertheless, it is possible to obtain only the substituted ureas 5 in this interaction.[2,6] For this result the strong intramolecular effects should take place in the compounds 5 (Scheme 2).

The mixture of the second type products, 4,5-dihydroxyimidazolidin-2-ones 2 and 3, and the third type of products, hydantoins 4, are obtained in all the other cases. This fact serves as clear evidence that the cyclization of substituted ureas into 5-arylimidazolidin-2-ones is an easy process. This process could be retarded by intramolecular effect or steric factor.[1,2,4,6]

Very often the second type products, 4,5-dihydroxyimidazolidin-2-ones 2 and 3, turn into third type products, hydantoins 4,[1,6] but not always.
Reaction of 4-carboxyphenyl glyoxal with N-alkoxy-N’-arylethers

Scheme 2. Formation of the substituted ureas as the only product in the interaction of arylglyoxals with N-alkoxyureas.

For now the most convenient method of getting only the third type product is using acetic acid as a solvent for the reaction of arylglyoxals with N-hydroxyurea or N-alkoxyureas. The products are only 3-hydroxyhydrantoines 6 or 3-alkoxyhydrantoines 7 respectively (Scheme 3).

Scheme 3. The products of interaction of arylglyoxals with N-hydroxyurea or N-alkoxyureas in acetic acid.

Only the second type products were formed in the reactions of 4-nitrophenylglyoxal with N-hydroxyurea or N-alkoxy-N-arylethers. In fact 4-nitrophenylglyoxal reacts with N-hydroxyurea producing only the mixture of 5-aryl-3,4,5-trihydroxyimidazolidin-2-ones 8a and 8b in molar ratio approximately 3:1 (Scheme 4).

Scheme 4. The products of 4-nitrophenylglyoxal interaction with N-hydroxyurea or N-alkoxy-N’-arylethers.

Also, 4-nitrophenylglyoxal reacts with N-alkoxy-N’-arylethers in acetic acid at room temperature mainly producing 3-alkoxy-1-aryl-4,5,5S-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-ones 9a-g (Scheme 4). These compounds have 4-hydroxyl and 5-hydroxyl groups in the cis-conformation to each other.

It was shown that the reaction of 4-nitrophenylglyoxal with N-n-propoxy-N’-methylurea in acetic acid leads mainly to the formation of 3-n-propoxy-1-methyl-4,5S-dihydroxy-5-(4-nitrophenyl)imidazolidin-2-one 11a (11a:11b=99:1) (Scheme 5).

Scheme 5. The products of 4-nitrophenylglyoxal interaction with N-n-propoxy-N’-methylurea.

The diastereomers of 5-aryl-4,5-dihydroxyimidazolidin-2-one 8a,9a,11a with cis-orientation of 4-HO- and 5-HO-groups to each other prevailed over the trans isomers for all the experiences.

To sum up all the information about arylglyoxals interaction with N-hydroxyurea derivatives we should note that the experimental investigation of the second type product formation overall pattern needed to be continued. For this reason we have chosen to explore the reaction of 4-carboxyphenylglyoxal with different N-alkoxy-N’-arylethers in acetic acid medium and for at least one case to change this alkoxyurea’s reagent to the one of the N-alkoxy-N’-arylethers.

EXPERIMENTAL

$^1$H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz) and VARIAN VNMRS 400 spectrometer (400 MHz). $^{13}$C NMR spectra were recorded on a Varian VXP-300 spectrometer (75 MHz). The solvents DMSO-d$_6$ and CDCl$_3$ were used. $^1$H NMR chemical shifts relative to the residual solvent protons as an internal standard [(CD$_3$)$_2$SO: 2.500 ppm, CDCl$_3$: 7.260 ppm] were reported. Solvent carbon atoms served as an internal standard for $^{13}$C NMR spectra [(CD$_3$)$_2$SO: 39.52 ppm]. Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). The solvents were purified and dried according to the standard procedures.

4-Nitrophenylglyoxal hydrate was obtained according to the standard procedure by oxidation of 4-nitrocetophenone with H$_2$SeO$_4$ in boiling acetic acid for 2h, then removing AcOH under vacuum and crystallization of the residue from boiling water, as yellow powder, m.p. 87–89 ºC. $^1$H NMR (400 MHz, DMSO-d$_6$): δ = 5.66 (1H, t, J = 6.8, CH$_3$(OH)$_2$), 7.03 (2H, d, J = 6.8, CH$_2$(OH)$_2$), 8.29 (2H, d, J = 9.2, H Ar), 8.34 (2H, d, J = 9.2, H Ar).

$^{339-344}$ http://dx.doi.org/10.17628/ecb.2020.9.339-344

4-Carboxyphenylglyoxal hydrate was obtained according to the similar standard procedure by oxidation 4-acetylbenzoic acid oxidation by H2SO4 in boiling acetic acid for 3h, then removing AcOH under vacuum and crystallization of the residue from boiling water, as an unstable pink powder. 1H NMR (400 MHz, DMSO-d6): δ = 5.672 (1H, s, CH), 6.885 (2H, br. s, OH), 8.051 (2H, d, J = 8.0 Hz, Ar), 8.161 (2H, d, J = 8.0 Hz, Ar), 13.321 (1H, br. s, COOH).

N-n-Butyloxy-N'-phenyleuene

A solution of phenylisocyanate (1.240g, 10.413 mmol) in benzene (5 mL) was added to a solution of n-butylamine (0.975 g, 10.933 mmol) in benzene (8 mL), the reaction mixture was kept at 60 °C for 30 min, then the solvent was evaporated under vacuum (2 mmHg) at 20 °С, the residue was washed by cold (-5ºC) hexane, evaporated under vacuum (20 mmHg) and hexane (8 mL) was added. After keeping at -5ºC for 20 h the obtained precipitate was filtered off, washed by cold (-5ºC) hexane, dried under vacuum (5 mmHg), giving 1.843 g (85 %) of N-n-butyloxy-N'-phenyleuene, colorless crystals, m.p. 77–79 °C. 1HNMR (300 MHz, DMSO-d6): δ = 0.900 (3H, t, J = 7.5 Hz, NO(CH2)3Me), 1.356 (2H, sex, J = 7.5 Hz, NOCH2CH2CH3Me), 1.608 (2H, quint, J = 7.2 Hz, NOCH2CH2CH3Me), 3.765 (2H, t, J = 7.2 Hz, NOCH2), 6.983 (1H, t, J = 7.8 Hz, C(4)H Ph), 7.257 (2H, t, J = 7.8 Hz, C(3)H, C(5)H Ph), 7.551 (2H, t, J = 7.8 Hz, C(2)H, C(6)H Ph), 8.665 (1H, s, NH), 9.431 (1H, s, NHO). MS (FAB) m/z 209 [M+H]+ (100). Calc. for C14H13NO2: C 63.44, H 7.74, N 13.45. Found: C 63.31, H 7.56, N 13.15.

3-n-Butyloxy-4,5-dihydroxy-5-(4-carboxyphenyl)-1-phenylimidazolidin-2-one (12)

4-Carboxyphenylglyoxal hydrate (71.2 mg, 0.3634 mmol) was added to the solution of N-n-butyloxy-N'-phenyleuene (75.9 mg, 0.364 mmol) in acetic acid (5 mL), the reaction mixture was stirred for 29 h at 22 °C, then the negligible precipitate was filtered off, the filtrate was evaporated under vacuum (4 mmHg) at 20 °С, the residue was washed by water and dried under vacuum (4 mmHg), giving 134 mg (91 %) of monohydrate of 3-n-butyloxy-4,5-dihydroxy-5-(4-carboxyphenyl)-1-phenylimidazolidin-2-one 12, colorless crystals, m.p. 108–111 °C. 1H NMR (300 MHz, DMSO-d6): δ = 0.899 (3H, t, J = 7.2 Hz, NO(CH2)3Me), 1.399 (2H, sex, J = 7.2 Hz, NOCH2CH2CH3Me), 1.611 (2H, quint, J = 7.2 Hz, NOCH2CH2CH3Me), 3.999 (2H, t, J = 6.0 Hz, NOCH2), 4.856 (1H, d, J = 6.3 Hz, CHOH), 6.987–7.082 (3H, m, OH, CHOH and C(4)H Ph), 7.188 (2H, t, J = 7.5 Hz, C(3)H, C(5)H Ph), 7.385 (2H, d, J = 7.5 Hz, C(2)H, C(6)H Ph), 7.586 (2H, d, J = 8.4 Hz, C(2)H, C(6)H2Cl), 7.875 (2H, d, J = 8.4 Hz, C(3)H, C(5)H2Cl), 12.977 (1H, s, COOH). 13C NMR (75 MHz, DMSO-d6): δ = 20.40 (Me), 63.95 (NOME), 87.23 (CHOH), 87.90 (COH), 125.13, 127.00, 127.98, 130.45, 133.41, 134.63 (C Ar), 144.67 [C(1) C6H4Me, C- N], 156.92 (NCO=O), 166.90 (COOH). MS (FAB) m/z 359 [M+H]+ (41), 341 [M+H+H2O]+ (10), 256 (7), 238 (9), 208 (100), 181 (37), 149 (76), 133 (28), 121 (8), 106 (19). Calc. for C14H13NO2H2O, %: C 54.63, H 4.83, N 8.18. Found, %: 55.78, H 5.54, N 7.42.

5-(4-Carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloxyimidazolidin-2-one (14)

4-Carboxyphenylglyoxal hydrate (74.6 mg, 0.380 mmol) was added to the solution of N-propoxy-N'-methylurea1 (89.9 mg, 0.499 mmol) in acetic acid (8 mL), the reaction mixture was stirred for 38 h at 20 °С, then the negligible precipitate was filtered off, and the filtrate was evaporated under vacuum (2 mmHg) at 20 °С, yielding 175 mg (93 %) of the mixture of diastereoisomers 13a and 13b in molar ratio 91:9 (1HNMR spectrum). This mixture was extracted by water (4 mL) at 43°C for 23 h, the obtained precipitate was filtered off and dried under vacuum, then precipitate was filtered off and dried under vacuum giving 118 mg (63 %) of monohydrate of 4,5-dihydroxy-5-(4-carboxyphenyl)-3-methoxy-1-(4-methylphenyl)imidazolidin-2-one 13a, white solid, mp. 81–83 °C. 1H NMR (300 MHz, DMSO-d6): δ = 2.164 (3H, s, Me), 3.817 (3H, s, NOME), 4.891 (1H, d, J = 5.4 Hz, CHOH), 6.991 (2H, d, J = 8.7 Hz, C(3)H, C(5)H C6H4Me), 7.017–7.076 (2H, m, CHOH and OH), 7.241 (2H, d, J = 8.7 Hz, C(2)H, C(6)H C6H4Me), 7.577 (2H, d, J = 8.1 Hz, C(2)H, C(6)H C6H4COOH), 7.842 (2H, d, J = 8.1 Hz, C(3)H, C(5)H C6H4COOH), 12.952 (1H, br. s, COOH). 13C NMR (75 MHz, DMSO-d6): δ = 20.40 (Me), 63.95 (NOME), 87.23 (CHOH), 87.90 (COH), 125.13, 127.00, 127.98, 130.45, 133.41, 134.63 (C Ar), 144.67 [C(1) C6H4Me, C- N], 156.92 (NCO=O), 166.90 (COOH). MS (FAB) m/z 359 [M+H]+ (41), 341 [M+H+H2O]+ (10), 256 (7), 238 (9), 208 (100), 181 (37), 149 (76), 133 (28), 121 (8), 106 (19). Calc. for C14H13NO2H2O, %: C 54.64, H 5.35, N 7.44. Found, %: 55.78, H 5.54, N 7.42.
diastereomer

*N-Octyloxy-*N'-phenylurea

A solution of phenylisocyanate (0.714 g, 5.994 mmol) in benzene (5 mL) was added to a solution of *N*-octyloxyamine (0.959 g, 6.600 mmol) in benzene (8 mL). The reaction solution was maintained at 20 °C for 95 h, after that it was boiled 0.5 h, then the benzene evaporated under vacuum (2 mmHg) for 23 h, the formed precipitate was filtered off, washed by water (10 mL) and dried under vacuum (2 mmHg) giving 1.335 (84 %) of *N*-octyloxy-1-phenylimidazolidin-2-one (16).

**RESULTS AND DISCUSSION**

We found that *N*-alkoxy-*N'*-arylamines react with 4-carboxyphenylglyoxal in acetic acid medium at room temperature yielding the mixtures of diastereomers of 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones, 12,13 (Scheme 6).

**N-Non-octyloxy-9'-phenylurea**

A solution of phenylisocyanate (0.596 g, 5.003 mmol) in benzene (5 mL) was added to a solution of *N*-non-octyloxyamine (1.007 g, 5.001 mmol) in benzene (8 mL). The reaction solution was maintained at 20 °C for 95 h, after that it was boiled 0.5 h, then the benzene evaporated under vacuum (2 mmHg) for 23 h, the formed precipitate was filtered off, washed by water (10 mL) and dried under vacuum (2 mmHg) giving 1.335 (84 %) of *N*-octyloxy-1-phenylimidazolidin-2-one (16).

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<th>3-N-Dodecyloxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-one (16)</th>
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We assume, in the interaction of 4-nitrophenylglyoxals with N-alkoxy-N'-aryleneureas, that the main product in both cases is similar. In the last case it is the diastereomer 12a or 13a with 4-hydroxyl- and 5-hydroxyl groups in the cis-conformation to each other. Their percentage in the products’ mixtures is approximately 91-98 %.

In a similar way the N-propyloxy-N'-methylurea’s interaction with 4-carboxyphenylglyoxal produces only 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propoxylimidazolidin-2-one 14 (Scheme 7). In this interaction the only one diastereomer 14 is formed. It becomes clear that it has cis orientation of 4-HO- and 5-HO-groups in the cis-conformation to each other. So, the result is similar to the 4-nitrophenylglyoxal’s interaction with N-propyloxy-N'-methylurea.

Thus, the formation pattern of the second type products, 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones, in the arylglyoxal reaction with N-alkoxyureas has been clarified. It is necessary to use arylglyoxals with a strong electron-withdrawing substituent in 4-position of the aryl moiety to obtain these products. Additionally we have studied the interaction of 4-nitrophenylglyoxal with N-n-alkoxy-N'-phenyleneurea which has a long carbon chain in order to obtain 3-alkoxy-4,5-dihydroxy-5-(aryl)-1-phenylimidazolidin-2-ones with lipophilic N-alkoxy moiety. The main reason for this was to find out whether the alkoxy substituent in urea reagent influences the reaction or not.

As the experimental results have shown, N-n-octyloxy-N'-phenyleneurea and N-n-dodecyloxy-N'-phenyleneurea interact with 4-nitrophenylglyoxal forming only a mixture of diastereomers of hydrophobic 3-alkoxy-4,5-dihydroxy-5-(4-nitrophenyl)-1-phenylimidazolidin-2-ones 15,16 (Scheme 8).

The mixture of these diastereomers contains more than 90 % of cis,4,5-dihydroxy diastereomers 15a,16a. The trace amounts of trans,4,5-dihydroxy diastereomers 15b,16b can be easily removed by crystallization. The products of the 4-nitrophenylglyoxal interaction with N-n-octyloxy-N'-phenyleneurea and N-n-dodecyloxy-N'-phenyleneurea demonstrate, that the nature of the N-alkoxy substituent in urea does not influence the reaction.

We propose the next scheme of the arylglyoxals interaction with N-hydroxyurea or N-alkoxyureas (Scheme 9) to explain the fact that diastereomers with cis orientation of 4-HO- and 5-HO-groups dominate over the trans 4,5-dihydroxy diastereomers in all the reactions which are reported in this study.

According to this scheme in the beginning of the interaction the open-chain N-substituted urea 17 is formed. Compounds 17 may be stabilized by the intramolecular hydrogen bond. The acyclic urea 17 form further the compounds 12–16. Thus, the diastereomers 12a-16a with 4-HO- and 5-HO-groups in the cis-conformation to each other have been produced. It is probable that the diastereomers 12a-16a are also stabilized by the intramolecular hydrogen bond. N-Alkoxylurea 17A slowly transforms into a conformation 17B by the rotation of carbamoyl moiety around N–C bond or the N-alkoxy nitrogen inversion. The conformation 17B eventually forms trans,4,5-dihydroxy diastereomers 12b-16b.

Probably the low process temperature (approximately 20°C) preserves the further isomerization of the formed cis,4,5-dihydroxy diastereomers 12a-16a into trans,4,5-dihydroxy diastereomers 12b-16b.
It is evident that the presence of a strong electronegative substituent in the forth position of 5-aryl moiety, such as carboxyl group or nitro group, destabilizes “benzylic” cation A and makes the further transformation of the compounds 12-16 into hydantoins 18 impossible.

CONCLUSIONS

We have shown that reaction of 4-carboxyphenylglyoxal with N-alkoxy-N'-arylureas in acetic acid at room temperature produces only 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones. It is the new practical evidence of the possibility of obtaining only the second type products, 3-alkoxy-4,5-dihydroxyimidazolidin-2-ones, from the interaction of arylglyoxals with N-hydroxyurea derivatives. Using N-propyloxyn-N'-methylurea as a reagent in this reaction leads to the similar product – 5-(4-carboxyphenyl)-4,5-dihydroxy-1-methyl-3-propyloximidazolidin-2-one. Obtaining 3-alkoxy-4,5-dihydroxy-5-arylimidazolidin-2-ones with lipophilicity fragment is also possible in this reaction. Thus, a new practical application of the interaction between arylglyoxals and N-alkoxyureas has been found.

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Received: 05.08.2020.
Accepted: 05.19.2020.