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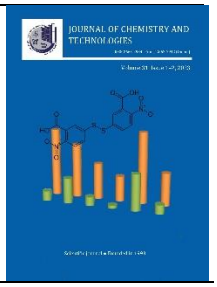

UDC 547.783

THE 4-HALOGENOPHENYLGLYOXALS INTERACTION WITH *N*-ALKOXY-*N'*-ARYLUREAS

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Abstract

Aim. To investigate the 4-X-phenylglyoxal (X = F, Cl, Br) interaction with *N*-alkoxy-*N'*-arylureas in acetic acid medium at room temperature. Methods. Mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy. Results. We have showed these reaction type peculiarities and several different tendencies depending on the aryl glyoxal moiety structure. In this article we have described the influence of this moiety at the stage of the hydantoin formation. It has been found that the 4-fluorophenylglyoxal hydrate interacts with *N*-methoxy-*N'*-phenylurea in acetic acid during 99 h at 26 °C yielding the mixture of 5-(4-fluorophenyl)-*cis*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one, 5-(4-fluorophenyl)-*trans*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one, and 5-(4-fluorophenyl)-3-methoxy-1-phenylimidazolidine-2,4-dione. The 5-(4-fluorophenyl)-3-methoxy-1-phenylimidazolidine-2,4-dione is yielded because of the additional exposure the products mixture in acetic acid during 260 h. The 4-chlorophenylglyoxal hydrate reacts with *N*-ethoxy-*N'*-phenylurea in acetic acid at 26–27 °C during 219 h yielding the mixture of 5-(4-chlorophenyl)-3-ethoxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one and 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione. After being processed by the *p*-toluenesulfonic acid this mixture is converted in pure 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione. 4-Bromophenylglyoxal hydrate interacts with *N*-*n*-butyloxy-*N'*-phenylurea in acetic acid during 52 h at 26 °C yielding only the mixture of the diastereomers of 5-(4-bromophenyl)-3-*n*-butyloxy-4,5-dihydroxy-1-phenylimidazolidin-2-one. The molar ratio of 5-(4-bromophenyl)-3-*n*-butyloxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one and 5-(4-bromophenyl)-3-*n*-butyloxy-*trans*-4,5-dihydroxy-1-phenylimidazolidin-2-one is 91 : 9. The diastereomers of 5-(4-bromophenyl)-3-*n*-butyloxy-4,5-dihydroxy-1-phenylimidazolidin-2-one were converted into 5-(4-bromophenyl)-3-*n*-butyloxy-1-phenylimidazolidine-2,4-dione because of the *p*-toluenesulfonic acid action. As a conclusion we have proposed the possible mechanism of 3-alkoxy-5-aryl-4,5-dihydroxy-1-phenylimidazolidin-2-ones conversion into 3-alkoxy-5-aryl-1-phenylhydantoins. Conclusions. It has been found that the 4-halogenophenylglyoxal interaction with *N*-alkoxy-*N'*-phenylureas in acetic acid at room temperature under the further processing by of *p*-toluenesulfonic acid is new way to synthetize 3-alkoxy-5-(4-halohenophenyl)-1-phenylhydantoins. It has been shown that there is a certain tendency depending on the 4-halogenophenyl substituent nature of the influence on the reaction.

Keywords: arylglyoxals; *N*-alkoxy-*N'*-arylureas; synthesis; 3-alkoxy-5-aryl-4,5-dihydroxy-1-phenylimidazolidin-2-ones; 3-alkoxy-5-aryl-1-phenylimidazolidine-2,4-diones.

ВЗАЄМОДІЯ 4-ГАЛОГЕНОФЕНІЛГЛІОКСАЛЕЙ З *N*-АЛКОКСИ-*N'*-АРИЛСЕЧОВИНАМИ

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Анотація

Мета. Дослідити взаємодію 4-Х-фенілгліоксалей (X = F, Cl, Br) з *N*-алкокси-*N'*-арилсечовинами в оцтовій кислоті за кімнатної температури. Методи. Мас-спектрометрія, ^{1}H та ^{13}C ЯМР спектроскопія. Результати. Нами показано, що особливості реакцій даного типу і деякі інші особливості залежать від будови арильного замісника гліоксалю. В цій статі ми демонструємо вплив замісника на стадію утворення гідантоїну. Знайдено, що гідрат 4-фторофенілгліоксалю реагує з *N*-метокси-*N'*-фенілсечовиною в оцтовій кислоті на протязі 99 год. за 26 °C з утворенням суміші of *цис*-4,5-дигідрокси-3-метокси-1-феніл-5-(4-фторофеніл)імідазолідин-2-ону, *транс*-4,5-дигідрокси-3-метокси-1-феніл-5-(4-фторофеніл)імідазолідин-2-ону та 3-метокси-1-феніл-5-(4-

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фторофеніл)імідазолідин-2,4-діоне. Внаслідок додаткової витримки цієї суміші продуктів в оцтовій кислоті на протязі 260 год. утворюється 3-метокси-1-феніл-5-(4-фторофеніл)імідазолідин-2,4-діон. 4-Хлорофенілгліоксальгідрат реагує з *N*-етокси-*N'*-фенілсечовиною в оцтовій кислоті за 26–27 °С на протязі 219 год. з утворенням суміші 3-етокси-*цис*-4,5-дигідрокси-1-феніл-5-(4-хлорофеніл)імідазолідин-2-ону та 3-етокси-1-феніл-5-(4-хлорофеніл)імідазолідин-2,4-діону. Після обробки *п*-толуенсульфокислотою ця суміш перетворюється у чистий 3-етокси-1-феніл-5-(4-хлорофеніл)імідазолідин-2,4-діон. 4-Бромофенілгліоксальгідрат взаємодіє з *N*-*н*-бутилокси-*N'*-фенілсечовиною в оцтовій кислоті на протязі 52 год. за 26 °С з утворенням тільки суміші діастереомерів 5-(4-бромофеніл)-3-*н*-бутилокси-4,5-дигідрокси-1-фенілімідазолідин-2-ону. Мольне співвідношення 5-(4-бромофеніл)-3-*н*-бутилокси-*цис*-4,5-дигідрокси-1-фенілімідазолідин-2-ону і 5-(4-бромофеніл)-3-*н*-бутилокси-*транс*-4,5-дигідрокси-1-фенілімідазолідин-2-ону становить 91 : 9. Діастереомери 5-(4-бромофеніл)-3-*н*-бутилокси-4,5-дигідрокси-1-фенілімідазолідин-2-ону були перетворені у 5-(4-бромофеніл)-3-*н*-бутилокси-1-фенілімідазолідин-2,4-діон дією *п*-толуенсульфокислоти. Ми запропонували можливий механізм перетворення 3-алкокси-5-арил-4,5-дигідрокси-1-фенілімідазолідин-2-онів у 3-алкокси-5-арил-1-фенілгідантоїни. Висновки. Знайдено, що взаємодія 4-галогенофенілгліоксалей з *N*-алкокси-*N'*-фенілсечовинами в оцтовій кислоті за кімнатної температури з подальшою обробкою *п*-толуенсульфокислотою є новим синтезом 3-алкокси-5-(4-галогенофеніл)-1-фенілгідантоїнів. Показано вплив 4-галогенофенільного замісника на перебіг цієї реакції.

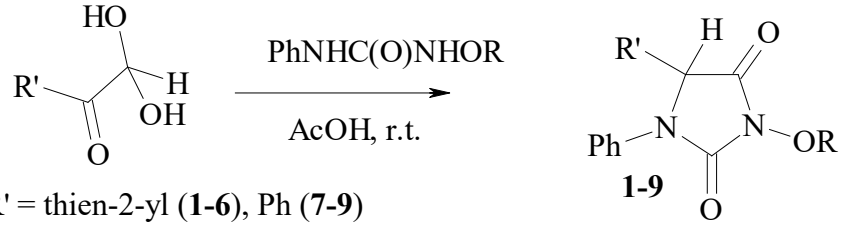
Ключові слова: арилгліоксалі; *N*-алкокси-*N'*-арилсечовини; синтез; 3-алкокси-5-арил-4,5-дигідрокси-1-фенілімідазолідин-2-они; 3-алкокси-5-арил-1-фенілімідазолідин-2,4-діони.

Introduction

Hydantoins are widely used in the pharmaceutical industry [1–8]. Their role is difficult to underestimate as they are used in target oriented syntheses as well as anticonvulsants, muscle relaxants, anti-androgen and antibacterial pharmaceuticals [4]. Also, *N*-hydroxyurea and it derivatives are valuable pharmaceutical materials [9]. We are deeply convinced that *N*-hydroxyhydantoins and *N*-alkoxyhydantoins may bring a huge practical value in the field of pharmaceutical and medical industries as well. Our recent research in the arylglyoxals [10] has shown a completely new way to receive the *N*-hydroxyhydantoins [11–14] and *N*-alkoxyhydantoins [12–21]. We would like to continue discussing these research results in this article.

Earlier we had studied the interaction of thien-2-ylglyoxal and phenylglyoxal hydrates with different kinds of *N*-alkoxy-*N'*-arylureas in acetic acid medium at room temperature [16].

As it is shown at the image below thien-2-ylglyoxal reacts with *N*-alkoxy-*N'*-phenylureas selectively forming 3-alkoxy-1-phenyl-5-(thien-2-yl)hydantoins **1**–**6** [16] (Scheme 1).



R' = thien-2-yl (**1-6**), Ph (**7-9**)

1-9

Scheme 1. Thien-2-ylglyoxal and phenylglyoxal interaction with the *N*-alkoxy-*N'*-phenylurea [16].
A. R'=2-C_4H_3S, R=Me (1), Et (2), n-Pr (3), i-Pr (4), n-Bu (5), CH_2CH_2Ph (6); B. R'=Ph, R=Et (7), n-Bu (8), $(CH_2)_7Me$ (9)

Phenylglyoxal reacts with the most of *N*-alkoxy-*N'*-phenylureas in the same way with a selective formation of 3-alkoxy-1,5-bis(phenyl)hydantoins **7**–**9** [16] (Scheme 1).

The interaction of phenylglyoxal hydrate with *N*-methoxy-*N'*-phenylurea yields the mixture of 4,5-dihydroxy-3-methoxy-1,5-bis(phenyl)imidazolidin-2-ones **10a**,**b** and *N*-methoxyhydantoin **11**. The separation of these products faced many difficulties. However, their mixture is converted into pure *N*-methoxyhydantoin **11** under the after being processed by the trifluoroacetic acid [16]. At the same time 3-methoxy-1,5-bis(phenyl)hydantoin **11** has been obtained by the one-step synthesis from *N*-methoxy-*N'*-phenylurea and phenylglyoxal with the further addition of only $TsOH \cdot H_2O$ to the reaction mixture [16] (Scheme 2).

Also, it has been found that phenylglyoxal interacts with *N*-benzyloxy-*N'*-(4-bromophenyl)urea and *N'*-4-bromophenyl-*N*-propyloxyurea in acetic acid at room temperature, selectively forming the mixture of the diastereomers of 3-benzyloxy-1-(4-bromophenyl)-4,5-dihydroxy-5-phenylimidazolidin-2-one **12a,b** and 1-(4-bromophenyl)-4,5-dihydroxy-5-phenyl-3-propyloxyimidazolidin-2-one **13a**,**b** [16] (Scheme 3). Compounds **12**, **13** have been easily converted in the proper *N*-alkoxyhydantoins after being processed by the trifluoroacetic acid or *p*-toluenesulphonic acid [16].

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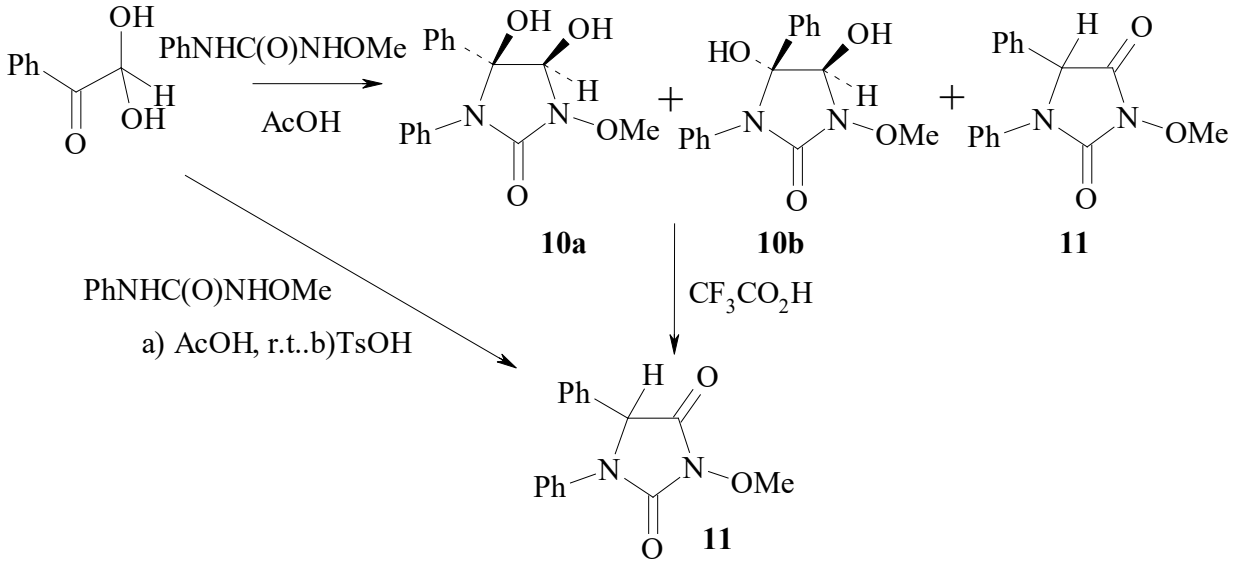
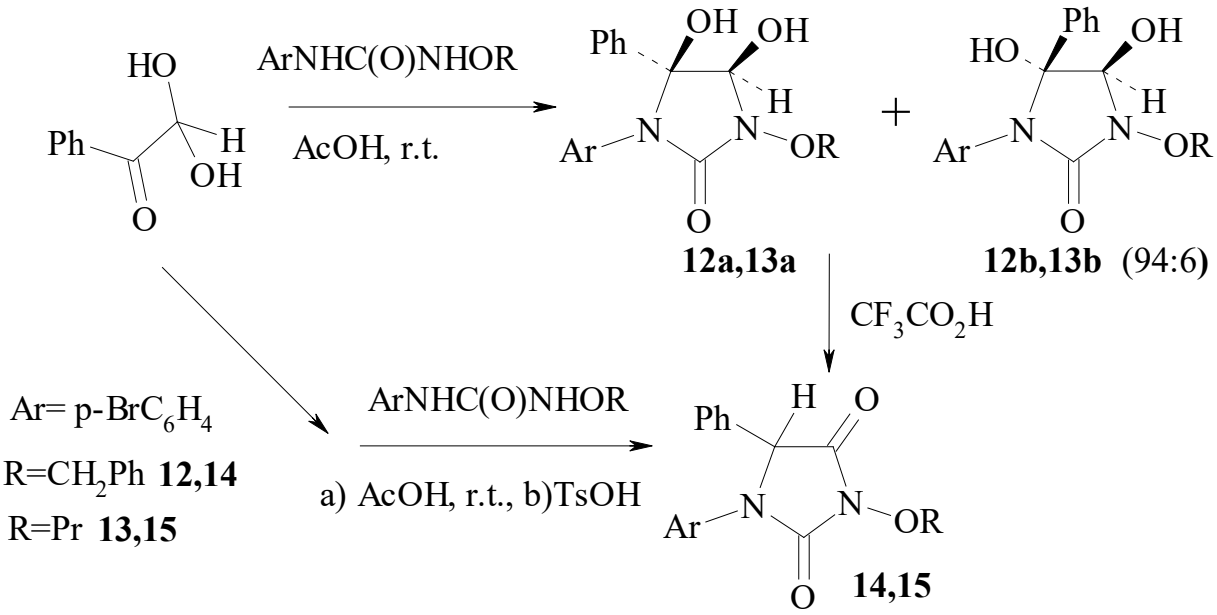


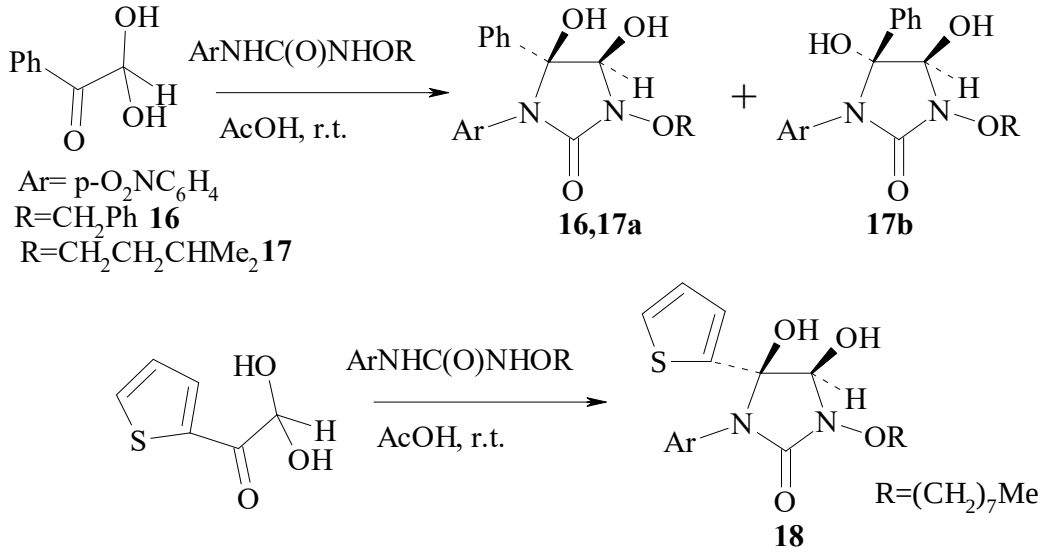
Scheme 2. Phenylglyoxal interaction with *N*-methoxy-*N'*-phenylurea. The synthesis of 3-methoxy-1,5-bis(phenyl)hydantoin (11) [16]



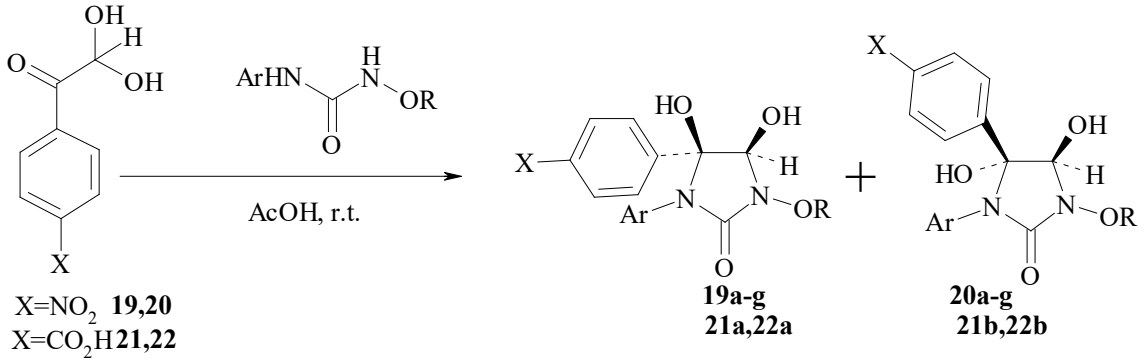
Scheme 3. Phenylglyoxal interaction with *N*-benzyloxy-*N'*-(4-bromophenyl)urea and *N'*-4-bromophenyl-*N*-propyloxyurea [16].

Phenylglyoxal interacts with *N*-benzyloxy-*N'*-(4-nitrophenyl)urea and *N*-(3-methylbutyloxy)-*N'*-(4-nitrophenyl)urea in acetic acid at room temperature, selectively forming 3-benzyloxy-*cis*-4,5-dihydroxy-1-(4-nitrophenyl)-5-phenylimidazolidin-2-one **16** and the mixture of the diastereomers of 4,5-dihydroxy-3-(3-methylbutyloxy)-1-(4-nitrophenyl)-5-phenylimidazolidin-2-one **17a,b**, respectively (Scheme 4). The molar ratio **17a**:**17b** is 95 : 5. Thien-2-ylglyoxal interacts with *N*-*n*-octyloxy-*N'*-4-nitrophenylurea in acetic acid at room temperature selectively forming *cis*-4,5-dihydroxy-3-*n*-octyloxy-1-(4-nitrophenyl)-5-(2-thienyl)imidazolidin-2-one **18** [16].

4-Nitrophenylglyoxal interacts with *N*-alkoxy-*N'*-phenylureas yielding 3-alkoxy-4,5-dihydroxy-5-aryl-1-phenylimidazolidin-ones **19a**,**b** and **20a**,**b** [17] (Scheme 5).



Scheme 4. Phenylglyoxal and thien-2-ylglyoxal interaction with *N*-alkoxy-*N'*-(4-nitrophenyl)ureas [16].



Scheme 5. 4-Nitrophenylglyoxal [17] and 4-oxaldehydoylbenzoic acid [15] interaction with the *N*-alkoxy-*N'*-phenylureas [15]. X=NO_2, 19,20 Ar=Ph, R=Me(a), Et(b), Bn(c); Ar=4-MeC_6H_4, R=Me(d), Bu(e); Ar=4-BrC_6H_4, R=Et(f), Bu(g); X=CO_2H, 21a,b Ar=Ph, R=Bu; 22a,b Ar=4-MeC_6H_4, R=Me

In the same way *N*-alkoxy-*N*'-arylureas react with 4-oxaldehydoylbenzoic acid yielding the mixtures of diastereomers of 3-alkoxy-1-aryl-5-(4-carboxyphenyl)-4,5-dihydroxyimidazolidin-2-ones **21a**,**b**, **22a**,**b** [15] (Scheme 5). In both cases the main product is the diastereomer **19a**–**g**, **21a** or **22a** with 4-hydroxyl- and 5-hydroxyl groups in the *cis*-conformation to each other (91–98 %).

But the interaction of other kinds of arylglyoxals with *N*-alkoxy-*N'*-arylureas remains unexplored. To determine the peculiarities of the reaction was extremely important because *N*-alkoxyhydantoins may bring as pharmaceutically relevant building blocks.

Thus, the goal of our present research was to investigate the 4-X-phenylglyoxal (X = F, Cl, Br) interaction with *N*-alkoxy-*N'*-phenylureas in acetic acid medium at room temperature. The novelty of this work lies in its investigation of the influence of the 4-X-phenyl moiety at the reaction stage of the hydantoin formation. We used ureas with different *N*-alkoxy groups to determine their effect on the reaction.

Experimental

^{1}H NMR spectra were recorded on a VARIAN VNMRS 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded ona VARIAN VNMRS 400 spectrometer (100 MHz). The solvent DMSO-d_6 was used. ^{1}H NMR chemical shifts relative to the residual solvent protons as an internal standard [$(CD_3)_2SO$: 2.500 ppm] were reported. Solvent carbon atoms served as an internal standard for ^{13}C NMR spectra [$(CD_3)_2SO$: 39.52 ppm; $CDCl_3$ 77.16 ppm]. Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB). Melting points were determined in a capillary with a PTOP sulfuric acid apparatus. The solvents were purified and dried according to the standard procedures.

4-Fluorophenylglyoxal interaction with N-methoxy-N'-phenylurea. A. 5-(4-Fluorophenyl)-3-methoxy-1-phenylimidazolidine-2,4-dione **(24).** 4-Fluorophenylglyoxal hydrate (68 mg, 0.397 mmol) was dissolved in the solution of *N*-methoxy-*N'*-phenylurea (60 mg, 0.361 mmol) [22] in acetic acid (4 ml). The obtained solution was maintained at 26 °C during 99 h. Then acetic acid was

evaporated under vacuum (2 mmHg), the residue was washing by water (10 ml). Then the residue was dried under vacuum (2 mmHg), yielding 108 mg white viscous oil. According to ^{1}H NMR, this product is a mixture of 5-(4-fluorophenyl)-*cis*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **23a**, 5-(4-fluorophenyl)-*trans*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **23b,** and 5-(4-fluorophenyl)-3-methoxy-1-phenylimidazolidine-2,4-dione **24** in the ratio **23a** : **23b** : **24** = 39.3 : 6.0 :5 4.7 (mol. %). This product (105 mg) was dissolved in acetic acid (4 ml). The obtained solution was maintained at 26 °C during 260 h. Then acetic acid was evaporated under vacuum (4 mmHg), the obtained residue was extracted by water (7 ml) at 11°C during 20h. Then the water extract was eliminated, the residue was dried under vacuum (2 mmHg), yielding 5-(4-fluorophenyl)-3-methoxy-1-phenylimidazolidine-2,4-dione **24** (58 mg, 53.5 %), as white amorphous solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 3.949 (3H, s, NOMe); 6.026 (1H, s, C(H) Hydantoin); 7.110 (1H, t, ^3J = 7.6 Hz, C(4)H, Ph); 7.188 (2H, t, ^3J = 7.6Hz, C(3)H, C(5)H Ph); 7.323 (2H, dd, ^3J = 8.2 Hz,^3J = 8.4 Hz, C(2)H C(6)HC_6H_4F); 7.450–7.523 (4H, m, C(2)H, C(6)H Ph and C(3)H, C(5)H C_6H_4F). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm): δ = 60.81 C(H), Hydantoin; 65.00 NOMe; 115.93 d, $^{C\text{-}F}J$ = 22.0 Hz, C(3)H, C(5)H C_6H_4F; 121.18 C(2)H, C(6)H Ph; 124.92 C(4)H Ph; 128.90 C(3)H, C(5)H Ph; 129.015d,$^{C\text{-}F}J$ = 3.0 Hz, C(1) C_6H_4F; 129.79 d,$^{C\text{-}F}J$ = 8.0 Hz, C(2)H, C(6)H C_6H_4F; 135.70 C(1) Ph; 150.47 N(C=O)N; 162.26 d,$^{C\text{-}F}J$ = 244.0 Hz, C(4)–F C_6H_4F; 164.64d,$^{C\text{-}F}J$ = 1.0 Hz, C=O. Mass spectrum (FAB), *m/z*(I_{rel},%): 301 $[M+H]^+$ (100); 123 (10). Anal. Calc. for $C_{16}H_{13}FN_2O_3$ %: C 64.00; H 4.36; N 9.33. Found, %: C 63.87; H 4.58; N 9.12.

B.5-(4-Fluorophenyl)-cis-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **(23a)** 4-Fluorophenylglyoxal hydrate (68.7 mg, 0.404 mmol) was dissolved in the solution of *N*-methoxy-*N*'-phenylurea (61 mg, 0.367 mmol) in acetic acid (4 ml). The obtained solution was maintained at 22–24 °C during 9 h, then acetic acid was quickly evaporated under vacuum (2 mmHg), the obtained residue was extracted by water (7 ml) at 10°C during 20 h. Then the water extract was eliminated, the residue was dried under vacuum (2 mmHg), yielding 5-(4-fluorophenyl)-*cis*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **23a** (81 mg, 69 %), white solid, mp. 59–62 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 3.814 (3H, s, NOMe); 4.876 (1H, d, ^3J = 6.8 Hz, CHOH); 6.975 (1H, s, C–OH); 7.010 (1H, d, ^3J = 6.8 Hz, CHOH); 7.057 (1H, t, ^3J = 7.6 Hz, C(4)H Ph); 7.110 (2H, t, ^3J = 8.6 Hz, C(3)H, C(5)H Ph); 7.197 (2H, dd, ^3J = 8.8 Hz, ^{HF}J = 8.0 Hz, C(3)H, C(5)H C_6H_4F); 7.365 (2H, d, ^3J = 8.0 Hz, C(2)H, C(6)H Ph); 7.494 (2H, dd, ^3J = 8.8 Hz, ^{HF}J = 5.6 Hz, C(2)H, C(6)H C_6H_4F). Mass spectrum (FAB), *m/z*(I_{rel},%): 341 $[M+Na]^+$ (30); 319 $[M+H]^+$(50); 301 $[M+H-H_2O]^+$(16); 182 (100); 123 (66).

4-Chlorophenylglyoxal interaction with N-ethoxy-N'-phenylurea. A. 4-Chlorophenylglyoxal hydrate (85 mg, 0.458 mmol) was dissolved in the solution of *N*-ethoxy-*N*'-phenylurea (75 mg, 0.416 mmol) in acetic acid (5 ml). The obtained solution was maintained at 25 °C during 5 h, then acetic acid was evaporated under vacuum (4 mmHg), the obtained residue was extracted by water (8 ml). Then the aqueous extract was eliminated, the residue was dried under vacuum (2 mmHg) yielding 140 mg of white amorphous solid. According to ^{1}H NMR, this product is a mixture of 5-(4-chlorophenyl)-3-ethoxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one **25a**, 5-(4-chlorophenyl)-3-ethoxy-*trans*-4,5-dihydroxy-1-phenylimidazolidin-2-one **25b** and 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione **26** in the molar ratio 84.7:10.2:5.1 (in $CDCl_3$), 81.3 : 10.6 : 8.1 [in $(CD_3)_2SO$)].

5-(4-Chlorophenyl)-3-ethoxy-cis-4,5-dihydroxy-1-phenylimidazolidin-2-one **25a,** white amorphous solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 1.222 (3H, t, ^3J = 7.4 Hz, $NOCH_2Me$); 3.960–4.089 (2H, m, $NOCH_2$); 4.832 (1H, d, ^3J = 6.8 Hz; CHOH); 6.980 (1H, s, C–OH); 7.001 (1H, d, ^3J = 6.8 Hz; CHOH); 7.052 (1H, t, ^3J = 7.6 Hz, C(4)H, Ph); 7.200 (2H, t, ^3J = 7.8 Hz, C(3)H, C(5)H Ph); 7.353 (2H, d_{AB}, ^3J = 9.2 Hz, C(2)H, C(6)H C_6H_4Cl); 7.373(2H, d, ^3J = 8.4 Hz, C(2)H, C(6H Ph); 7.474 (2H, d_{AB}, ^3J = 9.2 Hz, C(3)H, C(5)H C_6H_4Cl). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 14.00 Me; 72.63 $NOCH_2$; 87.28 CHOH; 87.50 C–OH; 124.48 C(2)H, C(6) PhN; 126.02 C(4)H PhN; 127.92 C(3)H, C(%)H C_6H_4Cl; 128.74 C(2)H, C(6)H C_6H_4Cl; 128.94 C(3)H, C(5)H PhN; 134.95 C(1) C_6H_4Cl; 135.28 C(1) PhN; 137.23 C(4)–Cl C_6H_4Cl; 157.99 C=O. Mass spectrum (FAB, *m/z*(I_{rel},%)): 333 $[M+H]^+$ (30); 331 $[M+H]^+$ (100). Mass spectrum (FAB), *m/z*(I_{rel},%): 373 $[M+Na]^+$ (4); 371 $[M+Na]^+$ (13); 351 $[M+H]^+$(17); 349 $[M+H]^+$(53); 333 $[M+H-H_2O]^+$(6); 331 $[M+H-H_2O]^+$(17); 214 (37); 212 (100); 141 (19); 139 (80).

4-Chlorophenylglyoxal interaction with N-ethoxy-N'-phenylurea. **B.** Chlorophenylglyoxal hydrate (107 mg, 0.573 mmol) was dissolved in the solution of *N*-ethoxy-*N*'-phenylurea (94 mg, 0.522 mmol) [16; 17] in acetic acid (5 ml). The obtained solution was maintained at 27–28 °C during 29 h, then acetic acid was evaporated under vacuum (4 mmHg), the obtained residue

was extracted by water (8 ml). Then the aqueous extract was eliminated, the residue was dried under vacuum (2 mmHg), yielding 208 mg of white amorphous solid. Accordingly ^{1}H NMR, this product is a mixture of the compounds **25a**, **25b** and **26** in the molar ratio18.3:3.0:75.2. This product (184 mg) was dissolved in acetic acid (4 ml). The obtained solution was maintained at 26 °C during 190 h. Then acetic acid was evaporated under vacuum (4 mmHg), the obtained residue was extracted by water (5 ml), the aqueous extract was eliminated. The residue was dried under vacuum (2 mmHg) yielding the mixture compounds **25a** and **26** in the molar ratio 12.3:87.7. This product was dissolved in acetic acid (5 ml), TsOH•H_2O (66 mg) was added. The obtained solution was maintained at 26 °C during 60 h, after that AcONa (200 mg) was added. Then acetic acid was evaporated under vacuum (4 mmHg), the obtained residue was extracted by water (8 ml), the aqueous extract was eliminated. The residue was dried under vacuum (2 mmHg) giving 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione **26** (115 mg, 66 %), white solid, mp. 28–31ºC. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 1.265 (3H, t, ^3J = 7.0 Hz, $NOCH_2Me$); 4.112–4.263 (2H, m, $NOCH_2$); 6.051 (1H, s; CH Hydantoin); 7.069–7.157 (1H, m, C(4)H, Ph); 7.267–7.363 (2H, m, C(3)H, C(5)H Ph); 7.392–7.5321 (6H, m, C(2)H, C(6)H Ph; C(2)H, C(6)H, C(3)H, C(5)H C_6H_4Cl). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm): δ = 13.43 Me; 60.75 C(H) Hydantoin; 73.12 $NOCH_2$; 121.06 C(2)H, C(6) PhN; 124.92 C(4)H PhN; 128.95 C(3)H, C(%)H C_6H_4Cl; 129.08 C(2)H, C(6)H C_6H_4Cl; 129.43 C(3)H, C(5)H PhN; 131.98 C(1) C_6H_4Cl; 133.71 C(1) PhN; 135.76 C(4)–Cl C_6H_4Cl; 150.84 NC(=O)N; 164.96 C=O. Mass spectrum (FAB), *m/z*(I_{rel}, %) : 333 $[M+H]^+$ (30); 331 $[M+H]^+$ (100). Anal. Calc. for $C_{17}H_{15}ClN_2O_3$ %: C 61.73; H 4.57; N 8.47. Found, %: C 61.80; H 4.76; N 8.23.

4-Bromophenyglyoxall interaction with N-n-butyloxy-N'-phenylurea. A. 5-(4-Bromophenyl)-3-n-butyloxy-4,5-dihydroxy-1-phenylimidazolidin-2-one **(27)**. 4-Bromophenylglyoxal hydrate (96 mg, 0.413 mmol) was dissolved in the solution of *N*-*n*-butyloxy-*N*'-phenylurea (82 mg, 0.394 mmol) [14; 16] in acetic acid (5 ml). The obtained solution was maintained at 26 °C during 52 h, then acetic acid was evaporated under vacuum (4 mmHg). The obtained residue was extracted by water (10 ml), the aqueous extract was eliminated. The residue was dried under vacuum (2 mmHg) yielding 5-(4-bromophenyl)-3-*n*-butyloxy-4,5-dihydroxy-1-phenylimidazolidin-2-one **27** (206 mg) as white amorphous solid. According to ^{1}H NMR, this product is mixture of 5-(4-bromophenyl)-3-*n*-butyloxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one **27a** and 5-(4-bromophenyl)-3-*n*-butyloxy-*trans*-4,5-dihydroxy-1-phenylimidazolidin-2-one **27b** in the molar ratio **27a** : **27b**=91 : 9 mol.%.

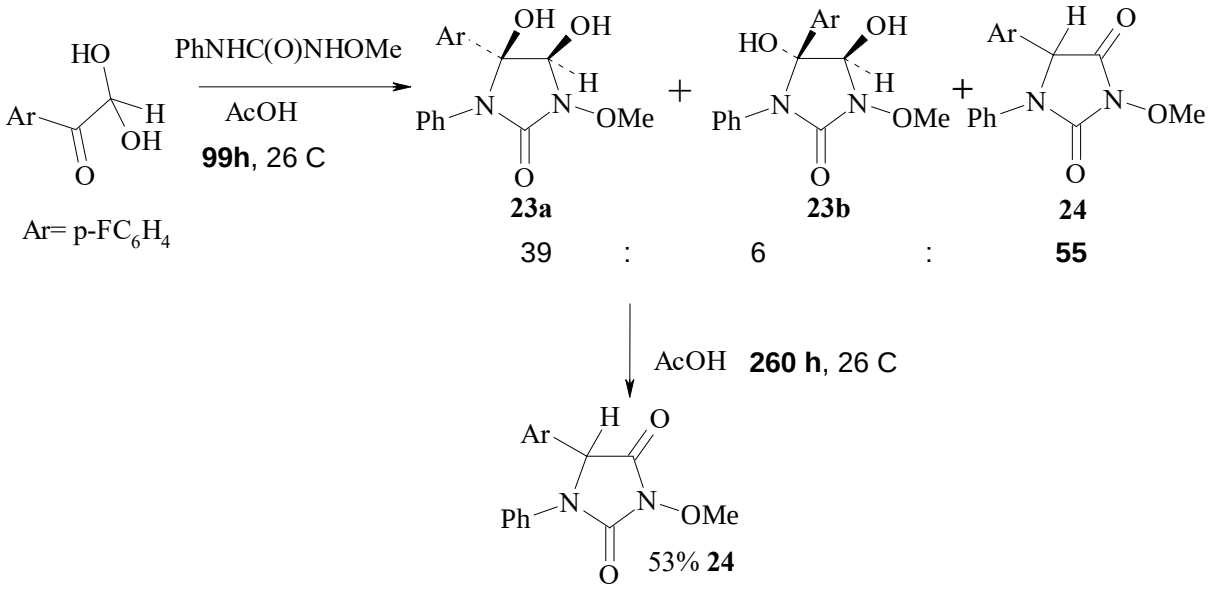
5-(4-Bromophenyl)-3-n-butyloxy-cis-4,5-dihydroxy-1-phenylimidazolidin-2-one **(27a)**, white amorphous solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 0.899 (3H, t, ^3J = 7.6 Hz, $NO(CH_2)_3$ Me); 1.398 (2H, sex, ^3J = 7.6 Hz, $NO(CH_2)_2CH_2Me$); 1.604 (2H, quint, ^3J = 6.8 Hz, $NOCH_2CH_2CH_2Me$); 3.939–4.027 (2H, m, $NOCH_2$); 4.828 (1H, d, ^3J = 6.0 Hz; CHOH); 6.968–7.005 (2H, m, C–OH, CHOH); 7.052 (1H, t, ^3J = 7.6 Hz, C(4)H, Ph); 7.198 (2H, t, ^3J = 7.6 Гц, C(3)H, C(5)H Ph); 7.355–7.391 (2H, m, C(2)H, C(6)H Ph); 7.406 (2H, d_{AB}, ^3J = 8.8 Hz, C(2)H, C(6)H C_6H_4Br); 7.488 (2H, d_{AB}, ^3J = 8.8 Гц, C(3)H, C(5)H C_6H_4Br). ^{1}H NMR (400 MHz,$CDCl_3$, ppm): δ = 0.922 (3H, t, ^3J = 7.4 Hz, $NO(CH_2)_3$ Me); 1.405 (2H, sex, ^3J = 7.4 Hz, $NO(CH_2)_2CH_2Me$); 1.657 (2H, quint, ^3J = 7.4 Hz, $NOCH_2CH_2CH_2Me$); 4.012–4.066 (2H, m, $NOCH_2$); 4.946 (1H, s; CHOH); 7.088 (1H, t, ^3J = 7.8 Hz, C(4)H, Ph); 7.197 (2H, t, ^3J = 7.8 Hz, C(3)H, C(5)H Ph); 7.348 (2H, d_{AB}, ^3J = 8.8 Hz, C(2)H, C(6)H C_6H_4Br); 7.365–7.403 (2H, m, C(2)H, C(6)H Ph); 7.451 (2H, d_{AB}, ^3J = 8.8 Hz, C(3)H, C(5)H C_6H_4Br). Mass spectrum (FAB), *m/z*(I_{rel},%): 445 $[M+Na]^+$(25); 443 $[M+Na]^+$(32); 423 $[M+H]^+$(64); 421 $[M+H]^+$(68); 405 $[M+H-H_2O]^+$(18); 403 $[M+H-H_2O]^+$(21); 286 (82); 284 (79); 185 (93); 183 (10). Anal. Calc. for $C_{19}H_{21}BrN_2O_4$ %: C 54.17; H 5.02; N 6.65. Found, %: C 53.91; H 5.35; N 6.52.

5-(4-Bromophenyl)-3-n-butyloxy-1-phenylimidazolidine-2,4-dione **(28).** 5-(4-Bromophenyl)-3-*n*-butyloxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one **27a** (86 mg, 0.204 mmol)) was dissolved in the solution of TsOH•H_2O (39 mg, 0.205 mmol) in acetic acid (4 ml). The obtained solution was maintained at 28ºC during 93 h, then AcONa (82 mg, 0.1 mmol) was added. Then acetic acid was evaporated under vacuum (4 mmHg), the obtained residue was extracted by water (11 ml), the aqueous extract was eliminated. The residue was dried under vacuum (2 mmHg) yielding 5-(4-bromophenyl)-3-*n*-butyloxy-1-phenylimidazolidine-2,4-dione **28** (80 mg, 97 %), as yellowish amorphous solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 0.906 (3H, t, ^3J = 7.2 Hz, $NO(CH_2)_3$ Me); 1.430 (2H, sex, ^3J = 7.2 Hz, $NO(CH_2)_2CH_2Me$); 1.634 (2H, quint, ^3J = 6.9 Hz, $NOCH_2CH_2CH_2Me$); 4.085–4.201 (2H, m, $NOCH_2$); 6.028 (1H, s, CH, Hydantoin); 7.109 (1H, t, ^3J = 7.2 Hz, C(4)H, Ph); 7.322 (2H, t, ^3J = 7.8 Hz, C(3)H, C(5)H Ph); 7.396 (2H, d_{AB}, ^3J = 8.8 Hz, C(2)H, C(6)H C_6H_4Br); 7.490 (2H, d, ^3J = 7.6 HzC(2)H, C(6)H Ph); 7.560 (2H, d_{AB},

^3J = 8.8 Hz, C(3)H, C(5)H C_6H_4Br). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, ppm): δ = 13.56 Me; 18.32, 29.48 CH_2; 60.75 C–H, Hydantoin; 77.04 $NOCH_2$; 120.93 C(2)H, C(6)H Ph; 122.28 C(4)–Br C_6H_4Br; 124.83 C(4)H Ph; 128.91 C(3)H, C(5)H Ph; 129.70 C(2)H, C(6)H C_6H_4Br; 131.94 C(3H, C(5)H C_6H_4Br; 132.35 C(1) C_6H_4Br; 135.70 C(1) Ph; 150.76 N(C=O)N; 164.73 C=O. Mass spectrum (FAB), *m/z* (I_{rel},%):405 $[M+H]^+$ (100); 403 $[M+H]^+$ (98); 348 $[M+H–Bu]^+$ (11); 346 $[M+H–Bu]^+$ (10); 331 (6); 329 (8); 212 (21); 210 (22). Anal. Calc. for $C_{19}H_{19}BrN_2O_3$ %: C 56.59; H 4.75; N 6.95. Found, %: C 56.38; H 4.82; N 6.77.

Results and discussion

The interaction of 4-fluorophenylglyoxal hydrate with *N*-methoxy-*N*'-phenylurea (acetic acid, 99 h, 26 °C) yields the mixture of 5-(4-fluorophenyl)-*cis*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **23a**, 5-(4-fluorophenyl)-*trans*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **23a**, and 5-(4-fluorophenyl)-3-methoxy-1-phenylimidazolidine-2,4-dione **24** (Scheme 6). The molar ratio of these products is **23a** : **23b** : **24** = 39 : 6 : 55 (^1H NMR).



Scheme 6. **4-Fluorophenylglyoxal interaction with *N*-methoxy-*N*'-phenylurea.**

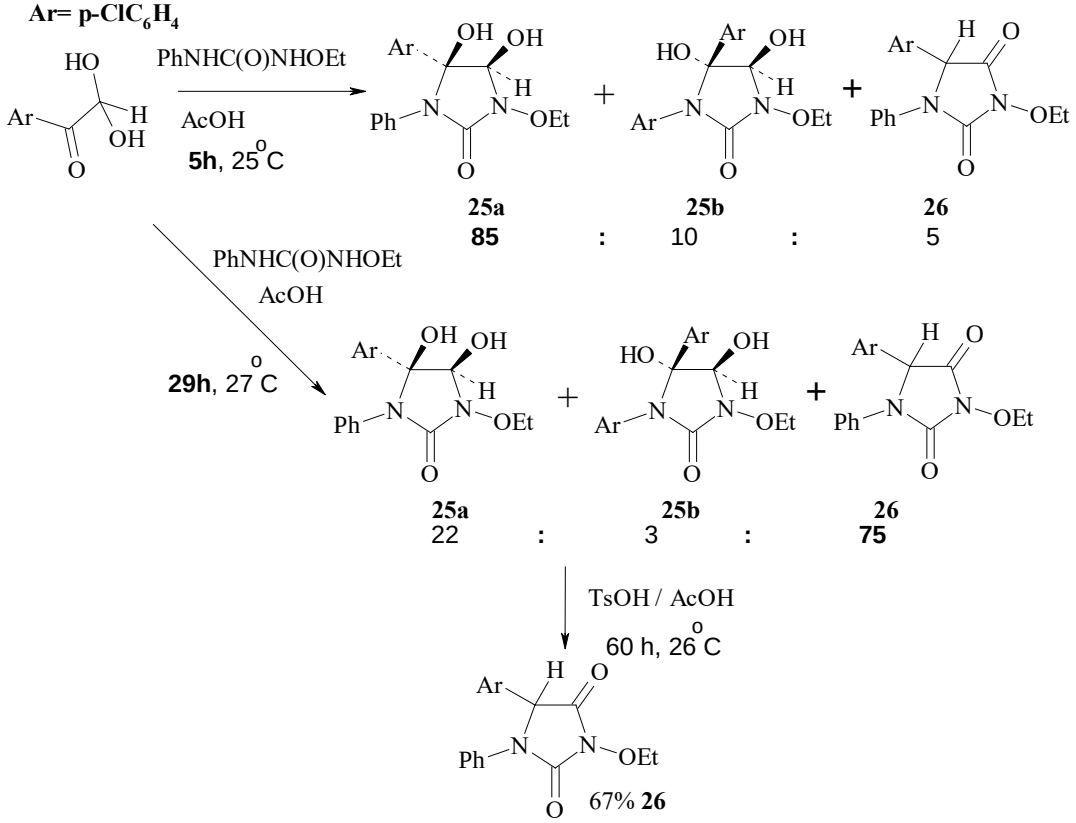
The separation of this mixture into the individual components is has been a very difficult process that took time and efforts. But this mixture has been converted in the pure *N*-methoxyhydantoin **24** because of the additional processing by acetic acid during 260 h at 26 °C. The structure of *N*-methoxyhydantoin **24** had been proved by the data of ^1H and ^{13}C NMR spectra and mass spectrum.

The interaction of 4-fluorophenylglyoxal with *N*-methoxy-*N*'-phenylurea in acetic acid during 9 h at 22–24 °C yields only 5-(4-fluorophenyl)-*cis*-4,5-dihydroxy-3-methoxy-1-phenylimidazolidin-2-one **23a**. The structure of compound **23a** has been proved by the ^1H NMR spectra and mass spectrum.

The hydrate of 4-chlorophenylglyoxal reacts with *N*-ethoxy-*N*'-phenylurea in acetic acid at 25°C during 5 h yielding the mixture of 5-(4-chlorophenyl)-3-ethoxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one **25a**, 5-(4-chlorophenyl)-3-ethoxy-*trans*-4,5-dihydroxy-1-phenylimidazolidin-2-one **25b** and 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione**26** in the molar ratio 85 : 10 : 5 (Scheme 7). 5-(4-Chlorophenyl)-3-ethoxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one**25a** has been described by the ^1H, ^{13}C NMR spectra and mass spectrum.

If this reaction occurs during 29 h at 27°C the ratio of these products is 22:3:75 (Scheme 7). The further maintaining the obtained reaction products in acetic acid during 190 h at 26 °C yields the mixture of compounds **25a** and **26** in the molar ratio 12 : 88.

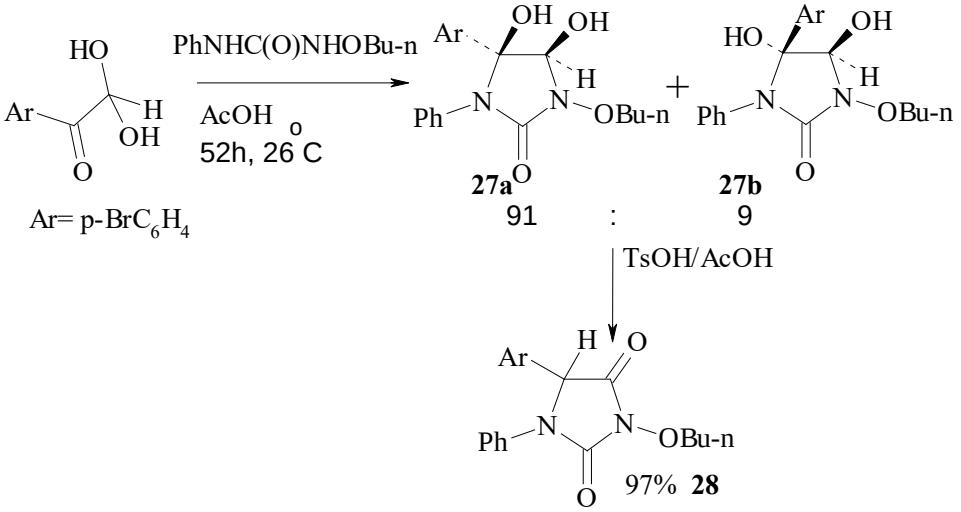
Being processed by of *p*-toluenesulfonic acid the last mixture is converted in pure 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione **26**. Its structure has been described by the ^1H, ^{13}C NMR and mass spectra.



Scheme 7. **4-Chlorophenylglyoxal interaction with *N*-ethoxy-*N'*-phenylurea**.

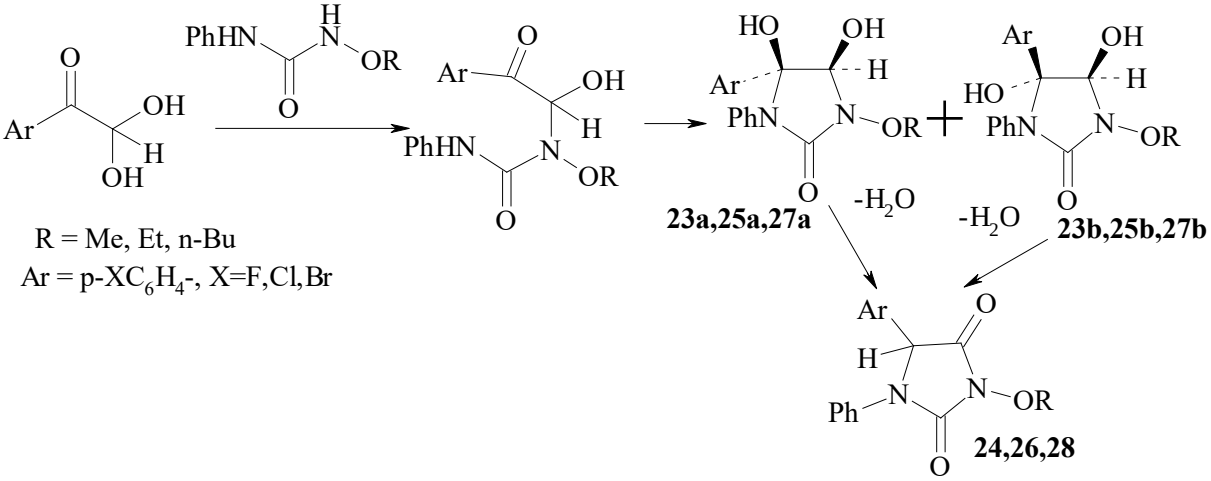
4-Bromophenylglyoxal hydrate interacts with *N*-*n*-butyloxy-*N'*-phenylyrea (AcOH, 52 h, 26°C) yielding only the mixture of the diastereomers of 5-(4-bromophenyl)-3-*n*-butyloxy-4,5-dihydroxy-1-phenylimidazolidin-2-one **27a**,**b** (Scheme 8). The molar ratio of 5-(4-bromophenyl)-3-*n*-butyloxy-*cis*-4,5-dihydroxy-1-phenylimidazolidin-2-one **27a** and 5-(4-bromophenyl)-3-*n*-butyloxy-*trans*-4,5-dihydroxy-1-phenylimidazolidin-2-one **27b** is 91:9. Compound **27a** has been displayed by the ^{1}H NMR and the mass spectra.

Compound **27a** is converted into 5-(4-bromophenyl)-3-*n*-butyloxy-1-phenylimidazolidine-2,4-dione **28** being processed by *p*-toluenesulfonic acid. The structure of *N*-*n*-butyloxyhydantoin **28** has been proved by the ^{1}H, ^{13}C NMR and mass spectra.



Scheme 8. **4-Bromophenylglyoxal interaction with *N*-*n*-butyloxy-*N'*-phenylurea**

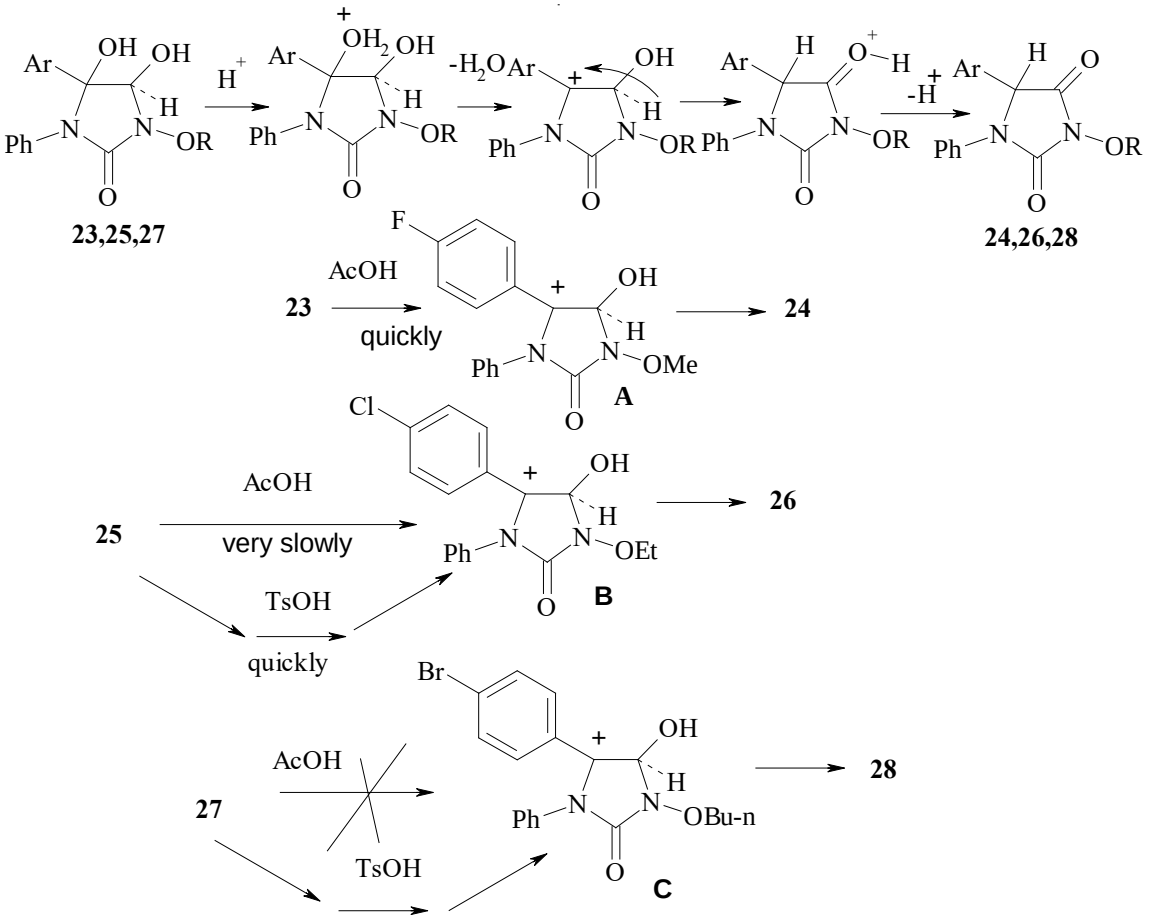
The overall mechanism of arylglyoxals interaction with *N*-alkoxy-*N'*-arylureas had been reported in our earlier studies [11–17]. Firstly the aldehydic moiety of arylglyoxal selectively reacts with nitrogen atom bearing *N*-alkoxy group. Then the cyclization into 3-alkoxy-5-aryl-4,5-dihydroxy-1-phenylimidazolidin-2-ones **23**, **25**, **27** occurs (Scheme 9). At this stage the nature of the *N*-alkoxy group of urea and the aryl group of arylglyoxal do not affect the course of the reaction.



Scheme 9. The overall mechanism of 4-halogenophenylglyoxal interaction with *N*-alkoxy-*N'*-phenylureas.

But the peculiarity is that the 3-alkoxy-5-(4-X-phenyl)-4,5-dihydroxy-1-phenylimidazolidin-2-ones **23**, **25**, **27 (**X= F, Cl, Br) form the proper *N*-alkoxyhydantoins **24**, **26**, **28** in very different way. The X nature affects on the reaction progress.

We suppose the following possible mechanism of 3-alkoxy-5-aryl-4,5-dihydroxy-1-phenylimidazolidin-2-ones transformation into 3-alkoxy-5-aryl-1-phenylhydantoins (Scheme 10).



Scheme 10. The possible route of 3-alkoxy-5-aryl-4,5-dihydroxy-1-phenylimidazolidin-2-ones 23, 25, 27 conversion into 3-alkoxy-5-aryl-1-phenylhydantoins 24,26,28. Ar = 4-FC$_6$H$_4$-, R=Me (23,24); 4-ClC$_6$H$_4$-, R=Et (25, 26); 4-BrC$_6$H$_4$-, R=n-Bu (27, 28)

At the first stage the protonation of 5-HO-moiety of 3-alkoxy-5-aryl-4,5-dihydroxy-1-phenylimidazolidin-2-ones with further elimination of the molecule of water yields "benzylic" cations **A**, **B**, **C**. The acetic acid may be a weak protonation agent, *p*-toluenesulfonic acid may be a strong protonation agent.

At the second stage the 1,2-schieft of the hydrogen atom (H4) from atom (C4) to atom C(5) causes the formation of the protonated *N*-

alkoxyhydantoin.4-X-phenyl (X=F,Cl,Br) moiety must stabilize these obtained cations **A**, **B**, **C** in a different way. 4-Fluorophenyl substituent stabilizes the "benzylic" cation **A** to the highest degree. Thus, 5-(4-fluorophenyl)-3-methoxy-1-phenylhydantoin **24** forms in acetic acid without being processed by *p*-toluenesulfonic acid.

4-Chlorophenyl moiety must stabilize cation **B** to a slightly lesser extent. Actually, 5-(4-chlorophenyl)-3-ethoxy-1-phenylimidazolidine-2,4-dione **26** is very slowly obtained in acetic acid. The catalyst of *p*-toluenesulfonic acid is required for the full conversion of 4,5-dihydroxyimidazolidin-2-ones **25a,b** in *N*-ethoxyhydantoin **26**.

It is evident that the 4-bromophenyl moiety such a weakly stabilized cation **C**, that only the catalyst of *p*-toluenesulfonic acid is needed to form the 5-(4-bromophenyl)-3-*n*-butyloxy-1-phenylhydantoin **28**.

Conclusions

It has been proved that the 4-halogenophenylglyoxal interaction with *N*-alkoxy-*N'*-phenylureas in acetic acid at room temperature is a brand new way to synthetize the 3-alkoxy-5-(4-halohenophenyl)-1-phenylhydantoins.

It has been shown that the nature of 4-halogenophenyl substituent has a significant influence on the reaction progress. This study may bring a huge practical value in the field of pharmaceutical and medical industries.

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