UDC 547.495: 547.93

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INTERACTION OF *N*-ALKOXY-*N*-CHLORO-*N'*-ARYLUREAS WITH TRIALKYL PHOSPHITES AS A ROUTE TO DIALKYL *N*-ALKOXY-*N*-(*N''*-ARYLCARBAMOYL)PHOSPHORAMIDATES. SYNTHESIS

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This article is dedicated to the study of the interaction of some kinds of *N*-alkoxy-*N*-chloroureas, such as *N*-alkoxy-*N*-chloro-*N'*-(4-nitrophenyl)ureas, *N*-ethoxy-*N*-chloro-*N'*-(2-nitrophenyl)urea, *N*-methoxy-*N*-chloro-*N'*-(4-chlorophenyl)urea, and *N*-alkoxy-*N*-chloro-*N'*-alkylureas, with trialkyl phosphites. The stable *N*-alkoxy-*N*-chloro-*N'*-(4-nitrophenyl)ureas interact with trialkyl phosphites in diethyl ether at room temperature with preferential formation of dialkyl *N*-alkoxy-*N*-(*N'*-4-nitrophenylcarbamoyl)phosphoramidates. *N*-Ethoxy-*N*-chloro-*N'*-(2-nitrophenyl)urea reacts with trimethyl phosphite in diethyl ether at room temperature giving dimethyl *N*-ethoxy-*N*-(*N'*-2-nitrophenylcarbamoyl)phosphoramidate. The interaction of unstable *N*-methoxy-*N*-chloro-*N'*-(4-chlorophenyl)urea with trialkyl phosphites in diethyl ether gives dialkyl *N*-methoxy-*N*-(*N'*-4-chlorophenylcarbamoyl)phosphoramidates with good yields. *N*-Alkoxy-*N*-chloro-*N'*-alkylureas react with trimethyl phosphite under the same conditions with selective formation of dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates with excellent yields. In all these cases, the nucleophilic substitution at the nitrogen atom is accompanied by a further Michaelis-Arbuzov rearrangement. The original method of creating molecules containing a P—N bond is proposed. The structures of dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates and dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates have been confirmed by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy, and mass spectrometry. The synthesized dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates and dimethyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates simultaneously possess structural features of both phosphoramidates and ureas, and may be regarded as potential biologically active substances.

Keywords: *N*-alkoxy-*N*-chloro-*N'*-arylureas, *N*-alkoxy-*N*-chloro-*N'*-alkylureas, trialkyl phosphites, dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates, synthesis.

DOI: 10.32434/0321-4095-2025-162-5-92-102

Introduction

Phosphoramidates and their derivatives are widely used in medicine, medicinal chemistry and agriculture [1]. Molecules, containing P—N bond, are found in a large array biologically active natural products [1]. While the synthetic routs to phosphoramidates are

not limited now [1], the creating of new route to obtain could be useful. Urea containing compounds are widely used in medicinal chemistry and drug design too [2]. Thus, the creation of new synthetic route of compounds, which would simultaneously possess structural features of both phosporamidates and ureas, it seems relevant.

The proposed route bases on the possibility of nucleophilic substitution at the nitrogen atom in *N*-alkoxy-*N*-chloroamides [3–14]. In *N*-alkoxy-*N*-chloroureas, the N–Cl bond is elongated and weakened due to action of $n_{O(Alk)} \rightarrow \sigma^*_{N-Cl}$ anomeric effect. This bond weakening facilitates the nucleophilic substitution of the chlorine atom by the different kinds of nucleophiles [3–14].

Earlier, we had found that unsubstituted *N*-alkoxy-*N*-chloroureas **1** readily reacts with trimethyphosphite with selective formation of formation of dimethyl *N*-alkoxy-*N*-(carbamoyl)phosphoramidates (*N*-alkoxy-*N*-phosphorylureas) **2** [3] (Scheme 1).

This reaction is an original kind of Michaelis-Arbuzov reaction. Thus, for the different *N*-alkoxy-*N*-chloroamides, the nature of the nucleophilic substitution products depends on its structure [3–14]. If *N*-alkoxy-*N*-chloro-*N'*-alkylureas **3** interact with AcONa selectively yielding *N*-acyloxy-*N*-alkoxy-*N'*-alkylureas **4** [4,7,8], *N*-alkoxy-*N*-chloro-*N'*-arylureas **5** undergo the intramolecular cyclization into 1-alkoxy-1,3-dihydrobenzimidazol-2-ones **6** by AcONa action [9] (Scheme 2). Compounds **5** were synthesized by the t-BuOCl action on *N*-alkoxy- *N'*-arylureas **7** [5,10,11].

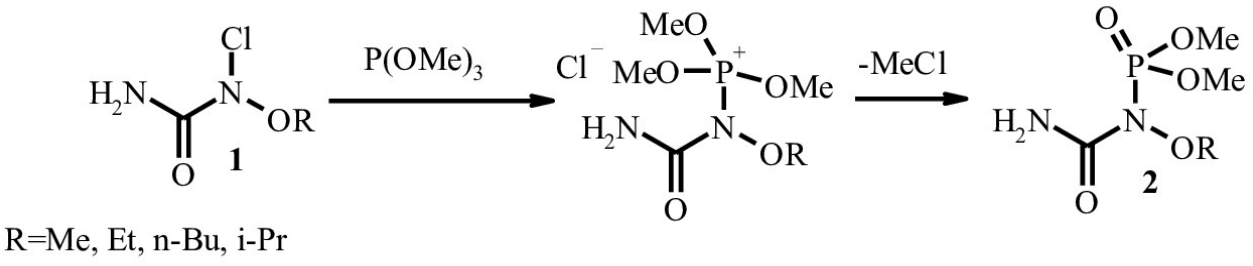
However, the interaction of *N*-alkoxy-*N*-chloro-*N'*-arylureas **5** and *N*-alkoxy-*N*-chloro-*N'*-alkylureas **3** with trialkyl phosphites had not been investigated. Therefore, the aim of our work was to explore this interaction and study the structure of its products.

Experimental

^{1}H NMR spectra were recorded on a VARIAN VNMRS 400 spectrometer (400 MHz). ^{13}C NMR spectra were recorded on a VARIAN VNMRS 400 spectrometer (100 MHz). $CDCl_3$ was used as the solvent. ^{1}H NMR chemical shifts relative to the residual solvent protons as an internal standard [$CDCl_3$: 7.260 ppm,] were reported. The solvent carbon atoms served as an internal standard for ^{13}C NMR spectra [$CDCl_3$: 77.16 ppm]. ^{31}P NMR spectra were recorded on a VARIAN VNMRS 400 spectrometer (161.95 MHz), the solvent $CDCl_3$ was used; 98% H_3PO_4 was used as external standard. Mass spectra were recorded in fast atom bombardment mode (FAB) on a VG 70-70EQ mass spectrometer.

N-Chloro-N-n-octyloxy-N'-(4-nitrophenyl)urea **5f** was synthesized according to standard procedure [5,11] by the *N*-*n*-octyloxy-*N'*-(4-nitrophenyl)urea **7f** [15] chlorination of t-BuOCl, yellow oil, m.p. 3^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=0.885 (3H, t, ^3J=6.8 Hz, $NO(CH_2)_7Me$); 1.236–1.446 (10 H, m, $NOCH_2CH_2(CH_2)_5Me$); 1.774 (2H, quint, ^3J=6.8 Hz, $NOCH_2CH_2(CH_2)_5Me$); 4.147 (1H, t, ^3J=6.8 Hz, $NOCH_2$); 7.685 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$) 8.222 (1H, br. s, NH); 8.256 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$). Mass spectrum (FAB), *m/z* (I_{rel}, %): 346 $[M+H]^+$ (7); 344 $[M+H]^+$ (21); 310 (100).

Dimethyl N-methoxy-N-(N'-4-nitrophenylcarbamoyl)phosphoramidate ***8***. The solution of trimethyl phosphite (115 mg, 0.928 mmol) in Et_2O (5 mL) was added to the solution of *N*-chloro-*N*-methoxy-*N'*-(4-nitrophenyl)urea **5a** (114 mg, 0.464 mmol) [5,11] in Et_2O (5 mL) at 28^{0}C. The reaction mixture was maintained at 28^{0}C during 48 h, then it was evaporated under vacuum, the obtained residue was maintained at 75–85^{0}C under vacuum (2 mm Hg), then it was mixed with Et_2O (5 mL) and was maintained at 12^{0}C during 22 h. The obtained precipitate was filtered off, dried under vacuum (2 mm Hg), giving 79 mg (53.4%) of dimethyl *N*-methoxy-*N*-(*N'*-4-nitrophenylcarbamoyl)phosphoramidate **8**, yellowish crystals, mp. 132–133^{0}C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=3.920 (3H, s, NOMe);

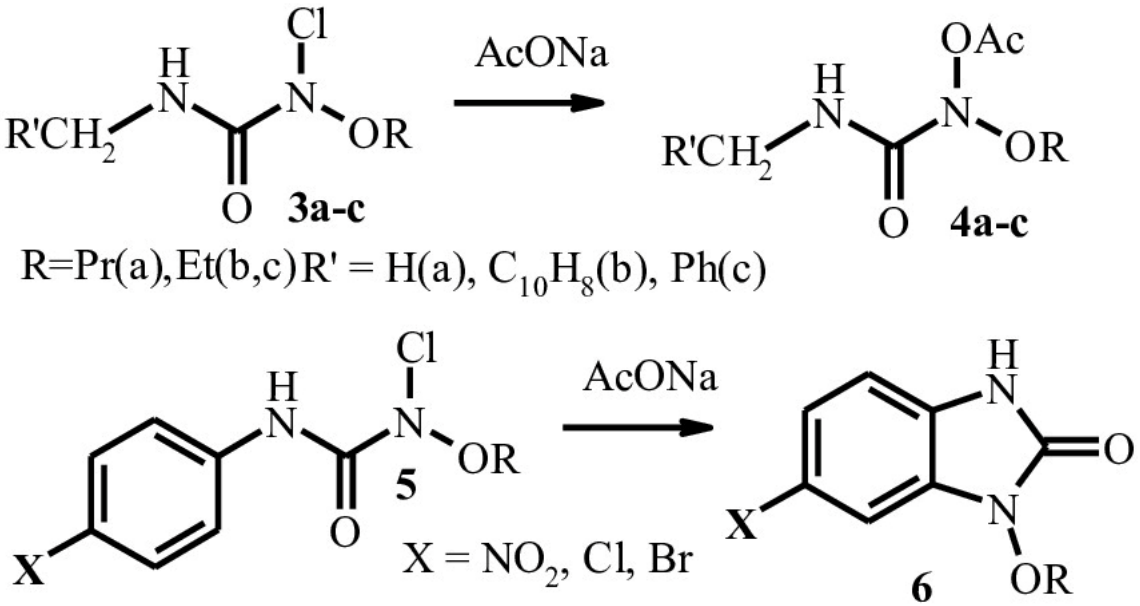


Scheme 1. Synthesis of dimethyl *N*-alkoxy-*N*-(carbamoyl)phosphoramidates **2** [3]

3.945 (6H, d, ^{HP}J=11.6 Hz, P(O)(OMe)$_2$); 7.657 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.202 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.719 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=55.50 d, ^{CP}J=6.036 Hz, P(O)(OMe)$_2$; 64.80 s NOMe; 118.98 s C(2)H, C(6)H $C_6H_4NO_2$; 125.24 s C(3)H, C(5)H $C_6H_4NO_2$; 143.47 s C(4)−NO_2 $C_6H_4NO_2$; 143.85 s C(1)$_q$ $C_6H_4NO_2$; 151.25 d, ^{CP}J=18.11 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): 0.241. Mass spectrum (FAB), *m/z* (I_{rel}, %): 320 $[M+H]^+$ (100); 127 (45). Found, %: C 37.46; H 4.57; N 13.04. $C_{10}H_{14}N_3O_7P$. Calculated, %: C 37.63; H 4.42; N 13.16. The Et_2O filtrate was evaporated under vacuum, the residue was washed by PhH (3 mL), undissolved precipitate was filtered off, dried under vacuum (2 mmHg), giving 10 mg (10.2%) of *N*-methoxy-*N'*-(4-nitrophenyl)urea **7a.**

Diethyl N-methoxy-N-(N'-4-nitrophenylcarbamoyl)phosphoramidate ***9***. The solution of triethyl phosphite (151 mg, 0.909 mmol) in Et_2O (5 mL) was added to the solution of *N*-chloro-*N*-methoxy-*N*'-(4-nitrophenyl)urea **5a** (112 mg, 0.455 mmol) [5] in Et_2O (3 mL) at 29^{0}C. The reaction mixture was maintained at 29^{0}C during 70 h, then it was evaporated under vacuum, the obtained residue was maintained at 75−85^{0}C under vacuum (2 mm Hg). The residue was extracted by hexane (7 mL) at 30^{0}C for 24 h, the obtained precipitates was filtered off, washed by hexane (4 mL) and dried under vacuum, yielding 108 mg (68.4%) of diethyl *N*-methoxy-*N*-(*N'*-4-nitrophenylcarbamoyl))phosphoramidate **9**, white powder, mp. 88−90^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.437 (6H, td, ^3J=7.1 Hz, ^{HP}J=1.2 Hz, P(O)(OCH$_2$Me)$_2$); 3.917 (3H, s, NOMe); 4.202−4.372 (4H, m, P(O)(OCH$_2$Me)$_2$); 7.656 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.201 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.869 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=16.19 d, ^{CP}J=7.043 Hz, P(O)(OCH$_2$Me)$_2$; 64.69 s NOMe; 65.68 d, ^{CP}J=6.036 Hz, P(O)(OCH$_2$Me)$_2$; 118.91 s C(2)H, C(6)H $C_6H_4NO_2$; 125.27 s C(3)H, C(5)H $C_6H_4NO_2$; 143.33 s C(1)$_q$ $C_6H_4NO_2$; 144.02 C(4)−NO_2 $C_6H_4NO_2$; 151.36 d, ^{CP}J=18.10 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): −2.412. Mass spectrum (FAB), *m/z* (I_{rel}, %): 348 $[M+H]^+$ (59); 332(38); 155 (100). Found, %: C 41.12; H 5.42; N 12.01. $C_{12}H_{18}N_3O_7P$. Calculated, %: C 41.51; H 5.22; N 12.10. The hexane filtrate was maintained at 10^{0}C for 10 days, the obtained precipitate was filtered off, yielding 7 mg (4.4%) of compound **9**.

Dimethyl N-ethoxy-N-(N'-4-nitrophenylcarbamoyl)phosphoramidate ***10***. The solution of trimethyl phosphite (110 mg, 0.888 mmol) in Et_2O (4 mL) was added to the solution of *N*-chloro-*N*-ethoxy-*N'*-(4-nitrophenyl)urea **5b** (115 mg, 0.444 mmol) [4] in Et_2O (14 mL) at 10^{0}C. The reaction mixture was maintained in the sealed ampoule at 10^{0}C during 3 h, at 20^{0}C during 48 h, then it was evaporated under vacuum, the obtained residue was maintained at 80−87^{0}C under vacuum (2 mm Hg) for 10 min, the residue was washed by hexane



Scheme 2. Interaction of *N*-alkoxy-*N*-chloroureas **3**, **5** with AcONa [4,10,11]

(7 mL) at 11^{0}C. The obtained precipitate was filtered off, dissolved in hot CCl_4 (5 mL), the CCl_4 solution was maintained at 10^{0}C for 5 days, the formed precipitate was filtered off, the hexane (5 mL) was added to the filtrate, the mixture was maintained at −26^{0}C for 24 h, the obtained precipitate was filtered off, giving 71 mg (47.7%) of dimethyl *N*-ethoxy-*N*-(*N'*-4-nitrophenylcarbamoyl))phosphoramidate **10**, white crystals, mp. 86−88^{0}C (CCl_4−hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.345 (3H, t, ^3J=7.2 Hz, $NOCH_2Me$); 3.941 (6H, d, ^{HP}J=11.6 Hz, $P(O)(OMe)_2$); 4.135 (3H, q, ^3J=7.2 Hz, $NOCH_2Me$); 7.656 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.202 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.714 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=13.64 $NOCH_2Me$; 55.51 d, ^{CP}J=6.036 Hz, $P(O)(OMe)_2$; 73.22 s $NOCH_2$; 118.93 s C(2)H, C(6)H $C_6H_4NO_2$; 125.24 s C(3)H, C(5)H $C_6H_4NO_2$; 143.39 s $C(1)_q$ $C_6H_4NO_2$; 143.89 C(4)−NO_2 $C_6H_4NO_2$; 151.56 d, ^{CP}J=18.11 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): 0.384. Mass spectrum (FAB), *m/z* (I_{rel}, %): 334 $[M+H]^+$ (100) 318(8); 127 (100). Found, %: C 39.77; H 4.90; N 12.53. $C_{11}H_{16}N_3O_7P$. Calculated, %: C 39.65; H 4.84; N 12.61.

*Dimethyl N-benzyloxy-N-(N'-4-nitrophenylcarbamoyl))phosphoramidate **11***. The solution of trimethyl phosphite (90 mg, 0.729 mmol) in Et_2O (5 mL) was added to the solution of *N*-benzyloxy-*N*-chloro-*N'*-(4-nitrophenyl)urea **5c** (117 mg, 0.364 mmol) [5] in Et_2O (5 mL) at 27^{0}C. The reaction mixture was maintained at 27^{0}C for 70 h. The formed precipitate was filtered off, the Et_2O-filtrate was evaporated under vacuum; the obtained residue was maintained at 80−87^{0}C under vacuum (2 mm Hg) for 10 min. The residue was twice extracted by boiling hexane (2r10 mL), the combine hexane extract was maintained at −14^{0}C for 90 h, the formed precipitate was filtered off, giving 67 mg (46.5%) of dimethyl *N*-benzyloxy-*N*-(*N'*-4-nitrophenylcarbamoyl))phosphoramidate **11**, yellowish crystals, m.p. 79−81^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=3.935 (6H, d, ^{HP}J=12.0 Hz, $P(O)(OMe)_2$); 5.067 (2H, s, $NOCH_2$); 7.386−7.454 (3H, m, C(3)H, C(4)H, C(5)H Ph); 7.483−7.527 (2H, m, C(2)H, C(6)H Ph); 7.640 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.203 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.600 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=55.04 d, ^{CP}J=6.037 Hz, $P(O)(OMe)_2$; 79.05 s $NOCH_2$; 119.51 s C(2)H, C(6)H $C_6H_4NO_2$; 124.62 s C(3)H, C(5)H $C_6H_4NO_2$; 128.27 s $2C_{Ph}$(H) Ph; 128.92 C(4)H Ph; 130.11 $2C_{Ph}$(H) Ph; 133.97 C_q(1) Ph; 142.43 s C(4)−NO_2 $C_6H_4NO_2$; 144.37 $C(1)_q$ $C_6H_4NO_2$; 152.28 d, ^{CP}J=14.09 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): 0.470. Mass spectrum (FAB), *m/z* (I_{rel}, %): 396 $[M+H]^+$ (75); 127 (57); 91 Bn^+(100). Found, %: C 48.34; H 4.68; N 10.45. $C_{16}H_{18}N_3O_7P$. Calculated, %: C 48.61; H 4.59; N 10.63.

*Diethyl N-benzyloxy-N-(N'-4-nitrophenylcarbamoyl))phosphoramidate **12***. The solution of triethyl phosphite (104 mg, 0.627 mmol) in Et_2O (4 mL) was added to the solution of *N*-benzyloxy-*N*-chloro-*N'*-(4-nitrophenyl)urea **5c** (101 mg, 0.313 mmol) [5] in Et_2O (5 mL) at 12^{0}C. The reaction mixture was maintained at 12^{0}C for 50 h, the formed precipitate was filtered off, the Et_2O-filtrate was evaporated under vacuum, the obtained residue was maintained at 90−96^{0}C under vacuum (2 mm Hg) for 10 min. The residue was extracted by hexane at 12^{0}C for 24 h; then the hexane extract was removed. The solid residue was extracted by CCl_4 (3 mL) at 5^{0}C for 4 days; the CCl_4-extract was separated, evaporated under vacuum, the obtained residue was dried at 60^{0}C under vacuum (2 mm Hg) for 10 min, giving 80 mg (60.3%) of diethyl *N*-benzyloxy-*N*-(*N'*-4-nitrophenylcarbamoyl))phosphoramidate **12**, white crystals, m.p. 78−80^{0}C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.425 (6H, td, ^3J=7.0 Hz, ^{HP}J=0.8 Hz, $P(O)(OCH_2Me)_2$); 4.206−4.381 (4H, m, $P(O)(OCH_2Me)_2$); 5.068 (2H, s, $NOCH_2$); 7.375−7.436 (3H, m, C(3)H, C(4)H, C(5)H Ph); 7.479−7.525 (2H, m, C(2)H, C(6)H Ph); 7.648 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.202 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.771 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=16.25 d, ^{CP}J=7.042 Hz, $P(O)(OCH_2Me)_2$; 65.68 d, ^{CP}J=7.043 Hz, $P(O)(OCH_2Me)_2$; 79.41 s $NOCH_2$; 118.89 s C(2)H, C(6)H $C_6H_4NO_2$; 125.24 s C(3)H, C(5)H $C_6H_4NO_2$; 128.83 s $2C_{Ph}$(H) Ph; 129.31 C(4)H Ph; 129.69 $2C_{Ph}$(H) Ph; 134.36 C_q(1) Ph; 143.35 s C(4)−NO_2 $C_6H_4NO_2$; 143.99 $C(1)_q$ $C_6H_4NO_2$; 151.64 d, ^{CP}J=18.11 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): −2.185. Mass spectrum (FAB), *m/z* (I_{rel}, %): 424 $[M+H]^+$ (26); 155 (55); 91 Bn^+(100). Found, %: C 49.90; H 5.37; N 9.75. $C_{18}H_{22}N_3O_7P$. Calculated, %: C 51.07; H 5.24; N 9.93.

*Dimethyl N-(N'-4-nitrophenylcarbamoyl)-N-(2-phenylethoxy)phosphoramidate **13***. The solution of trimethyl phosphite (70 mg, 0.564 mmol) in Et_2O (4 mL) was added to the solution of *N*-chloro-*N*-(2-phenylethoxy)-*N'*-(4-nitrophenyl)urea **5d** (95 mg, 0.282 mmol) [9] in Et_2O (4 mL), the reaction mixture

was maintained at 27°C for 71 h. Then the formed precipitate was filtered off, the Et_2O-filtrate was evaporated under vacuum, the residue was kept at 80−90°C under vacuum (2 mm Hg) for 10 min. The obtained residue was extracted by hexane (10 mL) at 30°C for 5 days, then the hexane extract was separated. The formed solid was dried under vacuum (2 mm Hg) at 30°C, yielding 71 mg (61.4%) of dimethyl *N-(N'*-4-nitrophenylcarbamoyl)-*N*-(2-phenylethoxy)phosphoramidate **13**, yellowish amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=3.043 (2H, t, ^3J=6.4 Hz, $NOCH_2CH_2$); 3.853 (6H, d, ^{HP}J=11.2 Hz, $P(O)(OMe)_2$); 4.344 (1H, t, ^3J=6.4 Hz, $NOCH_2CH_2$);); 7.278 (2H, d, ^3J=8.8 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.138 (2H, d, ^3J=8.8 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 8.830 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=34.76 s $NOCH_2CH_2$; 55.46 d, ^{CP}J=7.043 Hz, $P(O)(OMe)_2$; 78.13 s $NOCH_2$; 118.96 s C(2)H, C(6)H $C_6H_4NO_2$; 125.08 s C(3)H, C(5)H $C_6H_4NO_2$; 1278.06 s C(4)H Ph; 128.99 s $2C_{Ph}$(H) Ph; 129.21 s $2C_{Ph}$(H) Ph; 137.95 s C_q(1) Ph; 143.47 s and 143.50 s, C_q(1) and C(4)−NO_2 $C_6H_4NO_2$; 151.64 d, ^{CP}J=17.10 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): −0.019 . Mass spectrum (FAB), *m/z* (I_{rel}, %): 410 $[M+H]^+$ (46); 394 (14); 127 (100); 105 (50). Found, %: C 49.95; H 4.84; N 10.09. $C_{17}H_{20}N_3O_7P$. Calculated, %: C 49.88; H 4.92; N 10.27.

*Dimethyl N-isopropyloxy-N-(N'-4-nitrophenylcarbamoyl)phosphoramidate (**14**)*. The solution of triethyl phosphite (93 mg, 0.750 mmol) in Et_2O (4 mL) was added to the solution of *N*-chloro-*N*-isopropyloxy-*N'*-(4-nitrophenyl)urea **5e** (94 mg, 0.343 mmol) [9] in Et_2O (5 mL) at 11°C. The reaction mixture was maintained at 11°C for 46 h, then reaction solution was evaporated under vacuum, the obtained residue was maintained at 90−96°C under vacuum (2 mm Hg) for 10 min. The residue was extracted by hexane (7 mL) at 5°C for 2h, the hexane extract **A** was separated, the residue was secondly extracted by hexane (8 mL) at 17°C for 5 days, the hexane extract **B** was separated, the residue was extracted by CCl_4 (3mL) at 2°C for 5 days, the CCl_4-extract was separated, evaporated under vacuum, dried under vacuum (2 mm Hg) at 30°C, giving 88 mg (73.9%) of dimethyl *N*-isopropyloxy-*N*-(*N'*-4-nitrophenylcarbamoyl))phosphoramidate **14**, yellow oil, crystallizing into yellowish solid, m.p. 128−129°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.336 (6H, d, ^3J=6.4 Hz, $NOCHMe_2$); 3.932 (6H, d, ^{HP}J=12.0 Hz, $P(O)(OMe)_2$); 4.404 (1H, sept, ^3J=6.4 Hz, $NOCHMe_2$); 7.654 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 8.202 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.315 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): d=20.90, s, $NOCHMe_2$; 55.49 d, ^{CP}J=6.04 Hz, $P(O)(OMe)_2$; 80.20, s, $NOCHMe_2$; 118.92 s C(2)H, C(6)H $C_6H_4NO_2$; 125.26, s, C(3)H, C(5)H $C_6H_4NO_2$; 143.48 s, C(4)−NO_2 $C_6H_4NO_2$; 143.68, s, $C(1)_q$ $C_6H_4NO_2$; 152.72 d, ^{CP}J=15.09 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): 1.303. . Mass spectrum (FAB), *m/z* (I_{rel}, %): 348 $[M+H]^+$ (43); 332 (18); 185 (18); 129 (100). Found, %: C 41.43; H 5.37; N 11.97. $C_{12}H_{18}N_3O_7P$. Calculated, %: C 41.51; H 5.22; N 12.10. The hexane extract **B** was evaporated under vacuum, dried under vacuum (2 mm Hg) at 30°C, additionally giving 12 mg (10.1%) of dimethyl *N*-isopropyloxy-*N*-(*N'*-4-nitrophenylcarbamoyl))phosphoramidate **14**.

*Dimethyl N-(N'-4-nitrophenylcarbamoyl)-N-(n-octyloxy)phosphoramidate (**15**)*. The solution of trimethyl phosphite (91 mg, 0.737 mmol) in Et_2O (4 mL) was added to the solution of *N*-chloro-*N*-*n*-octyloxy-*N'*-(4-nitrophenyl)urea **5f** (114 mg, 0.333 mmol) in Et_2O (5 mL) at 20°C. The reaction mixture was maintained at 28°C for 71 h, then reaction solution was evaporated under vacuum, the obtained residue was maintained at 80−85°C under vacuum (2 mm Hg) for 10 min. The residue was extracted by hexane (6 mL) at 28°C for 70 h, the hexane extract was separated, the obtained residue was dried under vacuum (2 mm Hg), giving 83 mg (59.4%) of dimethyl *N-(N'*-4-nitrophenylcarbamoyl)-*N*-(*n*-octyloxy)phosphoramidate **15**, yellowish solid, m.p. 54−56°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=0.886 (3H, t, ^3J=6.8 Hz, $NO(CH_2)_7Me$); 1.263−1.379 (8H, m, $NOCH_2CH_2CH_2(CH_2)_4Me$); 1.392−1.471 (2H, m, $NOCH_2CH_2CH_2(CH_2)_4Me$); 1.691 (2H, quint, ^3J=6.8 Hz, $NOCH_2CH_2(CH_2)_5Me$); 3.936 (6H, d, ^{HP}J=12.0 Hz, $P(O)(OMe)_2$); 4.064 (1H, t, ^3J=6.4 Hz, $NOCH_2$); 7.654 (2H, d, ^3J=9.2 Hz, C(2)H,C(6)H $C_6H_4NO_2$) 8.200 (2H, d, ^3J=9.2 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.694 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=14.20, Me; 22.76, 26.02, 28.30, 29.26, 29.27, 31.92 CH_2; 54.45 d, ^{CP}J=6.04 Hz, $P(O)(OMe)_2$; 77.16 $NOCH_2$; 118.90 C(2)H, C(6)H $C_6H_4NO_2$; 125.23 C(3)H, C(5)H $C_6H_4NO_2$; 143.39 C(4)−NO_2 $C_6H_4NO_2$; 143.92 $C(1)_q$ $C_6H_4NO_2$; 151.54 d, ^{CP}J=18.11 Hz, C=O. ^{31}P NMR (161.94 MHz, $CDCl_3$, ppm): 0.449. Mass spectrum (FAB), *m/z* (I_{rel}, %): 418 $[M+H]^+$ (43); 388 (26); 213 (40); 187 (64); 152 (64); 127 (100). Found, %: C 48.85; H 6.84; N 9.98. $C_{17}H_{28}N_3O_7P$. Calculated, %: C 48.92; H 6.76; N 10.07. The hexane extract was evaporated under vacuum, the residue was solved in CCl_4 (2 mL) and hexane (3 mL) was added. The obtained solution was maintained at −32°C for

5 days, the formed precipitate was filtered off, dried under vacuum (2 mm Hg), giving 23 mg (16.6%) of compound **15**.

Dimethyl N-ethoxy-N-(N'-2-nitrophenylcarbamoyl)phosphoramidate (16). The solution of trimethyl phosphite (134 mg, 1.080 mmol) in Et_2O (4 mL) was added to the solution *N*-chloro-*N*-ethoxy-*N'*-(2-nitrophenyl)urea **5g** (113 mg, 0.435 mmol) [5] in Et_2O (4 mL) at 18°C. The reaction mixture was maintained at 18°C for 49 h, then reaction solution was evaporated under vacuum, the obtained residue was maintained at 90–96°C under vacuum (2 mm Hg) for 10 min. The residue was extracted by hexane (6 mL) at 14°C at stirring, the hexane extract **A** was separated off. The residue was extracted by boiling hexane (6 mL), the hexane extract **B** was separated off. The residue was dissolved in CCl_4 (2 mL) and hexane (4 mL) was added. This solution was maintained at 2°C for 5 days, the formed solid phase was separated off, the CCl_4–hexane phase was evaporated under vacuum, the obtained residue was dried under vacuum (2 mm Hg) at 50°C, giving 29 mg (20.0%) of dimethyl *N*-ethoxy-*N*-(*N'*-2-nitrophenylcarbamoyl)phosphoramidate **16**, yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.430 (3H, t, ^3J=7.2 Hz, $NOCH_2Me$); 3.943 (6H, d, ^{HP}J=12.0 Hz, $P(O)(OMe)_2$); 4.224 (2H, q, ^3J=7.2 Hz, $NOCH_2Me$); 7.191 (1H, td, ^3J=8.0 Hz, ^4J=1.6 Hz, C(4)H 2-$O_2NC_6H_4$); 7.649 (1H, td, ^3J=8.0 Hz, ^4J=1.6 Hz, C(5)H 2-$O_2NC_6H_4$); 8.237 (1H, dd, ^3J=8.6 Hz, ^4J=1.6 Hz, C(6)H 2-$O_2NC_6H_4$); 8.697 237 (1H, dd, ^3J=8.4 Hz, ^4J=1.2 Hz, C(3)H 2-$O_2NC_6H_4$); 11.131 (1H, br. s, NH). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ=13.44 s $NOCH_2Me$; 55.32 d, ^{CP}J=6.04 Hz, $P(O)(OMe)_2$; 74.28 s $NOCH_2$; 121.74 s C_{Ar}(H), 2-$O_2NC_6H_4$; 123.32 s C_{Ar}(H), 2-$O_2NC_6H_4$; 126.02 s C_{Ar}(H), 2-$O_2NC_6H_4$; 134.59 s $C(1)_q$ 2-$O_2NC_6H_4$; 136.00 s C_{Ar}(H), 2-$O_2NC_6H_4$; 136.97 C(4)–NO_2 2-$O_2NC_6H_4$; 152.83 d, ^{CP}J=15.09 Hz, C=O. ^{31}P NMR (161.95 MHz, $CDCl_3$, ppm): 0.378. Mass spectrum (FAB), *m/z* (I_{rel}, %): 334 $[M+H]^+$ (100); 318(41); 126 (88). Found, %: C 39.47; H 4.55; N 12.48. $C_{11}H_{16}N_3O_7P$. Calculated, %: C 39.65; H 4.84; N 12.61. The hexane extract **A** was evaporated under vacuum, the obtained residue was dried under vacuum (2 mm Hg) at 50°C, additionally giving 25 mg (17.2%) of dimethyl *N*-ethoxy-*N*-(*N'*-2-nitrophenylcarbamoyl)phosphoramidate **16**. The hexane extract **B** was evaporated under vacuum, the obtained residue was dried under vacuum (2 mm Hg) at 50°C, additionally giving 27 mg (18.6%) of dimethyl *N*-ethoxy-*N*-(*N'*-2-nitrophenylcarbamoyl)phosphoramidate **16**.

Dimethyl N-methoxy-N-(N'-4-chlorophenylcarbamoyl)phosphoramidate (17). The solution of *t*-BuOCl (170 mg, 1.570 mmol) in CH_2Cl_2 (4) was added to the mixture of *N*-methoxy-*N'*-(4-chlorophenyl)urea **7h** (105 mg, 0.523 mmol) [10] and CH_2Cl_2 (2 mL) at 24°C. The reaction mixture was maintained at 24°C for 40 min, then it was evaporated under vacuum, the residue was dried under vacuum (2 mm Hg) for 10 min. The obtained *N*-chloro-*N*-methoxy-*N'*-(4-chlorophenyl)urea **5h** (as white solid) was immediately disssolved in Et_2O (9 mL), and the solution of trimethyl phosphite (130 mg, 1.047 mmol) in Et_2O (5 mL) was added. The reaction mixture was maintained at 24°C for 49 h, then reaction solution was evaporated under vacuum, the residue was dried at 90–93°C under vacuum (2 mm Hg) for 10 min. The obtained residue was extracted by hexane (6 mL) at 24°C for 48 h, then the hexane extract **A** was separated off. The residue was dissolved in CCl_4 (3 mL) and hexane (2mL) was added. This solution was maintained at 10°C for 26 h, the CCl_4–hexane extract was separated off, evaporated under vacuum, the residue was dried under vacuum (2 mm Hg), giving 87 mg (53.8%) of dimethyl *N*-methoxy-*N*-(*N'*-4-chlorophenylcarbamoyl)phosphoramidate **17**, colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=3.908 (3H, s, NOMe); 3.925 (6H, d, ^{HP}J=12.0 Hz, $P(O)(OMe)_2$); 7.275 (2H, d, ^3J=8.8 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 7.442 (2H, d, ^3J=8.8 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.127 (1H, br. s, NH). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=55.29 d, ^{CP}J=6.04 Hz, $P(O)(OMe)_2$; 64.82 s NOMe; 120.96 s C(2)H, C(6)H C_6H_4Cl; 128.99 s C(4)–Cl C_6H_4Cl; 129.13 s C(3)H, C(5)H C_6H_4Cl; 136.29 s $C(1)_q$ C_6H_4Cl; 151.54 d, ^{CP}J=17.11 Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 0.643. Mass spectrum (FAB), *m/z* (I_{rel}, %): 311 $[M+H]^+$ (24); 309 $[M+H]^+$ (85); 293 (100); 155(29); 153 (30); 127(77). Found, %: C 38.74; H 4.69; N 9.14. $C_{10}H_{14}ClN_2O_5P$. Calculated, %: C 38.91; H 4.57; N 9.08. The hexane extract **A** was evaporated under vacuum, the residue was dried under vacuum (2 mm Hg) at 90°C, additionally giving 37 mg (22.9%) of compound **17**.

Diethyl N-methoxy-N-(N'-4-chlorophenylcarbamoyl)phosphoramidate (18). The solution of *t*-BuOCl (162 mg, 1.495 mmol) in CH_2Cl_2 (3) was added to the mixture of *N*-methoxy-*N'*-(4-chlorophenyl)urea **7h** (100 mg, 0.498 mmol) [10] and CH_2Cl_2 (2 mL) at 24°C. The reaction mixture was maintained at 24°C for 1 h, then it was evaporated under vacuum, the residue was dried under vacuum (2 mm Hg) for 10 min. The obtained *N*-chloro-*N*-

methoxy-*N'*-(4-chlorophenyl)urea **5h** (as white solid) was immediately disssolved in Et_2O (7 mL), and the solution of triethyl phosphite (166 mg, 0.997 mmol) in Et_2O (5 mL) was added. The reaction mixture was maintained at 24°C for 100 h, then reaction solution was evaporated under vacuum, the residue was dried at 93–95°C under vacuum (2 mm Hg) for 15 min. The obtained residue was extracted by hexane (6 mL) at 24°C for 24 h, then the hexane extract **A** was separated off. The remaining solid residue was dried under vacuum (2 mm Hg), giving 58 mg (34.5%) of diethyl *N*-methoxy-*N*-(*N'*-4-chlorophenylcarbamoyl)phosphoramidate **18**, colorless crystals, m.p. 65–68°C (Et_2O–hexane). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.417 (6H, td, ^3J=7.1 Hz, ^{HP}J=1.2 Hz, P(O)(OCH$_2$Me)$_2$); 3.898 (3H, s, NOMe); 4.182–4.351 (4H, m Hz, P(O)(OCH$_2$Me)$_2$); 7.265 (2H, d, ^3J=8.8 Hz, C(2)H,C(6)H $C_6H_4NO_2$); 7.439 (2H, d, ^3J=8.8 Hz, C(3)H,C(5)H $C_6H_4NO_2$); 9.284 (1H, br. s, NH). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=16.19 d, ^{CP}J=7.04 Hz, P(O)(OCH$_2$Me)$_2$; 64.70 s NOMe; 65.35 d, ^{CP}J=6.04 Hz, P(O)(OCH$_2$Me)$_2$; 120.89 s C(2)H, C(6)H C_6H_4Cl; 128.80 s C(4)–Cl C_6H_4Cl; 129.11 s C(3)H, C(5)H C_6H_4Cl; 136.48 s C(1)$_q$ C_6H_4Cl; 151.62 d, ^{CP}J=18.11 Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): −2.023. Mass spectrum (FAB), *m/z* (I_{rel}, %): 339 $[M+H]^+$ (27); 337 $[M+H]^+$ (100); 323 (24); 321(71); 153 (30); 156 (87). Found, %: C 42.69; H 5.65; N 8.16. $C_{12}H_{18}ClN_2O_5P$. Calculated, %: C 42.81; H 5.39; N 8.32. The hexane extract **A** was evaporated under vacuum, the residue was dried under vacuum (2 mm Hg) at 95°C, additionally giving 47 mg (28.0%) of compound **18**.

Dimethyl N-(N'-methylcarbamoyl)-N-propyloxyphosphoramidate (19). The solution of trimethyl phosphite (196 mg, 1.580 mmol) in Et_2O (4 mL) was added to the solution of *N*-chloro-*N*-propyloxy-*N'*-methylurea **3a** [7] (126 mg, 0.757 mmol) in Et_2O (5 mL) at 8°C. The reaction mixture was maintained at 8°C for 69 h, then reaction solution was evaporated under vacuum, the obtained residue was maintained at 85–90°C under vacuum (2 mm Hg) for 10 min. The residue was dissolved in CH_2Cl_2 (0.5 mL) and hexane (5 mL) was added. This solution was maintained at 8°C for 6 days, the hexane phase was separated off the formed bottom phase **A** and evaporated under vacuum. The residue dried under vacuum (2 mm Hg), giving 125 mg (68.7%) of dimethyl *N*-(*N'*-methylcarbamoyl)-*N*-propyloxyphosphoramidate **19**, colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=0.978 (3H, t, ^3J=7.2 Hz, NO(CH$_2$)$_2$Me); 1.684 (2H, sex, ^3J=7.2 Hz, NOCH$_2$CH$_2$Me); 2.839 (3H, d, ^3J=4.8 Hz, NHMe); 3.863 (6H, d, ^{HP}J=11.6 Hz, P(O)(OMe)$_2$); 3.957 (2H, t, ^3J=6.8 Hz, NOCH$_2$); 6.606 (1H, br. s, NH). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=10.43 s, NO(CH$_2$)$_2$Me; 21.57 s, CH$_2$; 26.83 s, NHMe; 54.90 d, ^{CP}J=6.04 Hz, P(O)(OMe)$_2$; 78.93 s, NOCH$_2$; 155.28 d, ^{CP}J=15.09 Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 1.246. Mass spectrum (FAB), *m/z* (I_{rel}, %): 241 $[M+H]^+$ (100). Found, %: C 34.96; H 7.28; N 11.45. $C_7H_{17}N_2O_5P$. Calculated, %: C 35.00; H 7.13; N 11.66. The formed bottom phase **A** was extracted by hot hexane (5 mL), the hexane extract evaporated under vacuum, the residue dried under vacuum (2 mm Hg), yielding additionally 42 mg (23.1%) of compound **19**.

Dimethyl N-ethoxy-N-(N'-(1-naphthyl)methylcarbamoyl)phosphoramidate (20). The solution of trimethyl phosphite (104 mg, 0.835 mmol) in Et_2O (5 mL) was added to the solution of *N*-chloro-*N*-ethoxy-*N'*-(1-naphthyl)methylurea **3b** [7] (116 mg, 0.418 mmol) in Et_2O (5 mL) at 9°C. The reaction mixture was maintained at 9°C for 71 h, then the negligible precipitate was filtered off, the filtrate was evaporated under vacuum, the obtained residue was maintained at 85–90°C under vacuum (2 mm Hg) for 10 min. The residue was washed by cold hexane (2 mL), dried under vacuum (2 mm Hg), yielding 145 mg (98%) of dimethyl *N*-ethoxy-*N*-(*N'*-(1-naphthyl)methylcarbamoyl)phosphoramidate **20**, colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.299 (3H, t, ^3J=7.2 Hz, NOCH$_2$Me); 3.834 (6H, d, ^{HP}J=12.0 Hz, P(O)(OMe)$_2$); 4.057 (2H, t, ^3J=6.8 Hz, NOCH$_2$); 4.919 (2H, d, ^3J=5.6 Hz, NHCH$_2$); 7.026 (1H, br. s, NH); 7.402–7.476 (2H, m, 2C$_{Ar}$(H) Napht); 7.490–7.570 (2H, m, 2C$_{Ar}$(H) Napht); 7.809 (1H, d, ^3J=8.4 Hz, C$_{Ar}$(H) Napht); 7.877 (1H, d, ^3J=8.0 Hz, C$_{Ar}$(H) Napht); 8.039 (1H, d, ^3J=8.0 Hz, C$_{Ar}$(H) Napht). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=13.56 s, NOCH$_2$Me; 42.35 s, NCH$_2$; 54.96 d, ^{CP}J=6.04 Hz, P(O)(OMe)$_2$; 73.11 s, NOCH$_2$; 123.36, 125.51, 125.99, 126.34, 126.57, 128.63, 128.89 s C$_{Ar}$(H) Napht; 131.40, 133.54, 133.96 s C$_q$ Napht; 154.58 d, ^{CP}J=15.09 Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 1.097. Mass spectrum (FAB), *m/z* (I_{rel}, %): 353 $[M+H]^+$ (22); 141 (100); 127 (10). Found, %: C 54.68; H 6.19; N 7.72.45. $C_{16}H_{21}N_2O_5P$. Calculated, %: C 54.55; H 6.01; N 7.95.

Dimethyl N-ethoxy-N-(N'-phenylmethylcarbamoyl)phosphoramidate (21). The solution of trimethyl phosphite (126 mg, 1.019 mmol) in Et_2O (5 mL) was added to the solution of *N*-

chloro-*N*-ethoxy-*N'*-phenylmethylurea **3c** [4] (117 mg, 0.510 mmol) in Et_2O (5 mL) at 14^{0}C. The reaction mixture was maintained at 14^{0}C for 76 h, then it was evaporated under vacuum, the obtained residue was maintained at 85–93^{0}C under vacuum (2 mm Hg) for 10 min. The residue was washed by cold hexane (2 mL), dried under vacuum (2 mm Hg), yielding 139 mg (90%) of dimethyl *N*-ethoxy-*N*-(*N'*-phenylmethylcarbamoyl)phosphoramidate **21**, colorless viscous oil that solidifies over time in the cold into colorless solid, m.p. 41–42^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.275 (3H, t, ^3J=7.2 Hz, $NOCH_2Me$); 3.866 (6H, d, ^{HP}J=12.0 Hz, $P(O)(OMe)_2$); 4.081 (2H, t, ^3J=7.2 Hz, $NOCH_2$); 4.452 (2H, d, ^3J=6.0 Hz, $NHCH_2$); 7.071 (1H, br. s, NH); 7.267–7.382 (5H, m, Ph). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=13.65 s, $NOCH_2Me$; 44.29 s, NCH_2; 55.02 d, ^{CP}J=6.04 Hz, $P(O)(OMe)_2$; 73.12 s, $NOCH_2$; 127.57 s, C(4)H Ph; 127.63 s, $2C_{Ph}$(H) Ph; 128.8 s, $2C_{Ph}$(H) Ph; 138.46 s C_q(1) Ph; 154.84 d, ^{CP}J=16.10 Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 1.112. Mass spectrum (FAB), *m/z* (I_{rel}, %): 303 $[M+H]^+$ (100). Found, %: C 47.39; H 6.42; N 9.05. $C_{12}H_{19}N_2O_5P$. Calculated, %: C 47.68; H 6.34; N 9.27.

Results and discussion

Chlorination of *N*-alkoxy-*N'*-4-nitrophenylureas **7a–f** and *N*-ethoxy-*N'*-2-nitrophenylurea **7g** by *tert*-butyl hypochlorite selectively gives *N*-alkoxy-*N*-chloro-*N'*-arylureas **5a–g**. *N*-Alkoxy-*N*-chloro-*N'*-arylureas **5a–g**, containing nitro group, are relatively stable compounds at room temperature [5,10] and were isolated and characterized by ^{1}H NMR [5,10,11].

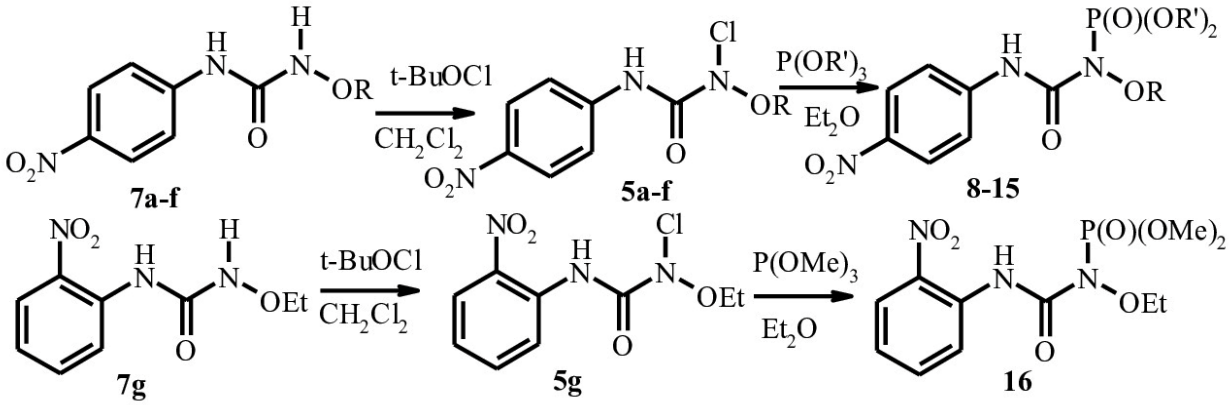
N-Alkoxy-*N*-chloro-*N'*-arylureas **10a–g** react with trialkyl phosphites in ether at room temperature with forming dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **13–21** as main products (Scheme 3). Also, in some cases *N*-alkoxy-*N'*-arylureas **7a–g** form as minor products in negligible or trace amounts.

N-Methoxy-*N*-chloro-*N'*-(4-chlorophenyl)urea **5h** are stable for small time at room temperature [5,10]. These compounds after isolation at room temperature were immediately introduced into the reaction with trialkyl phosphites in ether solution at room temperature. In this way, *N*-alkoxy-*N*-(*N'*-4-chlorophenyl)carbamoyl)phosphoramidates **17**, **18** were obtained with good yields (Scheme 4).

N-Alkoxy-*N*-chloro-*N'*-alkylureas **3a–c** react with trimethyll phosphite in ether at room temperature with forming dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19–21** with excellent yields (Scheme 5).

The structures of dialkyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **8–18** and dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19–21** have been proved by the ^{1}H, ^{13}C, ^{31}P NMR spectra and mass spectra. The ^{1}H NMR spectra of compounds **8–21** show such a common characteristic: 1) doublet of $(MeO)_2(O)P$-moiety or td and m of $(MeCH_2O)_2(O)P$-moiety; and 2) singlet of NH moiety. For dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **8–15**, **17**, **18**, the singlet of NH hydrogen atom in the region 8.961–9.869 ppm is characteristic. However, for *ortho*-substituted compound **16**, this singlet is situated at 11.131 ppm. For dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19–21**, this NH-moiety singlet is situated at 6.606–7.071 ppm.

In ^{31}P NMR spectra of dimethyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **8, 10, 11, 13–**



Scheme 3. Synthesis of dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **8–16** (R=R'=Me (**8**; 53%), R=Me, R'=Et (**9**; 68%); R=Et, R'=Me (**10**; 48%), R=Bn, R'=Me (**11**; 47%), R=Bn, R'=Et (**12**; 60%), R=CH_2CH_2Ph (**13**; 61%), R=i-Pr, R'=Me (**14**; 74%), R=n-C_8H_{17}, R'=Me (**15**; 76%). Compound **16** (56%)

17, the chemical shifts of the phosphorus atom lie in the range −0.02...1.30 ppm. In ^{31}P NMR spectra of diethyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **9, 12, 18**, the chemical shifts of the phosphorus atom lie in the range −2.41...−2.02 ppm. In ^{31}P NMR spectra of dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19−21**, the chemical shifts of the phosphorus atom lie in the range 1.10−1.25 ppm.

^{13}C NMR spectra of compounds **8−21** demonstrate numerous common characteristics. They include the chemical shifts the carbon atoms of dialkoxyphosphoryl group (doublet of $P(O)(OMe)_2$ moiety or two doublets of $P(O)(OCH_2Me)_2$ moiety), and doublet of the carbon atom of C=O bond. For dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **8−18**, the doublet of carbon atom of C−O group in the region 151.25−152.83 ppm is characteristic. For dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19−21**, this C=O-moiety doublet is situated at 154.58−155.28 ppm. For dimethyl phosphoramidates, the doublet of $(MeO)_2(O)P$ moiety is situated in the region 54.90−55.51 ppm. For diethyl phosphoramidates, two doublet of $(EtO)_2(O)P$ group are situated at 16.19−16.25 ppm and 65.35−65.68 ppm, respectively.

The mass spectra of compounds **8−21** display protonated molecular ion $[M+H]^+$ peaks at the appropriate *m/z* values with high intensity.

Conclusions

We have found that the reaction of *N*-alkoxy-*N*-chloro-*N'*-arylureas **5** with trialkyl phosphites is a novel synthetic pathway to dialkyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoramidates **8−18** by means of the nucleophilic substitution at the nitrogen atom accompanied by Michaelis-Arbuzov rearrangement. The reaction of *N*-alkoxy-*N*-chloro-*N'*-alkylureas **3a−c** with trimethylphosphite is a novel synthetic pathway to dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19−21**.

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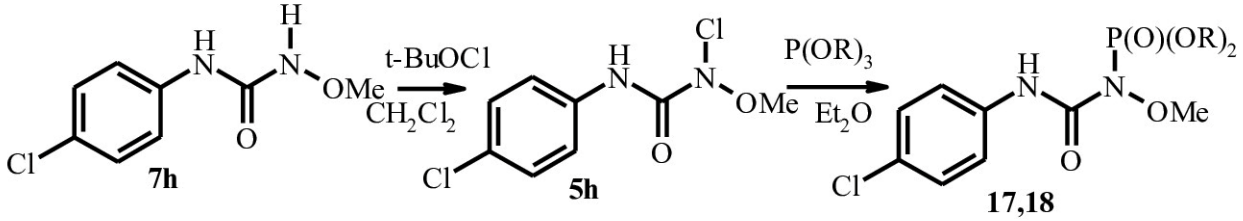
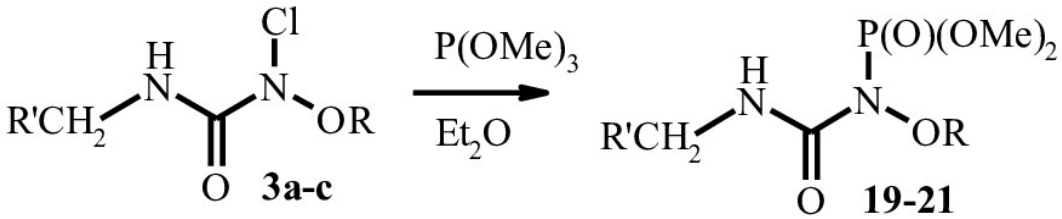


Scheme 4. Synthesis of dialkyl *N*-alkoxy-*N*-(*N'*-4-X-phenylcarbamoyl)phosphoramidates **17, 18** (R=Me (**17**; 54%), R=Et (**18**; 62%)



Scheme 5. Synthesis of dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **19−21**, R=Pr, R'=H (**19**; 69%); R=Et, R'=1-$C_{10}H_8$ (**20**; 98%); R=Et, R=Ph (**21**; 90%)

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Received 03.02.2025

ВЗАЄМОДІЯ *N*-АЛКОКСИ-*N*-ХЛОРО-*N'*-АРИЛСЕЧОВИН З ТРИАЛКІЛФОСФІТАМИ ЯК ШЛЯХ ДО ДІАЛКІЛ-*N*-АЛКОКСИ-*N*-(*N'*-АРИЛКАРБАМОЇЛ)ФОСФОРАМІДАТІВ. СИНТЕЗ

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Ця стаття присвячена дослідженню взаємодії деяких видів *N*-алкокси-*N*-хлоросечовин, таких як *N*-алкокси-*N*-хлор-*N'*-(4-нітрофеніл)сечовини, *N*-етокси-*N*-хлор-*N'*-(2-нітрофеніл)сечовина, *N*-метокси-*N*-хлор-*N'*-(4-хлорофеніл)сечовина, та *N*-алкокси-*N*-хлор-*N'*-алкілсечовини, з триалкілфосфітами. Стабільні *N*-алкокси-*N*-хлор-*N'*-(4-нітофеніл)сечовини взаємодіють із триалкілфосфітами в діетиловому етері за кімнатної температури з переважним утворенням діалкіл-*N*-алкокси-*N*-(*N'*-4-нітрофенілкарбамоїл)-фосфорамідатів. *N*-Етокси-*N*-хлор-*N'*-(2-нітрофеніл)сечовина реагує з триметилфосфітом у діетиловому етері за кімнатної температури, утворюючи диметил-*N*-етокси-*N*-(*N'*-2-нітрофенілкарбамоїл)фосфорамідат. Взаємодія нестабільної *N*-метокси-*N*-хлор-*N'*-(4-хлорофеніл)сечовини з триалкілфосфітами у діетиловому етері дає діалкіл-*N*-метокси-*N*-(*N'*-4-хлорофенілкарбамоїл)фосфорамідати з гарними виходами. *N*-Алкокси-*N*-хлор-*N'*-алкілсечовини реагують з триметилфосфітом у тих самих умовах із селективним утворенням диметил-*N*-алкокси-*N*-(*N'*-алкілкарбамоїл)фосфорамідатів із високими виходами. У всіх цих випадках нуклеофільне заміщення за атомом азоту супроводжується подальшим перегрупуванням Міхаеліса-Арбузова. Запропоновано оригінальний спосіб створення молекул, що містять зв'язок P–N. Будову діалкіл-*N*-алкокси-*N*-(*N'*-арилкарбамоїл)фосфорамідатів і диметил-*N*-алкокси-*N*-(*N'*-алкілкарбамоїл)фосфорамідатів було підтверджено ^{1}H, ^{31}P і ^{13}C ЯМР спектроскопією та мас-спектрометрією. Синтезовані діалкіл-*N*-алкокси-*N*-(*N'*-арилкарбамоїл)фосфорамідати та диметил-*N*-алкокси-*N*-(*N'*-алкілкарбамоїл)фосфорамідати одночасно мають структурні ознаки як фосфорамідатів, так і сечовин і можуть розглядатися як потенційно біологічно активні речовини.

Ключові слова: *N*-алкокси-*N*-хлоро-*N'*-арилсечовини, триалкілфосфіти, *N*-алкокси-*N*-хлоро-*N'*-алкілсечовини, діалкіл-*N*-алкокси-*N*-(*N'*-арилкарбамоїл)фосфорамідати, синтез.

INTERACTION OF N-ALKOXY-N-CHLORO-N'-ARYLUREAS WITH TRIALKYL PHOSPHITES AS A ROUTE TO DIALKYL N-ALKOXY-N-(N''-ARYLCARBAMOYL)PHOSPHORAMIDATES. SYNTHESIS

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This article is dedicated to the study of the interaction of some kinds of N-alkoxy-N-chloroureas, such as N-alkoxy-N-chloro-N'-(4-nitrophenyl)ureas, N-ethoxy-N-chloro-N'-(2-nitrophenyl)urea, N-methoxy-N-chloro-N'-(4-chlorophenyl)urea, and N-alkoxy-N-chloro-N'-alkylureas, with trialkyl phosphites. The stable N-alkoxy-N-chloro-N'-(4-nitrophenyl)ureas interact with trialkyl phosphites in diethyl ether at room temperature with preferential formation of dialkyl N-alkoxy-N-(N'-4-nitrophenylcarbamoyl)phosphoramidates. N-Ethoxy-N-chloro-N'-(2-nitrophenyl)urea reacts with trimethyl phosphite in diethyl ether at room temperature giving dimethyl N-ethoxy-N-(N'-2-nitrophenylcarbamoyl)phosphoramidate. The interaction of unstable N-methoxy-N-chloro-N'-(4-chlorophenyl)urea with trialkyl phosphites in diethyl ether gives dialkyl N-methoxy-N-(N'-4-chlorophenylcarbamoyl)phosphoramidates with good yields. N-Alkoxy-N-chloro-N'-alkylureas react with trimethyl phosphite under the same conditions with selective formation of dimethyl N-alkoxy-N-(N'-alkylcarbamoyl)phosphoramidates with excellent yields. In all these cases, the nucleophilic substitution at the nitrogen atom is accompanied by a further Michaelis-Arbuzov rearrangement. The original method of creating molecules containing a P–N bond is proposed. The structures of dialkyl N-alkoxy-N-(N'-arylcarbamoyl)phosphoramidates and dimethyl N-alkoxy-N-(N'-alkylcarbamoyl)phosphoramidates have been confirmed by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy, and mass spectrometry. The synthesized dialkyl N-alkoxy-N-(N'-arylcarbamoyl)phosphoramidates and dimethyl N-alkoxy-N-(N'-arylcarbamoyl)phosphoramidates simultaneously possess structural features of both phosphoramidates and ureas, and may be regarded as potential biologically active substances.

Keywords: N-alkoxy-N-chloro-N'-arylureas; N-alkoxy-N-chloro-N'-alkylureas; trialkyl phosphites; dialkyl N-alkoxy-N-(N'-arylcarbamoyl)phosphoramidates; synthesis.

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