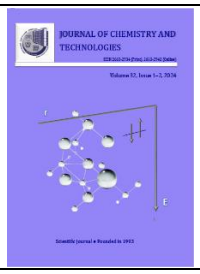
Journal of Chemistry and Technologies, 2024, *32*(1), 56-64

Journal of Chemistry and Technologies

pISSN 2663-2934 (Print), ISSN 2663-2942 (Online).

journal homepage: http://chemistry.dnu.dp.ua
editorial e-mail: chem.dnu@gmail.com



UDC 547.495:547.93

N-BENZYLOXY-*N*-METHOXYREA. SYNTHESIS AND STRUCTURE

Vasiliy G. Shtamburg[1], Andrey A. Anishchenko[2*], Evgeniy A. Klots,[1] Svitlana V. Shiskina[3,4], Svetlana V. Kravchenko[5], Alexander V. Mazepa[6*], Lina A. Sokolova,[1] Oxana V. Krishchik[1]

[1]*Ukrainian State University of Science and Technologies, Gagarina st., 8, Dnipro, 49005, Ukraine*
[2]*Oles Honchar Dnipro National University, Gagarina st., 72, Dnipro, 49050, Ukraine*
[3]*SSI Institute for Synle Crystals, National Academy of Sciences of Ukraine, 60 Naukave, Kharkiv, 61001, Ukraine*
[4]*Institute of Organic Chemistry of National Academy of Sciences of Ukraine, Academician Kukhar str., 5, Kyiv-94, 02660, Ukraine*
[5]*Dnipro State Agrarian and Economic University, Efremova st., 25, Dnipro, 49600, Ukraine*
[6] *A.V. Bogatsky Physico-Chemical Institute of National Academy of Sciences of Ukraine, Luystdorfskaya Doroga st., 86, Odessa, 65080, Ukraine*

Received 10 December 2023; accepted 8 March 2023; available online 25 April 2024

Abstract

Aim. To synthesize of *N*-benzyloxy-*N*-methoxyurea from the methanolysis of *N*-acetoxy-*N*-benzyloxyurea and to investigate its structure using the XRD study. Methods. Mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, XRD study. Results. *N*-Benzyloxy-*N*-chlorourea was synthesized with high yield of the *N*-benzyloxyurea by the chlorination by *tert*-butyl hypochlorite. We have proved that the interaction of with sodium acetate in acetonitrile medium at room temperature leads to the formation of *N*-acetoxy-*N*-benzyloxyurea with the moderate yield. It has been also found that the methanolysis of *N*-acetoxy-*N*-benzyloxyurea at room temperature is a convenient method of the *N*-benzyloxy-*N*-methoxyurea synthesis. The structure of the synthesized *N*-benzyloxy-*N*-chlorourea, *N*-acetoxy-*N*-benzyloxyurea and *N*-benzyloxy-*N*-methoxyurea was confirmed by the data of ^{1}H and ^{13}C NMR spectra, IR spectra and mass spectra. Also, the XRD study of *N*-benzyloxy-*N*-methoxyurea structure proved our assumptions: O–N–O nitrogen atom (N2) in *N*-benzyloxy-*N*-methoxyurea is sp^3 hybridized and has pyramidal configuration. The carbamoyl nitrogen atom (N1) has planar configuration. After comparison of the amide bond of the received *N*-benzyloxy-*N*-metoxyurea with the similar bond in unsubstituted *N*-benzyloxyurea and $H_2N(1)–C(=O)$ bond of *N*-benzyloxy-*N*-methoxyurea we have found the significant elongation of the amide BnO(MeO)N(2)–C(=O) bond of *N*-benzyloxy-*N*-methoxyurea. The molecular packings in the crystal of *N*-benzyloxy-*N*-methoxyurea and *N*-benzyloxyurea is different. Conclusions. As the result of our study the anomeric *N*-benzyloxy-*N*-chlorourea, *N*-acetoxy-*N*-benzyloxyurea and *N*-benzyloxy-*N*-methoxyurea have been synthesized. The structure of *N*-benzyloxy-*N*-methoxyurea has been thoroughly analyzed.

Keywords: N-acyloxy-N-alkoxyureas; N-alkoxy-N′-chloroureas; N,N-dialkoxyureas; N-benzyloxy-N′-methoxyurea; synthesis; structure.

N-БЕНЗИЛОКСИ-*N*-МЕТОКСИСЕЧОВИНА. СИНТЕЗ ТА БУДОВА

Василь Г. Штамбург[1], Андрій О. Аніщенко[2], Євген О. Клоц[1], Світлана В. Шишкіна[3,4], Світлана В. Кравченко[5], Олександр В. Мазепа[6], Ліна О. Соколова[1], Оксана В. Крищик[1]

[1]*Український державний університет науки і технологій, пр. Гагаріна, 8, м. Дніпро, 49005, Україна*
[2]*Дніпровський національний університет імені Олеся Гончара, просп.Гагаріна, 72, м. Дніпро, 49050, Україна*
[3]*Державна наукова установа «Інститут монокристалів» НАН України, вул. Наукова, 60, м. Харків, 61001, Україна*
[4]*Інститут органічної хімії НАН України, вул. Академіка Кухаря, 5, м. Київ, 02660, Україна*
[5] *Дніпровський державний аграрно-економічний університет, вул.. Єфремова., 25, м. Дніпро, 49600, Україна*
[6] *Фізико-хімічний інститут імені О.В. Богатського НАН України, вул. Люстдорфська дорога, 86, м. Одеса, 65080, Україна*

Анотація

Мета. Синтез *N*-бензилокси-*N*-метоксисечовини метанолізом *N*-ацетокси-*N*-бензилоксисечовини. Рентгеноструктурне дослідження будови *N*-бензилокси-*N*-метоксисечовини. Методи. Мас-спектрометрія, ^{1}H та ^{13}C ЯМР спектроскопія, ІЧ-спектроскопія, рентгеноструктурний аналіз. Результати. Синтезовано з високим виходом *N*-бензилокси-*N*-хлоросечовину хлоруванням *N*-бензилоксисечовини *трет*-бутилгіпохлоритом. Ми показали, що взаємодія *N*-бензилокси-*N*-хлоросечовини з ацетатом натрію в середовищі ацетонітрилу за кімнатної температури призводить до утворення *N*-ацетокси-*N*-бензилоксисечовини з помірним виходом. Знайдено, що метаноліз *N*-ацетокси-*N*-бензилоксисечовини за кімнатної температури є зручним методом синтезу *N*-бензилокси-*N*-метоксисечовини. Структуру синтезованих *N*-бензилокси-*N*-хлоросечовини, *N*-ацетокси-*N*-бензилоксисечовини та *N*-бензилокси-*N*-метоксисечовини підтверджено даними ^{1}H і ^{13}C ЯМР спектроскопії, ІЧ-спектроскопії та мас-спектрометрії.

**Corresponding author: e-mail: al.mazepa@ukr.net, koloxai@gmail.com*

doi: 10.15421/jchemtech.v32i1.292868

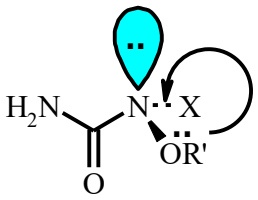
Journal of Chemistry and Technologies, 2024, *32*(1), 56-64

Проведено рентгеноструктурне дослідження будови *N*-бензилокси-*N*-метоксисечовини. В *N*-бензилокси-*N*-метоксисечовині атом азоту (N2) групи O–N–O є sp^3 гібридизованим і має пірамідальну конфігурацію. Карбамоїльний атом азоту (N1) має планарну конфігурацію. Ми знайшли значне подовження амідного зв'язку BnO(MeO)N(2)–C(=O) *N*-бензилокси-*N*-метоксисечовини порівнянно з тим же зв'язком в незаміщеній *N*-бензилоксисечовині та порівнянно з $H_2N(1)$–C(=O)-зв'язком саме *N*-бензилокси-*N*-метоксисечовини. Молекулярне пакування в кристалах *N*-бензилокси-*N*-метоксисечовини і *N*-бензилоксисечовини є різним. Висновки. Синтезовано аномерні *N*-бензилокси-*N*-хлоросечовину, *N*-ацетокси-*N*-бензилоксисечовину та *N*-бензилокси-*N*-метоксисечовину. Досліджено будову *N*-бензилокси-*N*-метоксисечовини.

Ключові слова: ***N*-**ацилокси-*N*-алкоксисечовини; *N*-хлоро-*N'*-алкоксисечовини; *N,N*-діалкоксисечовини; *N*-бензилокси-*N'*-метоксисечовина; синтез; будова.

Introduction

Anomeric amides are those amides that bear two heteroatoms at the amide nitrogen [1-22]. In anomeric amides the amide nitrogen responds to the collective electronegativity of the substituents by the rehybridizing from sp^2 to sp^3 [2]. Thus, the pyramidal configuration of the amide nitrogen atom in *N*-X-*N*-alkoxyamides (X = OC(O)R, OAlk, Cl) is favorable for the realization on $n_{OAlk} \rightarrow \sigma^*_{N\text{-}X}$ anomeric effect [1–3] and the weakening of the N–X bond [1–16; 18–25]. The pyramidality of the amide nitrogen was proved for *N*-acyloxy-*N*-alkoxyamides [8], *N,N*-dialkoxyamides [9], *N*-alkoxy-*N*-chloroamides [11], *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines [6; 21], *N*-acyloxy-*N*-alkoxyureas [14; 16; 17], *N*-acyloxy-*N*-alkoxycarbamates [14], *N*-alkoxy-*N*-chloroureas [15], *N,N*-dialkoxyureas [16; 18], *N*-alkoxy-*N*-chloro-*N'*-arylureas [15; 18], *N,N*-dialkoxy-*N'*-arylureas [19]. Also the pyramidality of amide nitrogen had been established for the salts of *N*-alkoxy-*N*-(1-pyridium) ureas [16; 20–24] and *N*-alkoxy-*N*-(1-pyridium) carbamates [25].



$$X = Cl,\ OAc,\ OAlk,\ \overset{+}{N}C_5H_5$$

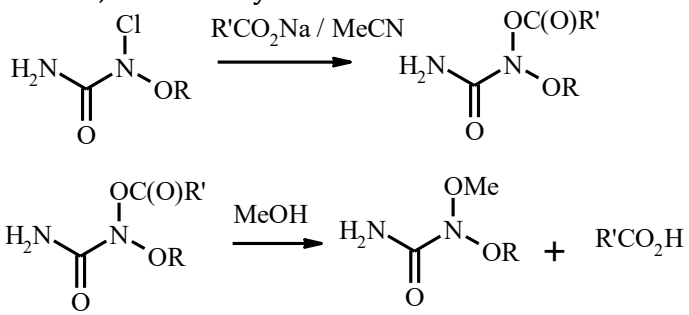
Scheme 1. The action of the $n_N \rightarrow \sigma^*_{N\text{-}X}$ anomeric effect in *N*-X-*N*-alkoxyureas

Earlier we had studied the influence of *N*-alkoxy group in *N*-acyloxy-*N*-alkoxyureas nature on the structural parameters of *N*-acyloxy-*N*-alkoxyureas [17]. For example, the pyramidality degree of amide nitrogen atom in ***N*-*n*-butyloxy-*N*-**(4-chlorobenzoyloxy)urea is bigger than the similar structural parameter of *N*-4-chlorobenzoyloxy-***N*-ethoxy**urea [17]. The influences of the nature of *N*-alkoxy group on the structural parameters was also registered for *N*-alkoxy-*N*-chloroureas [17; 18] and *N*-alkoxy-*N'*-aryl-*N*-chloroureas [18].

As for the *N,N*-dialkoxyureas previous investigations the XRD study had been conducted only for three compounds: *N,N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18] and *N*-*tert*-butyloxy-*N*-methoxyurea [18].

We would like to continue this research and investigate of the structure on *N*-benzyloxy-*N*-methoxyurea in this article more thoroughly.

Earlier we showed that the interaction of *N*-alkoxy-*N*-chloroureas with anhydrous sodium acetate in acetonitrile is a convenient way to obtain the unknown *N*-acyloxy-*N*-alkoxyureas [14; 16–18; 23]. Also we found that the alkoholysis of *N*-acyloxy-*N*-alkoxyureas by the primary alcohols, especially methanolysis, was a selective synthesis of *N,N*-dialkoxyureas [16; 18; 23] (Scheme 1).



Scheme 2. Syhthesis of *N*-acyloxy-*N*-alkoxyureas and *N,N*-dialkoxyureas [14; 16–18; 23]

It seemed possible to apply this approach to obtain *N*-benzyloxy-*N*-methoxyurea.

Thus, the goal of our present research was synthesis of *N*-benzyloxy-*N*-methoxyurea and the investigation of it structure by XRD-study.

Experimental

^{1}H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz) and a VARIAN VNMRS 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded on a 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]. IR spectra were recorded on a UR-20 in thin layer (cm^{-1}). Mass spectra were recorded on a VG 70-70EQ mass spectrometer in fast atom bombardment mode (FAB) and electron impact mode (EI). The chromatographic studies were carried out on a Shimadzu GCMS-QP2020E1. The solvents were purified and dried according to the standard procedures, AcONa was dried under 125 °C and 2 mmHg during 1 h.

N-Benzyloxyurea **(1) A.** The solution of 30 % hydrochloric acid (0.7 ml) in water (4 ml) was added at stirring to the solution of benzyloxyamine (0.661 g, 5.367 mmol) in dipropyl ether (20 ml) under 4 °C. Then NaOCN (0.697 g, 10.734 mmol) and water (5 ml) were added at stirring under 4°C. The reaction mixture was stirred during 1 h under 7 °C, 2h under 23 °C, and maintained during 20 h under 23 °C. The solid was filtrated off, dried under 4 mmHg and extracted by acetone (25 ml). The Me_2CO-extract was evaporated under vacuum (20 mmHg), the residue was maintained under 2 mmHg and 20°C during 1 h, yielding *N*-benzyloxyurea **1** (0.567 g, 63.5 %), white solid, mp. 137–139 °C, after crystallization from acetone-hexane mp. 140–141 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ =4.711 (2H, s, $NOCH_2$); 6.332 (2H, br. s, $C(O)NH_2$); 7.286–7.439 (5H, m, Ph); 9.004 (1H, s, NHO).

Pr_2O-phase of the filtrate was separated from the water phase, evaporated under vacuum (20 mmHg), the residue was maintained under 2 mmHg and 20°C during 1 h, extracted by acetone (30 ml). The obtained Me_2CO-extract was evaporated under vacuum yielding additionally *N*-benzyloxyurea **1** (0.092 g, 10.3%).

B. NaOCN (0.72 g, 10.13 mmol) was added to the mixture of $PhCH_2ONH_2$•HCl (0.879 g, 5.310 mmol), water (14 ml) and ether (30 ml) at stirring under 1–2 °C, the reaction mixture was stirred during 1 h under 4°C, then during 1 h under 10 °C, then acetic acid (0.4 ml) was added and the reaction mixture was stirred during 2 h at 20 °C. The solid was filtered off, extracted by ether (5·40 ml). The combined ether extracts and the filtrates were evaporated under vacuum (20 mmHg), the residue was maintained under 2 mmHg and 20 °C during 1 h. The obtained residue was washed by cold ether (5 ml), dried under vacuum (2 mmHg), yielding *N*-benzyloxyurea **1** (0.46 g, 50.3 %), as white solid, mp. 134–135°C, after crystallization acetone-hexane mp. 139–141°C (cf. with mp. 140–142°C [27]). ^{1}H NMR (300 MHz, $(CD_3)_2SO$, ppm): δ =4.717 (2H, s, $NOCH_2$); 6.339 (2H, br. s, $C(O)NH_2$); 7.263–7.461 (5H, m, Ph); 9.019 (1H, s, NHO).

N-Benzyloxy-N-chlorourea **(2)**. The solution of *tert*-butylhypochlorite (105 mg, 0.975 mmol) in CH_2Cl_2 (2 ml) was added to the mixture of *N*-benzyloxyurea **1** (54 mg, 0.325 mmol) and CH_2Cl_2(3 ml) at 15 °C and stirring, the obtained solution was stirred during 30 min in the dark. Then the solvent was evaporated under vacuum (20 mmHg), the residue was maintained under 2 mmHg and 15°C during 1h, washed by hexane, maintained under 2 mmHg yielding *N*-benzyloxy-*N*-chlorourea **2** (54 mg, 83 %) as colorless solid, mp 70–71°C (CH_2Cl_2–C_6H_{14}) (with decomp.).^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 5.006 (2H, s, $NOCH_2$); 5.506 (1H, br. s, $C(O)NH_2$); 5.896 (1H, br. s, $C(O)NH_2$); 7.400 (5H, s, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 77.29 $NOCH_2$; 128.98 C(2)H, C(6)H Ph; 129.45 C(4)H Ph; 129.73 C(3)H, C(5)H Ph; 133.84 C(1) Ph; 160.85 C=O. IR (υ, cm^{-1}): 1720 (C=O). Anal. Calc. for $C_8H_9ClN_2O_2$ %: Cl 17.67. Found, %: Cl 17.49.

N-Acetoxy-N-benzyloxyurea **(3).** The solution of *N*-benzyloxy-*N*-chlorourea **2** (0.155 g, 0.774 mmol) in acetonitrile (9 ml) was added to the mixture of AcONa (0.159 g, 1.935 mmol) and acetonitrile (5 ml) at stirring. The reaction mixture was stirred during 29 h at 15°C, then CH_2Cl_2 (6 ml) was added, the precipitate was filtered off and washed by CH_2Cl_2 (4 ml). The combined filtrate was evaporated under vacuum (20 mmHg), then the residue was maintained under 20°C and 2 mmHg. The obtained residue **A** was crystallized from mixture ether–hexane yielding ***N*-**acetoxy-*N*-benzyloxyurea **3** (0.098 g, 56.5 %) as colorless crystals, mp 64–65°C (with decomp.), 68–69°C (Et_2O–C_6H_{14}) (with decomp.). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 2.136 (3H, s, NOAc); 5.083 (2H, s, $NOCH_2$); 5.293 (1H, br. s, $C(O)NH_2$); 5.771 (1H, br. s, $C(O)NH_2$); 7.346–

7.442 (5H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 18.96 Me; 78.06 $NOCH_2$; 128.94 C(2)H, C(6)H Ph; 129.22 C(4)H Ph; 129.59 C(3)H, C(5)H Ph; 134.86 C(1) Ph; 159.84 $H_2N(C=O)N$; 168.72 NOC=O. IR (υ, cm^{-1}): 3486 (NH); 1800 (C=O); 1745 (C=O). MS spectrum (FAB, NaCl), *m/z* (I_{rel}, %): 247 $[M+Na]^+$ (100). Anal. Calc. for $C_{10}H_{12}N_2O_4$ %: C 53.57; H 5.39; N 12.49. Found, %: C 53.25; H 5.34; N 12.29.

The data of ^{1}H NMR spectrum of the residue **A** had shown that, in addition of compound **3**, it contains also benzyl acetate. This was achieved by comparison with the spectrum of known benzyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 2.110 (3H, s, OAc); 5.112 (2H, s, OCH_2); 7.309–7.404 (5H, m, Ph).

The recrystallization mother liquor was evaporated under vacuum (20 mmHg), the residue was extracted by cold hexane. The presence of benzyl acetate in this extract was determined using gas chromatography–mass spectrometry. The hexane extract was evaporated under vacuum (20 mmHg) yielding the residue **B**. The data of ^{1}H NMR spectrum of the residue **B** had shown that it contains benzyl acetate as the main component.

N-Benzyloxy-N-methoxyurea **(4)**. **A. *N*-**Acetoxy-*N*-benzyloxyurea **3** (0.257 g, 1.146 mmol) was dissolved in methanol (9 ml), the obtained solution was maintained at 20°C during 142 h, then it was evaporated under vacuum (20 mmHg), the residue was maintained under 20°C and 4 mmHg during 5 h. The obtained residue was crystallized from acetone-hexane at –20°C yielding *N*-benzyloxy-*N*-methoxyurea **4** (0.174 g, 77 %), as colorless crystals, mp 78–80 °C (acetone–hexane). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ = 3.584 (3H, s, NOMe); 4.908 (2H, s, $NOCH_2$); 7.083 (1H, br. s, $C(O)NH_2$); 7.250 (1H, br. s, $C(O)NH_2$); 7.327–7.408 (3H, m, C(3)H, C(4)H, C(5)H Ph); 7.413–7.459 (3H, m, C(2)H, C(6)H Ph). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 3.740 (3H, s, NOMe); 5.032 (2H, s, $NOCH_2$); 5.108 (1H, br. s, $C(O)NH_2$); 5.875 (1H, br. s, $C(O)NH_2$); 7.362–7.450 (5H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 61.39 NOMe; 77.00 $NOCH_2$; 128.76 C(2)H, C(6)H Ph; 128.84 C(4)H Ph; 129.34 C(3)H, C(5)H Ph; 135.67 C(1) Ph; 161.30 C=O. IR (υ, cm^{-1}): 3430 (NH); 1725 (C=O). MS spectrum (FAB), *m/z* (I_{rel}, %): 197 $[M+H]^+$ (11); 91 (100). MS spectrum (EI), *m/z* (I_{rel}, %): 196 M^+ (4.0); 181 (0.8); 180 (2.2); 149.(4.9); 121` (2.1); 107 (21.1); 106 (11.1); 105 (17.8); 92 (42.2); 91 (100); 79 (27.9); 78 (10.5); 77 (43.0); 47 (11.5); 45 (15.3); 44 (58.5). Anal. Calc. for $C_9H_{12}N_2O_3$ %: C 55.09; H 6.169; N 14.28. Found, %: C 55.01; H 6.19; N 14.03.

B. *N*-Acetoxy-*N*-benzyloxyurea **3** (44 mg, 0.196 mmol) was dissolved in methanol (3 ml), the obtained solution was maintained at 15°C during 22 h, then it was evaporated under vacuum (20 mmHg), the residue was maintained under 15°C and 4 mmHg during 2 h yielding *N*-benzyloxy-*N*-methoxyurea **4** (31 mg, 80 %).

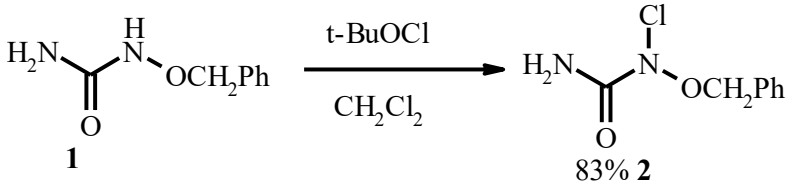
XRD structural study of the N-benzyloxy-N-methoxyurea (4). Crystals of compound **4** suitable for X-ray structural analysis were grown from a solution in acetone – hexane (2:1) mixture at -20 °C, monoclinic, $C_9H_{12}N_2O_3$, at -100.5°C, ***a*** = 5.9968(3), ***b*** = 5.1940(3), ***c*** = 15.5809(10) Å,*β* = 94.614(4), V = 483.73(5) $Å^3$, M_r = 196.21, Z = 2, space group $P2_1$, d_{calc}= 1.347 g/cm^3, μ(MoK_α) = 0.102мм$^{-1}$, F(000) = 208. Cell parameters and intensities of 6626 reflections (1713 independent reflections, R_{int}= 0.034) were measured using «Bruker APEX-IICCD» diffractometer (graphite-monochromated MoKα radiation, CCD detector, ***ω***-scan, $2\theta_{max}$= 50°).

The structure was solved by direct method using SHELX-2016 program package [26]. Positions of hydrogen atoms were located geometrically and refined using the riding model with U_{iso}=nU_{eqv} of the carrier atom (n=1.5 for methyl moieties and n=1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms to wR_2 = 0.084 for 1713 reflections (R_1 = 0.042 for 1547 reflections with F>4σ(F), S = 1.068). The final atomic coordinates, molecular geometry parameters, and crystallographic data of compound **4** were deposited in the Cambridge Crystallographic Data Center, 12 Union Road, CB2, 1EZ, UK (fax:+44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk) and is available on request quoting the deposition number CCDC 2305146.

Results and discussion

The chlorination of *N*-benzyloxyurea **1** (CH_2Cl_2, 1 h, 20°C) leads to the formation of the *N*-benzyloxy-*N*-chlorourea **2** with the high yield (Scheme 3).

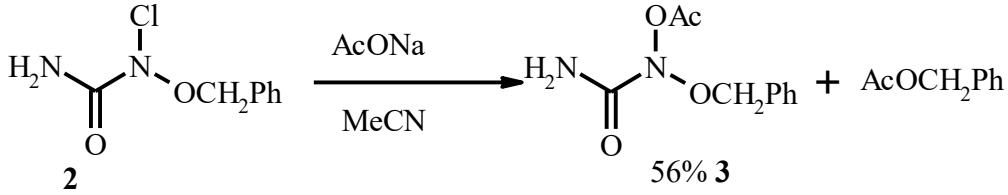
Journal of Chemistry and Technologies, 2024, *32*(1), 56-64



Scheme 3. **Synthesis of *N*-benzyloxy-*N*-chlorourea 2**

The structure of *N*-benzyloxy-*N*-chlorourea **2** has been proved by the data of ^{1}H and ^{13}C NMR spectra and IR spectrum.

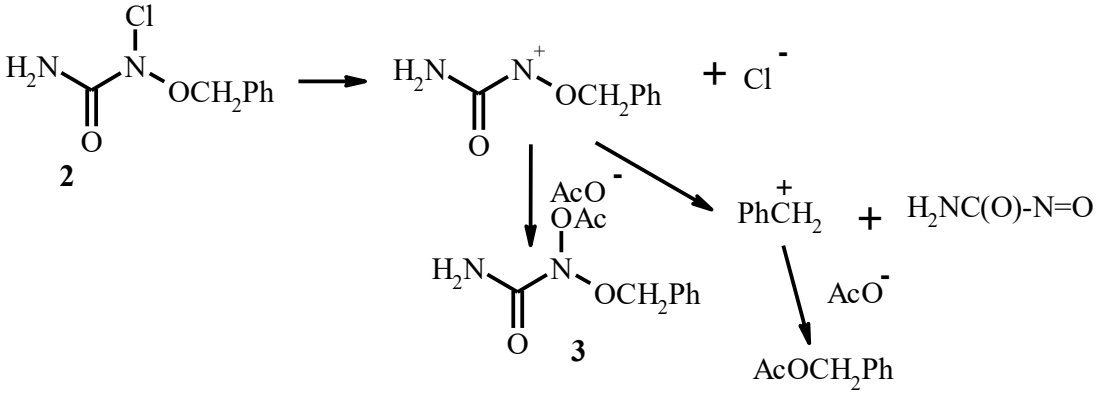
Usually *N*-alkoxy-*N*-chloroureas selectively interact with sodium acetate yielding the propers *N*-acetoxy-*N*-alkoxyureas [14; 16–18]. But the *N*-benzyloxy-*N*-chlorourea **2** interaction with anhydrous sodium acetate in acetonitrile (29 h, 20 °C) yields the *N*-acetoxy-*N*-benzyloxyurea **2** with the moderate yield (Scheme 4). Another product of this reaction is benzyl acetate.



Scheme 4. **Synthesis of *N*-acetoxy-*N*-benzyloxyurea 3**

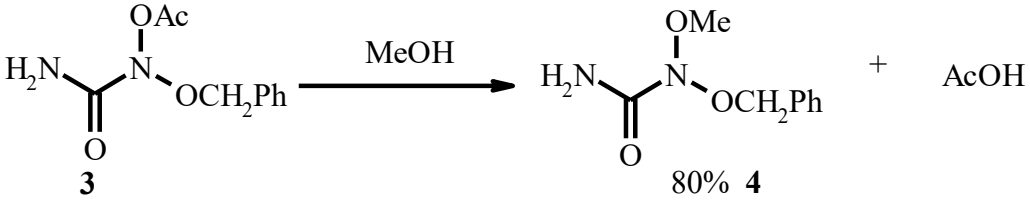
The structure of *N*-acetoxy-*N*-benzyloxyurea **3** had been proved by the data of ^{1}H and ^{13}C NMR spectra, IR spectrum and mass spectrum.

It can be assumed that in this reaction *N*-benzyloxy-*N*-chlorourea **2** is converted in nitrenium ion **A** which then either turns into *N*-acetoxy-*N*-benzyloxyurea **3** or fall apart to form a benzyl cation (Scheme 5). In its turn the benzyl cation with acetate anion forms benzyl acetate.



Scheme 5. **The possible mechanism of the interaction between *N*-benzyloxy-*N*-chlorourea 2 and AcONa**

N-Benzyloxy-*N*-methoxyurea **4** has been obtained by the methanolysis of *N*-acetoxy-*N*-benzyloxyurea **3** with high yield (80 %) (Scheme 6).



Scheme 6. **Synthesis of *N*-benzyloxy-*N*-methoxyurea 4**

The structure of *N*-benzyloxy-*N*-methoxyurea **4** has been proved by the data of ^{1}H and ^{13}C NMR spectra, IR spectrum and mass spectrum. Also, the structure of *N*-benzyloxy-*N*-methoxyurea **4** has been also proved by XRD study (Figures 1,3, Table 1–4).

Journal of Chemistry and Technologies, 2024, *32*(1), 56-64

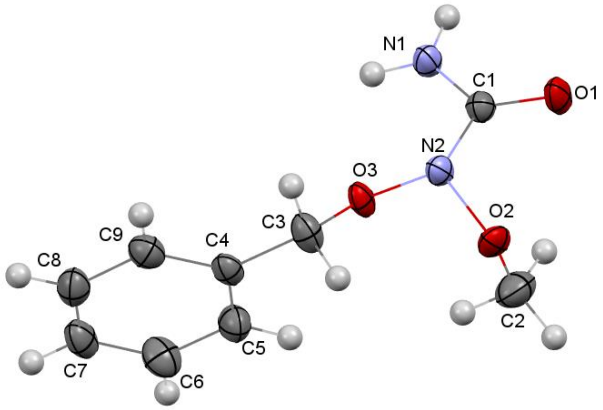


Fig. 1. Molecular structure of *N*-benzyloxy-*N*-methoxyurea (4) with atoms represented by thermal vibration ellipsoids at 50 % probability level

The analysis of bond lenghts of *N*-benzyloxy-*N*-methoxyurea **4** and their comparison with those in the previously studied *N*-benzyloxyurea **1** [27] (Figure 2), unsubstituted at the N(2) atom, showed that the replacement of the hydrogen atom with a methoxy group caused the sp^3 hybridization of N(2) atom and the significant elongation of the C(1)–N(2) bond.

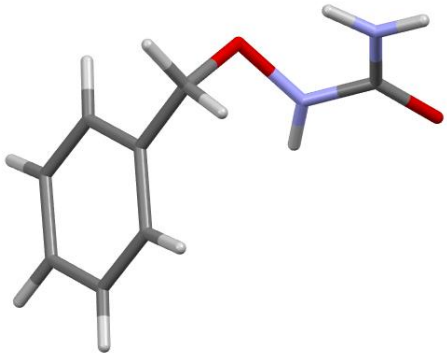


Fig. 2. Molecular structure of *N*-benzyloxyurea (1) [27]

In *N*-benzyloxy-*N*-methoxyurea **4** N(2) atom has pyramidal configuration. The sum of the bond angles centered on N(2) atom (Σβ) is 331.4°. Thus, the sp^3 hybridization of N(2) atom is confirmed by its pyramidal configuration. The N(1) atom has planar configuration, Σβ is 360°. In the molecule of *N*-benzyloxyurea **1** the N(2) atom has planar configuration, Σβ is 360° [27].

The significant elongation of the C(1)–N(2) bond relative to this in *N*-benzyloxyurea **1** [27] (See Table 1) is typical for the C_{sp2}–N_{sp3} fragment (1.416 Å) [28; 29].

Table 1

Some structural parameters in molecules of *N*-benzyloxy-*N*-methoxyurea 4 and *N*-benzyloxyurea 1 [27].

Parameter	*N*-benzyloxy-*N*-methoxyurea **4**	*N*-benzyloxyurea **1** [27]
Bond lenghts, Å		
C(1)–O(1)	1.219(4)	1.220(3)
C(1)–N(1)	1.323(4)	1.326(3)
C(1)–N(2)	**1.448(4)**	1.274(3)
N(2)–O(3)	1.421(3)	1.406(3)
Torsion angles, degree		
C(5)–C(4)–C(3)–O(3)	47.1(4)	125.1(3)
C(4)–C(3)–O(3)–N(2)	–175.7(2)	–71.5(2)
C(3)–O(3)–N(2)–C(1)	–156.7(2)	–105.1(2)
O(3)–N(2)–C(1)–O(1)	–157.4(3)	–163.8(2)

The large nonequivalence the amide C(1)–N(2) and C(1)–N(1) bonds of *N*-benzyloxy-*N*-methoxyurea **4** is caused more by the weaker conjugation (or its absence) of the lone pair (LP) of the sp^3-hybridized nitrogen N(2) with the carbamoyl carbonyl C(1)=O(1) than by the strong conjugation of the LP of the sp^2-hybridized nitrogen atom N(1) with carbonyl C(1)=O(1). The

same nonequivalence the amide C–N bonds was discovered for *N*,*N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18] and *N*-*tert*-butyloxy-*N*-methoxyurea [18] (See Table 2). The length of the amide C–N of *N*,*N*-dialkoxybenzamides is similar, 1.409(4) and 1.421(2) Å [29].

Table 2

The comparison of the bonds' length in the molecules of *N*-benzyloxy-*N*-methoxyurea 4, *N*,*N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18], *N*-*tert*-butyloxy-*N*-methoxyurea [18] and *N*-methoxyurea [18]

Compound	length of bond, Å				
	C(1)–N(1)	C(1)–N(2)	C(1)=O(1)	N(2)–OMe	N(2)–OR
$H_2NC(O)N(OMe)OBn$ **4**	1.323(4)	1.449(4)	1.219(4)	1.406(3)	1.421(3)
$H_2NC(O)N(OMe)_2$[16]	1.320(3)	1.438(2)	1.220(2)	1.397(2) 1.401(2)	
$H_2NC(O)N(OMe)OPr^i$[18]	1.304(4)	1.449(3)	1.217(4)	1.401(3)	1.408(3)
$H_2NC(O)N(OMe)OBu^t$[18]	1.322(3)	1.438(3)	1.217(2)	1.406(2)	1.408(2)
$H_2NC(O)NHOMe$[18]	1.322(3)	1.367(3)	1.244(2)	1.411(2)	-

The length of the N(2)–O(2)Me bond in *N*-benzyloxy-*N*-methoxyurea **4** is close to those in *N*,*N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18], *N*-*tert*-butyloxy-*N*-methoxyurea [18]. In *NH*-*N*-methoxyurea the N–OMe bond is longer due to the absence of $n_O \rightarrow \sigma^*_{N\text{-}OMe}$ anomeric effect [18].

The lengths of the carbamoyl carbonyl C(1)=O(1) in *N*-benzyloxy-*N*-methoxyurea **4** is close to those *N*,*N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18], *N*-*tert*-butyloxy-*N*-methoxyurea [18] and *N*-benzyloxyurea **1** [27].

Table 3

Some structural parameters in molecules of *N*-benzyloxy-*N*-methoxyurea 4, *N*,*N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18], *N*-*tert*-butyloxy-*N*-methoxyurea [18], *N*,*N*-dimethoxy-*N'*-4-nitrophenylurea [19] and *N*-methoxyurea [18]

Compound	parameter	
	Σβ, °	$\upsilon_{C=O}$, cm^{-1}
$H_2NC(O)N(OMe)OBn$ **4**	331.4	1725
$H_2NC(O)N(OMe)_2$[16]	332.1(1)	1720
$H_2NC(O)N(OMe)OPr^i$[18]	332.0(6)	
$H_2NC(O)N(OMe)OBu^t$[18]	331.6(2)	1712
$H_2NC(O)NHOMe$[18]	338.0	1685
$4\text{-}O_2NC_6H_4HNC(O)N(OMe)_2$[18,19]	324.0(2)	

The N(2) nitrogen pyramidality degree (Σβ) in *N*-benzyloxy-*N*-methoxyurea **4** is close to the pyramidality degree of similar nitrogen atom in *N*,*N*-dimethoxyurea [16], *N*-isopropyloxy-*N*-methoxyurea [18], *N*-*tert*-butyloxy-*N*-methoxyurea [18] (Table 3). But in *N*,*N*-dimethoxy-*N'*-4-nitrophenylurea the nitrogen pyramidality degree is higher [18; 19].

For *N*-benzyloxy-*N*-methoxyurea **4**, *N*,*N*-dimethoxyurea and *N*-*tert*-butyloxy-*N*-methoxyurea the IR carbonyl vibrational frequency is higher than the similar vibration frequency for non-anomeric *NH*-*N*-methoxyurea (Table 3). This phenomenon is caused by the diminishment of the conjugation between the carbonyl group and LP of O-N-O-nitrogen as it had been earlier predicted by S.A. Glover [1–3; 29].

The molecules of *N*-benzyloxy-*N*-methoxyurea **4** form different intermolecular hydrogen bonds in the crystal than *N*-benzyloxyurea **1** molecules (Figure 3, Table 4).

Table 4

The intermolecular hydrogen bonds in the crystal of *N*-benzyloxy-*N*-methoxyurea 4 and *N*-benzyloxyurea 1 [27]

interaction	symmetry operation	structural parameter	
		length H…A, Å	angle D–H…A, °
N-benzyloxy-*N*-methoxyurea **4**			
N1–H…O1'	-x,-0.5+y,1-z	2.03	163
N1–H…O2'	x,-1+y,z	2.23	155
N-benzyloxyurea **1** [27]			
N1–H…O1'	1-x,-0.5+y,2.5-z	1.90	163
N1–H…O1'	x,-1+y,z	2.29	133

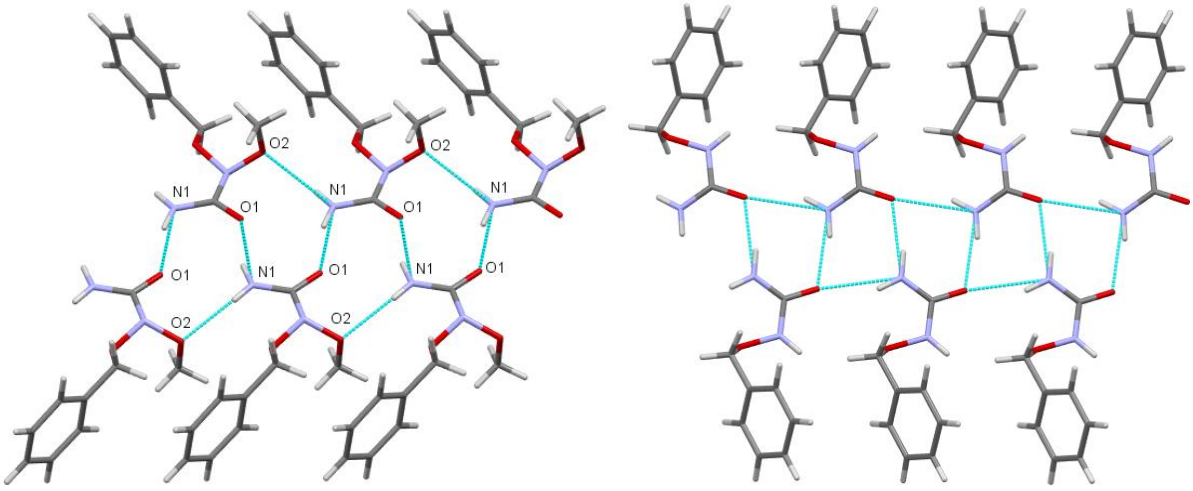


Fig. 3. Molecular packing in the crystal of *N*-benzyloxy-*N*-methoxyurea 4 (left) and *N*-benzyloxyurea 1 (on right [27]) formed due to intermolecular hydrogen bonds

In the crystal the molecules *N*-benzyloxy-*N*-methoxyurea **4** formed chains along the [010] crystallographic direction (Figure 3, left) as a result of the intermolecular hydrogen bonds N(1)–H…O(1') and N(1)–H…O(2') formation (Table 4). It should be noted that the hydrogen atoms of the carbamoyl group [$H_2NC(=O)$] are associated with the different proton acceptors in the crystal of compound **4**: with the oxygen atom of the carbamoyl group and with the oxygen atom of the methoxy group. In the crystals formed by *N*-benzyloxyurea **1** [27], the molecules also form chains due to hydrogen bonds, but both hydrogen atoms of the carbamoyl group are connected to the oxygen atom of the carbamoyl group (Figure 3, on right [27]).

Thus, the specific influence of *N*-benzyloxy group on the structure of *N*-benzyloxy-*N*-methoxyurea **4** is remains still unknown. We will continue our research to find out more about it.

Conclusion

As the result of our study the anomeric *N*-benzyloxy-*N*-chlorourea, *N*-acetoxy-*N*-benzyloxyurea and *N*-benzyloxy-*N*-methoxyurea have been synthesized. The structure of *N*-benzyloxy-*N*-methoxyurea has been thoroughly analyzed. The results of this research may be used in medical and pharmaceutical area as they cover the hitherto unknown way of synthesis as well as main characteristics of these ureas.

References

[1] Glover, S.A. (1998). Anomeric Amides – Structure, Properties and Reactivity. *Tetrahedron*, *54*(26), 7229–7271.https://doi.org/10.1016/S0040-4020(98)00197-5

[2] Glover, S. A. (2009). *N-Heteroatom-substituted hydroxamic esters, in The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Eds Rappoport, Z., Liebman, J. F., John. Wiley and Sons, New York. PATAI'S Chemistry of Funcional Groups, *1*, 839–923. https://doi.org/10.1002/9780470682531.pat0470

[3] Glover, S.A., Rosser, A.A. (2018). Heteroatom Substitution at Amide Nitrogen – Resonance Reduction and HERON Reactions of Anomeric Amides. *Molecules*, *23*(11), 2384. https://doi.org/10.3390/molecules23112834

[4] Campbell, J. J., Glover, S. A., Hammond, G. P., Rowbottom, C.A. (1991). Evidence for the Formation of Nitrenium Ions in the Acid-catalysed Solvolysis of Mutagenic *N*-Acetoxy-*N*-Alkoxybenzamides. *J. Chem. Soc., Perkin Trans., 2(12)*, 2067–2079. https://doi.org/10.1039/P29910002067

[5] Campbell, J.J., Glover, S.A. (1999). Bimolecular Reactions of Mutagenic *N*-Acyloxy-*N*-alkoxybenzamides with Aromatic Amines. *J. Chem. Reseach (S)*, (8), 474–475. https://doi.org/10.1039/A903555I

[6] Glover, S.A., Mo, G., Rauk, A., Tucker, D.J., Turner, P. (1999). Structure, conformation, anomeric effects and rotational battiers in the HERON amides, *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines. *J. Chem. Soc., Perkin Trans., 2*, (10), 2053–2058. https://doi.org/10.1039/A904575I

[7] Glover, S.A., Rauk, A. (1999). Conformational Stereochemistry of the HERON Amide, *N*-Methoxy-*N*-dimethylaminoformamide: A Theoretical Study. *J. Org. Chem.*, *64*(7), 2340–2345. https://doi.org/10.1021/jo982048p

[8] Gillson, A.-M., Glover, S.A., Tucker, D.J., Turner, P. (2003). Crystal structures and properties of mutagenic *N*-acyloxy-*N*-alkoxyamides – "most pyramidal" acyclic amides. *Org. Biomol. Chem*., *1*(19), 3430–3437. https://doi.org/10.1039/B306098P

[9] Glover, S.A., White, J.M., Rosser, A.A., Digianantonio, K.M. (2011). Structure of N,N-Dialkoxyamides: Pyramidal Anomeric Amides with Low Amidicity, *J. Org. Chem*., *76*(23), 9757–9763. https://doi.org/10.1021/jo201856u

[10] Digianantonio, K.M., Glover, S.A., Johns, J.P., Rosser, A.A. (2011). Synthesis and thermal decomposition of *N,N-*

dialkoxyamides. *Org. Biomol. Chem*., *9*(11), 4116–4126. https://doi.org/10.1039/C1OB00008J

[11] Shtamburg, V.G., Tsygankov, A.V., Shishkin, O.V., Zubatyuk, R.I., Uspensky, B.V., Shtamburg, V.V., Mazepa, A.V., Kostyanovsky, R.G. (2012). The properties and structure of *N*-chloro-*N*-methoxy-4-nitrobenzamide. *Mendeleev Commun.*, *22*(3), 164–166. https://doi.org/10.1016/j.mencom.2012.05.019

[12] Cavanagh, K.L., Glover, S.A., Price, H.L., Schumacher, R.R. (2009). S_N2 Substitution reactions at the Amide Nitrogen in the Anomeric Mutagens, *N*-Acyloxy-*N*-alkoxyamides. *Aust. J. Chem.*, *62*(7), 700–710. https://doi.org/10.1071/CH09166

[13] Glover, S.A., Taherpour, A., Greatrex, B.W. (2014). Formation and HERON Reactivity of Cyclic *N*,*N*-Dialkoxyamides. *Aust. J. Chem.*, *67*(3), 507–520. https://doi.org/10.1071/CH13557

[14] Shishkin, O.V., Zubatyuk, R.I., Shtamburg, V.G., Tsygankov, A.V., Klots, E.A., Mazepa, A.V., Kostyanovsky, R.G. (2006). Pyramidal Amide Nitrogen in *N*-Acyloxy-*N*-alkoxyureas and *N*-Acyloxy-*N*-alkoxycarbamates, *Mendeleev Commun*., *16*(4), 222–223. https://doi.org/10.1070/MC2006v016n04ABEH002195

[15] Shtamburg, V.G., Shishkin, O.V., Zubatyuk, R.I., Kravchenko, S.V., Tsygankov, A.V., Mazepa, A.V., Klots, E.A., Kostyanovsky, R.G. (2006). *N*-Chloro-*N*-alkoxyureas: synthesis, structure and properties. *Mendeleev Commun., 16*(6), 323–325. https://doi.org/10.1070/MC2006v016n06ABEH002382

[16] Shtamburg, V.G., Shishkin O.V., Zubatyuk R.I., Kravchenko, S.V., Shtamburg, V.V., Distanov, V.B., Tsygankov A.V., Kostyanovsky, R.G. (2007). Synthesis, structure and properties of *N*-alkoxy-*N*-(1-pyridinium)urea salts, *N*-alkoxy-*N*-acyloxyureas and *N,N*-dialkoxyureas. *Mendeleev Commun*., *17*(3), 178–180. https://doi.org/10.1016/j.mencom.2007.05.016

[17] Shishkin, O.V., Shtamburg, V.G., Zubatyuk R.I., Olefir, D.A., Tsygankov, A.V., Prosyanik, A.V., Mazepa,A.V., Kostyanovsky, R.G. (2009). Chiral Ureas with Two Electronegative Substituents at 1-*N* and Unusual Case of Coexisting a Pyramidal and Almost Planar 1-*N* in The Same Crystal. *Chirality*, *21*(7). 642–647. https://doi.org/10.1002/chir.20668

[18] Shtamburg, V.G., Kostyanovsky, R.G., Tsygankov, A.V., Shtamburg, V.V., Shishkin, O.V., Zubatyuk, R.I., Mazepa, A.V., Kravchenko, S.V. (2015). Geminal Systems. Communication 64. *N*-Alkoxy-*N*-chloroureas and *N,N*-Dialkoxyureas, *Russ. Chem. Bulletin. Intern. Ed.*, *64*(1), 62–75. https://doi.org/10.1007/s11172-015-0822-9

[19] Shtamburg, V.G., Tsygankov, A.V., Gerasimenko, M.V., Shishkin, O.V., Zubatyuk, R.I., Mazepa, A.V.; Kostyanovsky, R.G. (2011). New approach to *N,N*-dialkoxy-*N'*-arylureas and *N,N*-dialkoxycarbamates. *Mendeleev Commun*., *21*(12), 50–32. https://doi.org/10.1016/j.mencom.2011.01.021

[20] Shtamburg, V.G., Tsygankov, A.V., Shishkin, O.V., Zubatyuk, R. I., Shtamburg, V.V., Gerasimenko, M.V., Mazepa, A.V., Kostyanovsky, R.G. (2012). 1-Alkoxyamino-4-dimethylaminopyridinium derivatives as new representatives of O-N-N^+geminal systems and their structure. *Mendeleev Commun*., *22*(2), 92–94. https://doi.org/10.1016/j.men.com.2012.02.014

[21] Shtamburg, V.G., Shishkin, O.V., Zubatyuk, R.I., Shtamburg, V.V., Tsygankov, A.V., Mazepa, A.V., Kadorkina, G.K., Kostyanovsky, R.G. (2013). Synthesis and structure of *N*-alkoxyhydrazines and *N*-alkoxy-*N*',*N*',*N*-trialkylhydrazinium salts, *Mendeleev Commun*., *23*(5), 289–291. https://doi.org./10.1016/j.men.com.2013.09.018

[22] Shtamburg, V.G., Shtamburg, V.V., Tsygankov, A.V., Anishchenko, A.A., Zubatyuk, R.I., Shishkina, S.V., Mazepa, A.V., Klots, E.A. (2016). Synthesis and Structure of New *N*-Alkoxy-*N*-(1-pyridinium)urea Chlorides. *Eur. Chem. Bull.*, *5*(4), 142–146. doi: 10.17628/ECB.2016.5.142

[23] Shtamburg, V.G., Klots, E.A., Pleshkova, AP., Avramenko, V.I., Ivonin, S.P., Tsygankov, A.V, Kostyanovsky, R.G. (2003). Geminal systems. 50. Synthesis and alcoholysis on *N*-acyloxy-*N*-alkoxy derivatives of ureas, carbamates and benzamide. *Russ. Chem. Bull., Int. Ed., 52* 2251–2260. https://doi.org./10.1023/B:RUCB.0000011887.405.29.b0

[24] Shtamburg, V.G., Shtamburg, V.V., Kravchenko, S.V., Mazepa, A.V., Anishchenko, A.A., Posokhov, E.A. (2017). A New Synthesis of N-Alkoxyaminopyridinium Salts. *Bulletin of National University "KhPI". Series: New solutions in modern technology, 7*, 211–218. https://doi.org/10.20998/2413–4295.2017.07.30

[25] Shtamburg, V.G., Anishchenko, A.A., Shishkina, S.V., Konovalova, I.S., Shtamburg, V.V., Mazepa, A.V., Kravchenko, S.V. (2017). 1-(N-Ethoxycarbonyl-N-isopropyloxy)amino-4-dimethylaminopyridinium Chloride. Synthesis and Structure. *Eur. Chem. Bull.*, *6*(10), 470–474. https://doi.org/10.17628/ecb.2017.6.470-474

[26] Sheldrick, G.M. (2008). A short history of SHELX. *Acta Cryst., Sect. A*., *A64*, 112–122. https://doi.org/10.1107/S0108767307043930

[27] Mai, X., Xia, H.-Y., Cao Y.-S., Lu X.-S., Liao, Y.-J. (2009). Crystal structure of 1-(benzyloxy)urea, $C_8H_{10}N_2O_2$. *Z. Kristallogr. NCS*, *224*, 547–548. https://doi.org/10.1524/ncrs.2009.0238

[28] Burgi, H.-B., Dunitz, J.D. (1994). VCH. Weinheim., *Structure correlation*, 2, 741–784. https://doi.org./10.1107/S0108768195009931

[29] Glover, S. A., White, J. M., Rosser, A. A., Digianantonio, K.M. (2011). Structure of *N,N*-Dialkoxyamides: Pyramidal Anomeric Amides with Low Amidicity. *J. Org. Chem*., *76*(23), 9757–9763. https://doi.org/10.1021/jo201856u