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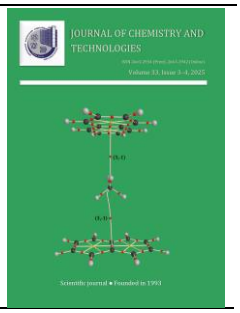

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INTERACTION OF LABILE *N*-ALKOXY-*N*-CHLORO-*N'*-ARYLUREAS AND *N*-ACETOXY-*N*-ALKOXYUREAS WITH TRIMETHYL PHOSPHITE

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Abstract

The freshly synthesized *N*-alkoxy-*N*-chloro-*N'*-4-bromophenylureas undergo reaction with trimethyl phosphite in diethyl ether at room temperature yielding respectively dimethyl *N*-alkoxy-*N*-(*N'*-4-bromophenylcarbamoyl)phosphoroamidates with high yields. The unstable *N*-alkoxy-*N*-chloro-*N'*-phenylureas, freshly synthesized at -30°C, interact with trimethyl phosphite in diethyl ether at this low temperature to produce previously unknown dimethyl *N*-alkoxy-*N*-(*N'*-phenylcarbamoyl)phosphoroamidates. This reaction is the first example of the nucleofilic substitution at the nitrogen atom for unstable *N*-alkoxy-*N*-chloro-*N'*-phenylureas. Careful conditions selection and precise control made it possible to pevent premature destruction of the starting *N*-alkoxy-*N*-chloro-*N'*-4-bromophenylureas and *N*-alkoxy-*N*-chloro-*N'*-phenylureas. In contrast, *N*-acetoxy-*N*-alkoxyureas do not react with trimethyl phosphite under the same conditions. The structures of the resulting dimethyl *N*-alkoxy-*N*-(*N'*-4-bromophenylcarbamoyl)phosphoroamidates and dimethyl *N*-alkoxy-*N*-(*N'*-phenylcarbamoyl)phosphoroamidates were confirmed by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy, as well as mass spectrometry. A comparative analysis of ^{1}H, ^{31}P and ^{13}C NMR spectra of these dimethyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoroamidates with those of dialkyl *N*-alkoxy-*N*-(*N'*-4-nitrophenylcarbamoyl)phosphoroamidates revealed numerous shared features and general structural characteristics of *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoroamidates.

Keywords: *N*-alkoxy-*N*-chloro-*N'*-arylureas; trimethyl phosphite; dimethyl *N*-alkoxy-*N*-(*N'*-arylcarbamoyl)phosphoroamidates; synthesis.

ВЗАЄМОДІЯ ЛАБІЛЬНИХ *N*-АЛКОКСИ-*N*-ХЛОРО-*N'*-АРИЛСЕЧОВИН ТА *N*-АЦЕТОКСИ-*N*-АЛКОКСИСЕЧОВИН З ТРИМЕТИЛФОСФІТОМ

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Анотація

Досліджено взаємодію свіжо отриманих *N*-алкокси-*N*-хлоро-*N'*-4-бромофенілсечовин із триметилфосфітом у діетиловому етері за кімнатної температури, яка приводить до утворення відповідних диметил-*N*-алкокси-*N*-(*N'*-4-бромофенілкарбамоїл)фосфорамідатів з високими виходами. Вперше синтезовані за температури -30 °С дуже нестабільні *N*-алкокси-*N*-хлоро-*N'*-фенілсечовини взаємодіють з триметилфосфітом у діетиловому етері за температури -30 °С, утворюючи диметил-*N*-алкокси-*N*-(*N'*-фенілкарбамоїл)фосфорамідати. Ця реакція є першим прикладом нуклеофільного заміщення при атомі азоту у дуже нестабільних *N*-алкокси-*N*-хлоро-*N'*-фенілсечовинах. Ретельний підбір умов для проведення цих реакцій дозволив уникнути передчасного руйнування вихідних *N*-алкокси-*N*-хлоро-*N'*-4-бромофенілсечовин та *N*-алкокси-*N*-хлоро-*N'*-

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фенілсечовин. Структури синтезованих диметил-*N*-алкокси-*N*-(*N'*-4-бромофенілкарбамоїл)фосфорамідатів та діметил-*N*-алкокси-*N*-(*N'*-фенілкарбамоїл)фосфорамідатів підтверджено ^{1}H, ^{31}P, ^{13}C ЯМР-спектроскопією та мас-спектрометрією. Проведено порівняльний аналіз ^{1}H, ^{31}P та ^{13}C ЯМР спектрів отриманих діметил-*N*-алкокси-*N*-(*N'*-арилкарбамоїл)фосфорамідатів та діалкіл-*N*-алкокси-*N*-(*N'*-4-нітрофеніл-карбамоїл)фосфорамідатів. Встановлено численні спільні особливості та спільні характеристики.

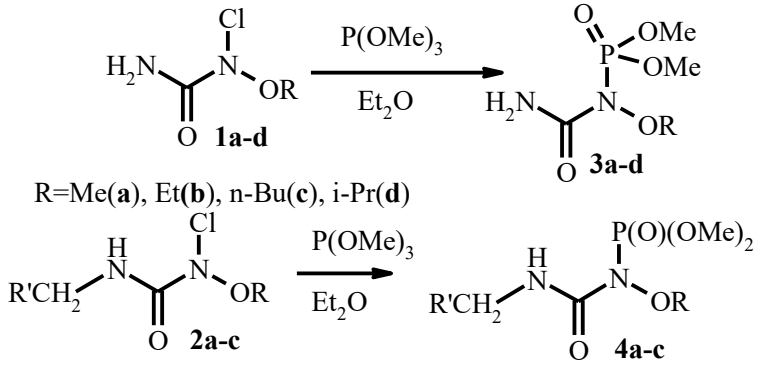
Ключові слова: *N*-алкокси-*N*-хлоро-*N'*-арилсечовини; триметилфосфіт; диметил-*N*-алкокси-*N*-(*N'*-арилкарбамоїл)фосфорамідати; синтез.

Introduction

Urea and its derivatives find extensive application in medicine, medicinal chemistry and agriculture [1]. Phosphoramidates are also widely used in medicinal chemistry and drug development [2]. Although the routes for synthesizing phosphoramidates are diverse [2], the exploring new synthetic pathways could offer valuable advancements.

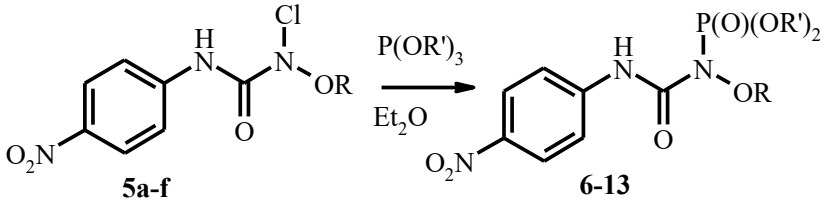
Recently, we have synthesized dialkyl *N*-alkoxy-*N*-(carbamoyl)phosphoramidates (*N*-alkoxy-*N*-(dialkoxyphosphoryl)ureas), characterized by the coexistence of structural aspects from both ureas and phosphoramidates [3; 4].

The proposed synthesis is based on the possibility of interaction of *N*-alkoxy-*N*-chloroureas **1a-d** [3] and *N*-alkoxy-*N*-chloro-*N'*-alkylureas **2a-c** with trimethyl phosphite in ether at room temperature to form dimethyl *N*-alkoxy-*N*-(carbamoyl)phosphoramidates **3a-d** [3] and dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates **4a-c** [4; 5], respectively.



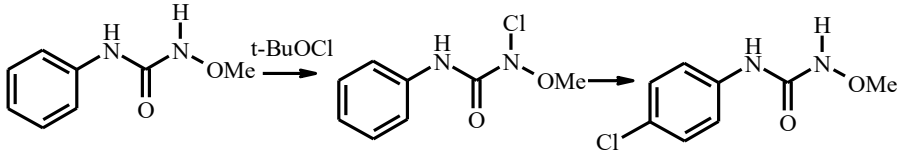
Scheme 1. The synthesis of dimethyl *N*-alkoxy-*N*-(carbamoyl)phosphoramidates 3a-d [3] and dimethyl *N*-alkoxy-*N*-(*N'*-alkylcarbamoyl)phosphoramidates 4a-c, R=Pr, R'=H (a); R=Et, R'=1-$C_{10}H_8$ (b); R=Et, R'=Ph (c) [4]

N-Alkoxy-*N*-chloro-*N'*-(4-nitrophenyl)ureas **5a-f** are relatively stable compounds [6; 7]. They react with trialkyl phosphites in ether at room temperature to form dialkyl *N*-alkoxy-*N*-(*N'*-4-nitrophenylcarbamoyl)phosphoramidates **6–13** as the major products [4; 5](Scheme 2).



Scheme 2. The synthesis of dialkyl *N*-alkoxy-*N*-(*N'*-4-nitrophenylcarbamoyl)phosphoramidates 6–13 (R=R'=Me (6), R=Me, R'=Et (7); R=Et, R'=Me (8), R=Bn, R'=Me (9), R=Bn, R'=Et (10), R=CH_2CH_2Ph (11), R=i-Pr, R'=Me (12), R=n-C_8H_{17}, R'=Me (13)[4]

As known, *N*-alkoxy-*N*-chloro-*N'*-phenylureas cannot exist at room temperature [5]. Clorination of *N*-methoxy-*N'*-phenylurea **14** has been reported to give unstable *N*-methoxy-*N*-chloro-*N'*-phenylurea **15**. Compound **15** isomerizes to *N*-methoxy-*N'*-(4-chlorophenyl)urea **16** by intramolecular chlorination at room temperature and lower temperatures [5] (Scheme 3).



14 **15** **16**

Scheme 3. *N*-Methoxy-*N*-chloro-*N'*-phenylurea 14 isomerization into *N*-methoxy-*N'*-(4-chlorophenyl)urea 15 at room temperature [5]

As demonstrated by Glover's research, in *N*-alkoxy-*N*-chloroamides the N–Cl bond is

lengthened and weakened as a result of the action of the $n_{O(Alk)} \rightarrow \sigma^*_{N\text{-}Cl}$ anomeric effect [8–18]. This bond weakening facilitates the substitution of the chlorine atom by various types of nucleophiles [8–18].

However, the interaction of unstable *N*-alkoxy-*N*-chloro-*N*'-4-bromophenylureas and *N*-alkoxy-*N*-chloro-*N*'-phenyllureas with trialkyl phosphites has not been studied. Therefore, the aim of our work was to investigate this interaction and characterize the structure of the resulting products.

Experimental part

^{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). $CDCl_3$ and $(CD_3)_2SO$ were used as the solvent. ^{1}H NMR chemical shifts relative to the residual solvent protons as an internal standard [$(CD_3)_2SO$: 2.500 ppm, $CDCl_3$: 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 ona 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. The solvents were purified and dried according to standard procedures.

*N-Benzyloxy-N'-4-bromophenylurea (**17**).* The solution of benzyloxyamine (0.641 g, 5.205 mmol) in benzene (4 mL) was added to the solution of 4-bromophenylisocyanate (0.859g, 4.337 mmol) in benzene (9 mL), the reaction mixture was maintained at 20 °C during 35 h, then it was boiled during 0.25 h, cooled, the obtained precipitate was filtered off, washed by benzene (4 mL), dried under vacuum (5 mmHg), giving 1.100 g (79 %) of *N*-benzyloxy-*N*'-4-bromophenylurea **17**, colorless crystals, mp 142–143 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.821 (2H, s,$NOCH_2$); 7.298–7.483 (7H, m, C(2)H, C(6)H C_6H_4Br, Ph); 7.533 (2H, d, *J* = 8.7 Hz, C(3)H, C(5)H C_6H_4Br); 8.915 (1H, s NH); 9.587 (1H, s, NHO). Mass spectrum (FAB), *m/z* (I_{rel}, %): 323 $[M+H]^+$ (11); 321 $[M+H]^+$ (11); 91 Bn^+ (100). Found, %: C 52.03; H 4.24; N 8.65. $C_{14}H_{13}BrN_2O_2$. Calculated, %: C 52.36; H 4.08; N 8.72.

*N-Propyloxy-N'-4-bromophenylurea (**18**)* The solution of *n*-propyloxyamine (0.696 g, 9.266 mmol) in benzene (3 mL) was added to the solution of 4-bromophenylisocyanate (1.332 g, 6.726 mmol) in benzene (12 mL), the reaction mixture was maintained at 20 °C during 12 h, then it was boiled during 0.5 h, cooled, the obtained precipitate was filtered off, washed by benzene (4 mL), dried under vacuum (5 mmHg), giving 1.290 g (70%) of *N*-propyloxy-*N'*-4-bromophenylurea **18**, colorless crystals, mp 114–116 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.897 (3H, t, *J* = 7.2 Hz, $NO(CH_2)_2Me$); 1.628 (2H, sex, *J* = 7.2 Hz, $NOCH_2\underline{CH_2}Me$); 3.716 (2H, t, *J* = 7.2 Hz, $NOCH_2$); 7.431 (2H, d, *J* = 8.8 Hz, C(2)H, C(6)H C_6H_4Br); 7.569 (2H, d, *J* = 8.8 Hz, C(3)H, C(5)H C_6H_4Br);8.858 (1H, s NH); 9.548 (1H, s, NHO). Mass spectrum (FAB), *m/z*(I_{rel},%): 275 $[M+H]^+$ (100); 273 $[M+H]^+$ (97); 195(36). Found, %: C 43.94; H 4.92; N 10.06. $C_{10}H_{13}BrN_2O_2$. Calculated, %: C 43.98; H 4.80; N 10.26.

*N-Ethoxy-N'-phenylurea (**19**).* The solution of phenylisocyanate (801 mg, 6.720 mmol) in dry benzene (5 mL) was added to the solution of ethoxyamine (588 mg, 9.636 mmol) in dry benzene (6 mL). The reaction mixture was maintained in closed flask at 20 °C during 17 h, the obtained precipitate was filtered off, washed out by benzene (3ml), dried under vacuum (2 mmHg) yielding 725 mg (60%) of *N*-ethoxy-*N*'-phenylurea **19**, colorless crystals, mp 101-104 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.213 (3H, t, *J* = 7.2 Hz, $NOCH_2\underline{Me}$); 3.823 (2H, q, *J* = 7.2 Hz, $NO\underline{CH_2}Me$); 6.985 (1H, t, *J* = 7.6 Hz, C(4)H Ph); 7.257 (2H, t, *J* = 7.6, Hz C(3)H, C(5)H Ph); 7.567 (2H, d, *J* = 7.6 Hz, C(2)H, C(6)H Ph); 8.702 (1H, s, NH); 9.410 (1H, s, NHO). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.337 (3H, t, *J* = 7.0 Hz, $NOCH_2\underline{Me}$); 3.988 (2H, q, *J* = 7.0 Hz, $NO\underline{CH_2}Me$); 7.101 (1H, t, *J* = 7.4 Hz, C(4)H Ph); 7.331 (2H, td, ^3J = 8.0 Hz, ^4J = 0.8 Hz, C(3)H, C(5)H Ph); 7.477 (2H, dd, ^3J = 8.6Hz, ^4J = 1.2 Hz,C(2)H, C(6)H Ph); 7.567 (1H, s, NH). Mass spectrum (FAB), *m/z*(I_{rel},%): 361 $[2M+H]^+$ (4); 181 $[M+H]^+$(100). Found, %: C 59.81; H 6.83; N 15.44. $C_9H_{12}N_2O_2$. Calculated, %: C 59.99; H 6.71; N 15.55.

*N-n-Butyloxy-N'-phenylurea (**20**).* The solution of phenylisocyanate (1.240g, 10.413 mmol) in benzene (5 mL) was added to the solution of n-butyloxyamine (0.975 g, 10.933 mmol) in benzene (8 mL), the reaction mixture was kept at 60 °C during 30 min, then the solvent was evaporated under vacuum (20 mmHg), hexane (8 mL) was added. After keeping at -5 °C during 20 h the obtained precipitate was filtered off, washed by cold (-5 °C) hexane, dried under vacuum (5 mmHg), giving 1.843 g (85 %) of *N*-*n*-butyloxy-*N*'-phenylurea **20**, colorless crystals, mp. 77–79 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.900 (3H, t,

^{3}J = 7.5 Hz, NO(CH$_2$)$_3$Me); 1.356 (2H, sex, ^{3}J = 7.5 Hz, NOCH$_2$CH$_2$CH$_2$Me); 1.608 (2H, quint, ^{3}J = 7.2 Hz, NOCH$_2$CH$_2$CH$_2$Me); 3.765 (2H, t, ^{3}J = 7.2 Hz, NOCH$_2$); 6.983 (1H, t, ^{3}J = 7.8 Hz, C(4)H Ph); 7.257 (2H, t, ^{3}J = 7.8 Hz, C(3)H, C(5)H Ph); 7.551 (2H, t, ^{3}J = 7.8 Hz, C(2)H, C(6)H Ph); 8.665 (1H, s, NH); 9.431 (1H, s, NHO). Mass spectrum (FAB), *m/z*(*I*$_{rel}$,%): 209 [M+H]$^+$ (100). Found, %: C 63.31; H 7.56; N 7.15. $C_{11}H_{16}N_2O_2$. Calculated, %: C 63.44; H 7.74; N 13.45.

D*imethyl N-benzyloxy-N-(N'-4-bromophenyl-carbamoyl)phosphoramidate (**22**).* The solution of *t*-BuOCl (89 mg, 0.820 mmol) in CH_2Cl_2 (3 mL) was added to the mixture of *N*-benzyloxy-*N'*-4-bromophenylurea **17** (88 mg, 0.274 mmol) and CH_2Cl_2 (2 mL) at 15 °C. The reaction mixture was maintained at 15 °C for 1 h, then it was evaporated under vacuum, the residue was dried under vacuum (2 mmHg) for 10 min. The obtained *N*-chloro-*N*-benzyloxy-*N*'-(4-brmophenyl)urea **21** (as white solid) was immediately disssolved in Et_2O (5mL), and the solution of trimethyl phosphite (93 mg, 0.750 mmol) in Et_2O (5mL) was added. The reaction mixture was maintained at 15 °C for 47 h, at 28 °C for 23 h, then reaction solution was evaporated under vacuum, the residue was dried at 80–85 °C under vacuum (2 mmHg) for 15 min. The obtained residue was extracted by hexane (5 mL) at 20 °C for 23 h, the formed precipitate was filtered off, dried under vacuum (2 mmHg), giving 82 mg (69.7%) of dimethyl *N*-benzyloxy-*N*-(*N*'-4-bromophenylcarbamoyl)phosphoramidate **22**, colorless crystals, m.p. 89–92 °C (Et_2O–hexane).^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 3.916 (6H, d, ^{HP}J= 12.0 Hz, P(O)(OMe)$_2$); 5.058 (2H, s, NOCH$_2$); 7.350 (2H, d, ^3J= 8.8 Hz, C(2)H, C(6)H C_6H_4Br); 7.382–7.436 (5H, m, C(3,4,5)H Ph and C(3,5)H C_6H_4Br); 7.479–7.521 (2H, m, C(2)H, C(6)H Ph); 8.990 (1H, br. s, NH). ^{13}C NMR (100.6093MHz, $CDCl_3$, ppm): δ=55.35 d, ^{CP}J= 6.04Hz, P(O)(OMe)$_2$;79.67 s, NOCH$_2$; 116.59 s, C(4)$_q$–Br, C_6H_4Br; 121.30 s C(2)H, C(6)H C_6H_4Br; 128.87 s, 2C$_{Ph}$(H) Ph; 129.36 s, C(4)H Ph; 129.86 s, 2 C$_{Ph}$(H) Ph; 132.09 s C(3)H, C(5)H C_6H_4Br; 134.34 C(1)$_q$ Ph; 136.78 C(1)$_q$ C_6H_4Br; 151.85 d, ^{CP}J= 16.10 Hz, C=O. ^{31}P NMR(161.9439 MHz, $CDCl_3$, ppm): 0.846. Mass spectrum (FAB), *m/z* (*I*$_{rel}$, %): 431 [M+H]$^+$ (32); 429 [M+H]$^+$ (27); 351 (12); 127 (64); 91 Bn$^+$ (100). Found, %: C 44.58; H 4.61; N 6.37. $C_{16}H_{18}BrN_2O_5P$. Calculated, %: C 44.77; H 4.23; N 6.53.

The hexane extract was evaporated under vacuum, the residue was dried at 80–85 °C under vacuum (2 mmHg) and crystallized from cold hexane, additionally yielding 19 mg (16.1 %) of compound **22**.

*Dimethyl N-(N'-4-bromophenylcarbamoyl)-N-propyloxyphosphoramidate (**24**).* The solution of *t*-BuOCl (120 mg, 1.109 mmol) in CH_2Cl_2 (3 mL) was added to the solution of *N*-propyloxy-*N'*-(4-bromophenyl)urea **18** (101 mg, 0.370 mmol) in CH_2Cl_2 (4 mL) at 20 °C. The reaction mixture was maintained at 20 °C for 1 h, then it was evaporated under vacuum, the residue was dried under vacuum (2 mmHg) for 10 min. The obtained *N*-chloro-*N*-propyloxy-*N*'-(4-brmophenyl)urea **23** (as colorless oil) was immediately disssolved in Et_2O (5mL), and the solution of trimethyl phosphite (92 mg, 0.740 mmol) in Et_2O (5mL) was added. The reaction mixture was maintained at 20 °C for 22 h, then reaction solution was evaporated under vacuum, the residue was dried at 90–95 °C under vacuum (2 mmHg) for 10 min. The obtained residue was stirred with hexane (5 mL) at 20 °C for 1 h, the hexane extract **A** was separated off, the remaining oil was dried under vacuum (2 mmHg), giving 34 mg (24.1 %) of dimethyl *N*-(*N*'-4-bromophenylcarbamoyl)-*N*-propyloxyphosphoramidate **24**, colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ =1.015 (3H, t, ^3J= 7.6Hz, NOCH$_2$CH$_2$Me); 1.729 (2H, sex, ^3J= 7.12Hz, NOCH$_2$CH$_2$Me); 3.912 (6H, d, ^{HP}J= 11.6Hz, P(O)(OMe)$_2$); 4.095 (2H, t, ^3J= 6.6Hz,NOCH$_2$); 7.377 (2H, d, ^3J= 9.6Hz, C(2)H, C(6)HC_6H_4Br); 7.412 (2H, d, ^3J= 9.6Hz, C(3)H, C(5)HC_6H_4Br); 9.068 (1H, br. s, NH). ^{1}H NMR (400 MHz, $(CD_3)_2SO$, ppm): δ =0.933 (3H, t, ^3J= 7.6 Hz, NOCH$_2$CH$_2$Me); 1.688 (2H, sex, ^3J= 7.12 Hz, NOCH$_2$CH$_2$Me); 3.803 (6H, d, ^{HP}J= 12.0Hz, P(O)(OMe)$_2$); 3.942 (2H, t, ^3J= 6.8Hz, NOCH$_2$); 7.497 (2H, d, ^3J= 9.2Hz, C(2)H, C(6)HC_6H_4Br); 7.5302 (2H, d, ^3J= 9.2Hz, C(3)H, C(5)HC_6H_4Br); 9.369 (1H, br. s, NH). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=10.53, s, Me; 21.64 s, NOCH$_2$CH$_2$Me; 55.29 d, ^{CP}J= 6.04Hz, P(O)(OMe)$_2$; 79.09 s, NOCH$_2$; 116.48 s, C(4)$_q$–Br, C_6H_4Br; 121.23 s C(2)H, C(6)H C_6H_4Br; 132.08 s C(3)H, C(5)H C_6H_4Br; 136.85 s C(1)$_q$ C_6H_4Br; 151.83 d, ^{CP}J= 17.10 Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 0.809. Mass spectrum (FAB), *m/z*(*I*$_{rel}$,%): 383 [M+H]$^+$ (87); 381 [M+H]$^+$ (100); 183 (83); 126 (99). Found, %: C 37.73; H 4.82; N 7.26. $C_{12}H_{18}BrN_2O_5P$. Calculated, %: C 37.81; H 4.76; N 7.35.

The hexane extract **A** was evaporated under vacuum, the residue was dried at 85–90 °C under vacuum (2 mmHg) for 15 min, additionally giving 88 mg (62.4 %) of compound **24**.

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*Dimethyl N-ethoxy-N-(N'-phenylcarbamoyl)-phosphoramidate (**25**).* The solution of *t*-BuOCl (57 mg, 0.5216 mmol) in Et_2O (6 mL) was added to the mixture of *N*-ethoxy-*N'*-phenylurea **19** (94 mg, 0.5216 mmol) and Et_2O (4 mL) at –32 °C at stirring. The reaction mixture was maintained at –32– –25 °C for 1 h 20 min, then the solution of trimethyl phosphite (140 mg, 1.128 mmol) in Et_2O (5 mL) was slowly added. The reaction mixture was maintained at –25 °C for 24 h, then solid phase was filtered off, the Et_2O-filtrate was evaporated under vacuum, the residue was dried at 90–95 °C under vacuum (2 mmHg) for 10 min. The obtained residue was extracted by hexane (7 mL) at 20 °C for 22 h, the hexane extract was separated from residue **A**, evaporated under vacuum, the obtained residue was dried at 90 °C under vacuum (2 mmHg) for 10 min, giving 46 mg (30.6%) of dimethyl *N*-ethoxy-*N-(N'*-phenylcarbamoyl)phosphoramidate **25**, colorless oil that solidifies over time in the cold into colorless amorphous substance. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ=1.339 (3H, t, ^3J=7.2 Hz, $NOCH_2\underline{Me}$) ; 3.920 (6H, d, ^{HP}J= 11.6 Hz, $P(O)(OMe)_2$); 4.140 (2H, q, ^3J= 7.2 Hz, $NOCH_2$); 7.086 (1H, t, ^3J= 7.2 Hz, C(4)H Ph); 7.137 (2H, t, ^3J= 8.0 Hz, C(3)H, C(5)H Ph); 7.488 (2H, dd, ^3J= 8.4Hz, ^4J= 1.2Hz, C(2)H, C(6)H Ph); 8.968 (1H, br. s, NH).^{13}C NMR (100. 6093 MHz, $CDCl_3$, ppm): δ=13.64 s, $NOCH_2\underline{Me}$; 55. 20 d, ^{CP}J= 6.04 Hz, $P(O)(OMe)_2$; 73.19 s, $NOCH_2$; 119.72 s, C(2)H, C(6)H Ph; 123.99 s, C(4)H Ph; 129.12 s, C(3)H, C(5)H Ph; 137.62C$(1)_q$ Ph; 151. 93 d, ^{CP}J= 16.10 Hz, C=O. ^{31}P NMR (161.9439 MHz , $CDCl_3$, ppm): 0.927. Mass spectrum (FAB), *m/z*(I_{rel},%): 289 $[M+H]^+$ (100); 169 (67); 163 (39); 126 (95). Found, %: C 45.69; H 6.05; N 9.63. $C_{11}H_{17}N_2O_5P$. Calculated, %: C 45.84; H 5.94; N 9.72.

The residue **A** was dissolved in boiling hexane, the solution was maintained at –32 °C for 48 h, the formed precipitate was filtered off. The hexane filtrate was evaporated under vacuum, the obtained residue was dried under vacuum (2 mmHg), additionally yielding 37 mg (24.6 %) of compound **25**.

*Dimethyl N-n-butyloxy-N-(N'-phenylcarbamoyl)phosphoramidate (**26**).* The solution of *t*-BuOCl (55 mg, 0.50417 mmol) in Et_2O (4 mL) was added to the solution of *N-n*-butyloxy-*N'*-phenylurea **20** (105 mg, 0.505417 mmol) in Et_2O (7 mL) at –34 °C at stirring. The reaction mixture was maintained at –34– –30 °C for 1 h, then the solution of trimethyl phosphite (125 mg, 1.008 mmol) in Et_2O (5 mL) was slowly added. The reaction mixture was maintained at –25 °C for 24 h, then it was evaporated under vacuum, the residue was dried at 90–95 °C under vacuum (2 mmHg) for 10 min. The obtained residue was extracted by hexane (8 mL) at 14 °C for 18 h, the hexane extract was separated off, evaporated under vacuum, the residue was dried under vacuum (2 mmHg), yielding 126 mg (79.0 %) of dimethyl *N-n*-butyloxy-*N-(N'*-phenylcarbamoyl)-phosphoramidate **26**, colorless oil.^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ =0.966 (3H, t, ^3J= 7.2 Hz, $NO(CH_2)_3\underline{Me}$); 1.471 (2H, sex, ^3J= 7.2 Hz, $NOCH_2CH_2\underline{CH_2}Me$); 1.698 (2H, quint, ^3J= 7.2 Hz, $NOCH_2\underline{CH_2}CH_2Me$); 3.915 (6H, d, ^{HP}J= 12.0Hz, $P(O)(OMe)_2$); 4.081 (2H, t, ^3J= 6.8Hz, $NOCH_2$); 7.084 (1H, td, ^3J= 7.4 Hz, ^4J= 1.2 Hz, C(4)H Ph); 7.313 (2H, t, ^3J= 8.0 Hz, C(3)H, C(5)H Ph); 7.485 (2H, dd, ^3J= 7.6 Hz, ^4J= 0.8 Hz, C(2)H, C(6)H Ph); 8.939 (1H, br. s, NH).^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=13.98 s, $NO(CH_2)_3\underline{Me}$; 19.34 s, CH_2; 30.34 s, CH_2; 55.17 d, ^{CP}J= 6.04 Hz, $P(O)(OMe)_2$; 77.38 s, $NOCH_2$; 119.71s, C(2)H, C(6)HPh; 123.99 s, C(4)H Ph; 129.15 s, C(3)H, C(5)HPh; 137.67 s C$(1)_q$Ph; 151.93 d, ^{CP}J= 17.10 Hz, C=O.^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 1.010. Mass spectrum (FAB), *m/z*(I_{rel},%): 317 $[M+H]^+$ (100). Found, %: C 49.25; H 6.85; N 8.71. $C_{13}H_{21}N_2O_5P$. Calculated, %: C 49.37; H 6.69; N 8.86.

*Dimethyl N-ethoxy-N-(N'-4-chlorophenylcarbamoyl)phosphoramidate (**28**).* The solution of *t*-BuOCl (146 mg, 1.348 mmol) in CH_2Cl_2 (2 mL) was added to the mixture of *N*-ethoxy-*N'*-phenylurea **19** (81 mg, 0.449 mmol) and CH_2Cl_2 (1 mL) at 10 °C at stirring. The reaction mixture was maintained at 10 °C for 23 h, then the solution of *t*-BuOCl (90mg, 0.829 mmol) in CH_2Cl_2 (1 mL) was added, the reaction mixture was maintained at 9 °C for 1 h. Then the reaction mixture was evaporated under vacuum, the residue was dissolved in in Et_2O (3 mL) and trimethyl phosphite (101 mg, 0.814 mmol) in Et_2O (3 mL) was added. The reaction mixture was maintained at 10 °C for 48 h, then it was evaporated under vacuum, the residue was dried at 85 °C under vacuum (2 mmHg) for 10 min. The obtained residue was extracted by boiling hexane (10 mL), the hexane extract cooled to 0 °C. The obtained precipitated was filtered off, dried under vacuum, yielding 29 mg (19.9 %) of dimethyl *N*-ethoxy-*N-(N'*-4-chlorophenylcarbamoyl)phosphoramidate **28**, colorless oil. H NMR (400 MHz, $CDCl_3$, ppm): δ =1.327 (3H, t, ^3J= 7.2Hz, $NOCH_2\underline{\mathbf{Me}}$); 3.916 (6H, d, ^{HP}J= 11.6 Hz, $P(O)(OMe)_2$); 4.123 (2H, q, ^3J= 7.2Hz, $NOCH_2$); 7.265 (2H, d, ^3J= 8.8Hz, C(2)H, C(6)H $C_6H_4NO_2$);

7.433 (2H, d, ^3J= 8.8Hz, C(3)H, C(5)H $C_6H_4NO_2$); 9.077 (1H, br. s, NH). ^{13}C NMR (100.6093 MHz, $CDCl_3$, ppm): δ=13.65 s, $NOCH_2\underline{Me}$; 55.31 d, ^{CP}J= 5.03 Hz,$P(O)(OMe)_2$; 73.21 s, $NOCH_2$; 120.94 s, C(2)H, C(6)HPh; 123.99 s, 128.96s C(4)–Cl C_6H_4Cl; 129.13 s C(3)H, C(5)H C_6H_4Cl; 136.32s $C(1)_q$ C_6H_4Cl; 151.89 d, ^{CP}J= 16.10Hz, C=O. ^{31}P NMR (161.9439 MHz, $CDCl_3$, ppm): 0.730. Found, %: C 40.72; H 5.13; N 8.39. $C_{11}H_{16}ClN_2O_5P$. Calculated, %: C 40.94; H 5.00; N 8.68.

The hexane filtrate was evaporated under vacuum, the residue was dried under vaccum (2 mmHg), additionally yielding 45 mg (44.8 %) of dimethyl *N*-ethoxy-*N-(N'*-4-chlorophenyl-carbamoyl)phosphoramidate **28**.

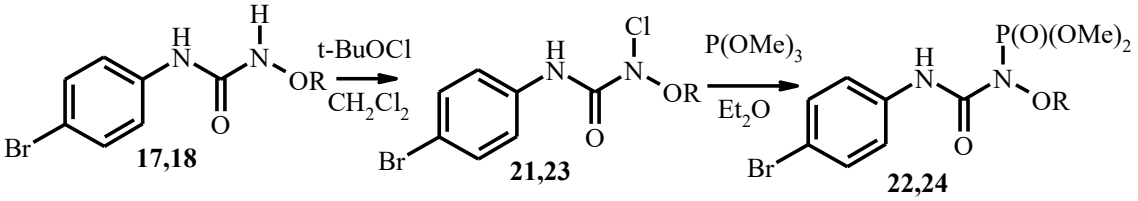
*N-Acetoxy-N-n-butyloxyurea (**29a**) interaction with trimethyl phosphite.* The solution of trimethylphosphite (146 mg, 1.176 mmol) in Et_2O (3 mL) was added to the solution of *N*-acetoxy-*N-n*-butyloxyurea **29a** (66 mg, 0.347 mmol) [19] in Et_2O (5 mL). The reaction mixture was maintained at 20 °C for 115 h, then it was evaporated under vacuum, the residue was maintained at 25 °C at stirring under vacuum (2 mmHg) for 2h, yielding 65 mg (98.5%) of unreacted starting *N*-acetoxy-*N-n*-butyloxyurea **29a**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.940 (3H, t, ^3J= 7.6Hz, $NO(CH_2)_3\underline{CH_3}$); 1.386 (2H, sex, ^3J= 7.6 Hz, $NO(CH_2)_2\underline{CH_2}Me$); 1.670 (2H, quint, ^3J= 7.2 Hz, $NOCH_2\underline{CH_2}CH_2Me$); 2.181 (3H, s, NOC(O)Me); 4.087 (2H, t, ^3J= 6.8 Hz, $NOCH_2$); 5.579 (1H, br. s, NH); 5.963 (1H, br. s, NH).

*N-Acetoxy-N-n-octyloxyurea (**29b**) interaction with trimethyl phosphite.* The solution of trimethylphosphite (34 mg, 0.274 mmol) in Et_2O (3 mL) was added to the solution of *N*-acetoxy-*N-n*-octyloxyurea **29b** (17 mg, 0.0690 mmol) in Et_2O (3 mL). The reaction mixture was maintained at 18 °C for 73 h, then it was evaporated under vacuum, the residue was maintained at 25–30 °C at stirring under vacuum (2 mmHg) for 2h, yielding 17 mg (100 %) of unreacted *N*-acetoxy-*N-n*-octyloxyurea **29b**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.875 (3H, t, ^3J= 6.8Hz, $NO(CH_2)_7\underline{CH_3}$); 0.858–0.892 (10H, m, $NO(CH_2)_2(\underline{CH_2})_5Me$); 1.677 (2H, quint, ^3J= 7.2Hz, $NOCH_2\underline{CH_2}(CH_2)_5Me$); 2.180 (3H, s, NOC(O)Me); 4.076 (2H, t, ^3J= 7.2Hz, $NOCH_2$); 5.533 (1H, br. s, NH); 5.988 (1H, br. s, NH).

*N-Acetoxy-N-ethoxy-N'-benzylurea (**29c**) interaction with trimethyl phosphite.* The solution of trimethylphosphite (64 mg, 0.516 mmol) in Et_2O (3 mL) was added to the solution of *N*-acetoxy-*N*-ethoxy-*N'*-benzylurea **29c** (48 mg, 0.190 mmol) [20] in Et_2O (5 mL). The reaction mixture was maintained at 18 °C for 68 h, then it was evaporated under vacuum, the residue was maintained at 25 °C at stirring under vacuum (2 mmHg) for 2h, yielding 47.5 mg (99 %) of unreacted *N*-acetoxy-*N*-ethoxy-*N'*-benzylurea **29c**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ =1.285 (3H, t, ^3J= 7.2Hz, $NOCH_2\underline{CH_3}$); 2.182 (3H, s, NOC(O)Me); 4.125 (2H, q, ^3J= 7.2Hz, $NOCH_2$); 4.468 (2H, d, ^3J= 6.4Hz, $Ph\underline{CH_2}NH$); 6.417(1H, br. s, NH); 7.280–7.378 (5H, m, Ph).

Results and discussion

N-Alkoxy-*N*-chloro-*N'*-(4-bromophenyl)ureas **17, 18** are stable only for a short time at room temperature [7]. To prevent the decomposition, these compounds were immediately treated with trimethyl phosphite in ether solution after isolation at room temperature. Thus, dimethyl *N*-alkoxy-*N*-(*N'*-4-bromophenylcarbamoyl)phos-phoramidates **22, 24** were obtained in high yields (Scheme 4).



Scheme 4. The synthesis of dimethyl *N*-alkoxy-*N*-(*N'*-4-bromophenylcarbamoyl)phosphoramidates R=Bn (22, 86 %), R=Pr (24, 86 %)

Chlorination of *N*-alkoxy-*N'*-phenylureas **19,20** by *tert*-butyl hypochlorite gives unstable *N*-alkoxy-*N*-chloro-*N'*-phenylureas **27a,b** (Scheme 5). But we had obtained *N*-alkoxy-*N*-chloro-*N'*-phenylureas **27a,b** at – 30 °C in ether followed by treatment with trimethyl phosphite in these conditions. As a result of this procedure, dimethyl *N*-alkoxy-*N*-(*N'*-phenylcarba-moyl)phosphoramidates **25**, **26** were obtained by a one-pot synthesis. This reaction represents the first example of the nucleofilic substitution at the nitrogen atom in the highly unstable *N*-alkoxy-*N*-chloro-*N'*-phenylureas.

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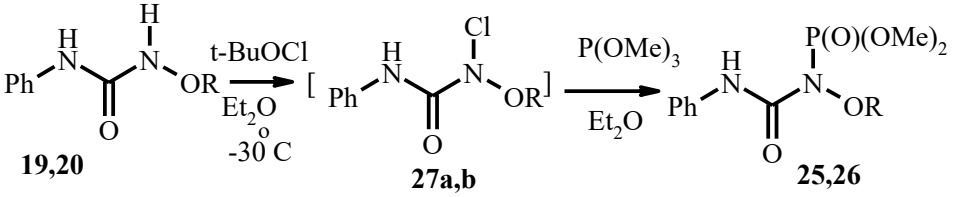
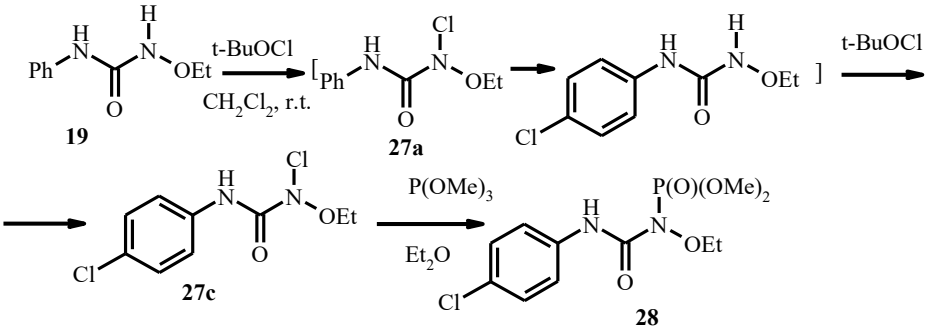


Scheme 5. One-pot synthesis of dimethyl *N*-alkoxy-*N*-(*N*'-phenylcarbamoyl)phosphoramidates 25,26, R=Et (27a, 25, 55 %); n-Bu (27b, 26, 79 %)

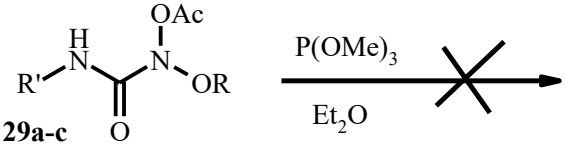
Careful optimization of reaction conditions allowed us to prevent the premature decomposition of the initial *N*-alkoxy-*N*-chloro-*N*'-4-bromophenylureas **21**, **23** and *N*-alkoxy-*N*-chloro-*N*'-phenylureas **27a,b**.

Heating of *N*-ethoxy-*N*-chloro-*N*'-phenylurea **27a** to room temperature followed by repeated *N*-chlorination and subsequent treatment with trimethyl phosphite allows the synthesis dimethyl *N*-ethoxy-*N-(N'*-4-chlorophenylcarbamoyl)phosphoramidate **28** from *N*-ethoxy-*N*'-phenylurea **19** in a one-step synthesis (Scheme 6):



Scheme 6. The one-step synthesis of dimethyl *N*-ethoxy-*N-(N'*-4-chlorophenylcarbamoyl)phosphoramidate 28 from of *N*-ethoxy-*N*'-phenylurea 19

Unlike *N*-alkoxy-*N*-chloroureas, *N*-acetoxy-*N*-alkoxyureas **29a-c** do not react with trimethylphosphite under the same conditions (Scheme 7).



R'=H, R=n-C_4H_9(a), n-C_8H_{17}(b), R'=Bn, R=Et(c)

Scheme 7. *N*-Acetoxy-*N*-alkoxyureas 29a-c interaction with trimethyl phosphite

The structure of dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **22, 24, 25, 26, 28** was proven by the ^{1}H, ^{13}C, ^{13}P NMR spectra and mass spectra.

The ^{1}H NMR spectra of compounds **22, 24, 25, 26, 28** demonsrate the following general characteristics: 1) a doublet of $(MeO)_2(O)P$-moiety, 2) a triplet of $NOCH_2$ group; 3) a broad singlet of NH moiety (Table 1).

Table 1

The typical ^{1}H NMR and ^{31}P NMR chemical shifts of dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates 6, 8, 9, 11–13 [4] and 22, 24–26, 28 (ppm, in $CDCl_3$)

Compound	$P(O)(OMe)_2$(^{HP}J,Hz),d	$NOCH_2$, NOMe s*, $O\underline{CH_2}Ph$**	NH	^{31}P NMR ppm
6 [4]	3.945(11.6)	3.920s*	9.719	0.24
8 [4]	3.941(11.6)	4.135t	9.714	0.38
9[4]	3.935(12.0)	5.067s**	9.590	0.47
11 [4]	3.853(11.2)	4.344t	8.830	-0.02
12 [4]	3.932(12.0)	4.404 sept	9.315	1.30
13 [4]	3.936(12.0)	4.064t	9.694	0.45
22	3.916(12.0)	5.058 s**	8.990	0.85
24	3.912(11.6)	4.095 t	9.068	0.81
25	3.918(11.6)	4.138t	8.961	0.93
26	3.915(12.0)	4.081t	8.939	1.01
28	3.916(11.6)	4.123q	9.077	0.73

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Dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)-phosphoramidates **6, 8, 9, 11–13** [4,5], **22, 24–26, 28** are characterized by a singlet of NH hydrogen atom in the region of 8.961–9.869 ppm.

In the ^{31}P NMR spectra of dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **6, 8, 9, 11–13, 22, 24–26, 28**, the chemical shifts of the phosphorus atom lie in the range of –0.02–1.30 ppm.

The ^{13}C NMR spectra of compounds **6–13** and **22, 24–26, 28** exhibit numerous common features and characteristics. They include the chemical shifts of the carbon atoms of NOMe or $NOCH_2$ groups, the carbon atoms of dialkoxyphosphoryl group (a doublet of the $P(O)(OMe)_2$ fragment or two doublets of the $P(O)(OCH_2Me)_2$ fragment), and the doublet of the carbon atom of the C=O bond (Table 2).

Table 2

The typical ^{13}C NMR chemical shifts of carbon atoms of dialkyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates 6–13 [4,5] and 22, 24–26, 28 (ppm, in $CDCl_3$)

Comp.	^{13}C NMR, ppm			
	$P(O)(OMe)_2$, d	$P(O)(OEt)_2$, d, d	$NOCH_2$Alk, NOMe*, $NOCH_2$Ph** s	C=O, d
6 [4]	55.50	-	64.80*	151.25
7 [4]	-	16.19, 65.68	64.69*	151.36
8 [4]	55.51	-	73.22	151.56
9[4]	55.04	-	79.05**	152.28
10[4]	-	16.25, 65.68	79.41**	151.64
11[4]	55.46	-	78.13	151.64
12[4]	55.49	-	80.20 (OCH)	152.72
13[4]	54.45	-	77.16	151.54
22	55.35	-	79.67**	151.85
24	55.29	-	79.09	151.83
25	55.20	-	73.19	151.93
26	55.17	-	77.38	151.93
28	55.31		73.21	151.89

Dialkyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **6–13** [4,5] and **22, 24–26, 28** are characterized by a doublet of the carbon atom of the C=O group in the region of 151.25–152.72 ppm.

For dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **6, 8, 9, 11–13** [4] and **22, 24–26, 28**, the doublet of $(MeO)_2(O)P$ fragment is located in the range of 54.45–55.51 ppm. For diethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **7, 10**, two doublet of $(EtO)_2(O)P$ group are located at 16.19–16.25 pppm and 65.35–65.68 ppm, respectively.

The mass spectra of compounds **22, 24–26** show peaks of protonated molecular ion $[M+H]^+$ at the corresponding *m/z* values with high intensity.

Conclusions

For the first time, we have found that the interaction of unstable *N*-alkoxy-*N*-chloro-*N*'-arylureas **21, 23, 27, 28** with trimetyl phosphite under mild conditions allows to synthesize of previously inaccessible dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **22, 24, 25, 26, 28**. Remarkably, *N*-acetoxy-*N*-alkoxyureas **29a-c** do not react with trimethylphosphite under the same conditions. The structure of the synthesized dimethyl *N*-alkoxy-*N*-(*N*'-arylcarbamoyl)phosphoramidates **22, 24–26, 28** was confirmed by ^{1}H, ^{13}C, ^{31}P NMR spectra, as well as by mass spectra.

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