Chem. Chem. Technol., 2019,
Vol. 13, No. 2, pp. 145–149

Chemistry

SYNTHESIS OF ANNELATED P- AND N-CONTAINING HETEROCYCLES BASED ON METHYL 5-AMINOTHIOPHENE-2-CARBOXYLATE DERIVATIVES

Svitlana Kovaleva[1, *], Olena Mayboroda[1], Natalia Simurova[1], Larysa Mazur[1]

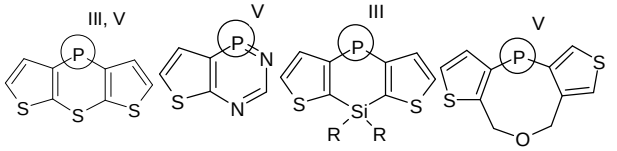
https://doi.org/10.23939/chcht13.02.145

Abstract. Derivatives of new bicyclic systems – 1*H*-thieno[3,2-*c*][1,5,2]oxazaphosphinine and 1,2-dihydrothieno[2,3-*b*][1,4]azaphosphinine have been obtained by phosphorylation of *N*-substituted derivatives of 5-amino-2-methoxycarbonylthiophene with phosphorus (III) tribromide. These heterocyclizations can be carried out in the basic medium and under mild conditions. The end reaction products were studied by means of chemical analysis, ^{1}H and ^{31}P NMR spectroscopy.

Keywords: thiophene, azaphosphinine, oxazaphosphinine, fused rings, heterocycle, phosphorylation.

1. Introduction

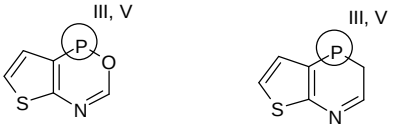
Annelated phosphorus-containing heterocycles are widely studied as promising compounds for creating of new types of ligands for a metal-complex catalyst and complexons on their basis [1]. Five-, six- and seven-membered P-containing heterocycles annelated with the thiophene nucleus were reported [2-9]. The main methods for their synthesis are based on interactions between lithium derivatives of thiophene and tri- or pentavalent phosphorus halides or esters [10-18]. Synthesis of complex systems with several endocyclic heteroatoms in the same ring seems to be interesting since such compounds are promising for creation of new biologically active substances on their basis. Only few types of heterocycles 1-4 fused with thiophene and containing, besides phosphorus atom, other endocyclic heteroatoms have been obtained and reported [11, 19-22].



1 2 3 4

To design such compounds, the choice of initial reactants is of great importance, since, on the one hand, they have to be synthetically accessible, and on the other hand, they have to have a high synthetic potential.

The aim of this work is synthesis of new annelated heterocyclic systems 5, 6 with endocyclic phosphorus, nitrogen and oxygen atoms based on *N*-substituted derivatives of 5-amino-2-methoxycarbonylthiophene containing exocyclic nucleophilic centres.



5 6

2. Experimental

2.1. Materials and Methods

The initial substance 5-amino-2-methoxycarbonylthiophene was synthesized by reducing 2-nitro-5-methoxycarbonylthiophene. *N*-substituted 2-aminothiophene derivatives **1.1** and **2.1** (see Schemes 1 and 2) used as starting reagents in heterocyclization reactions with phosphorus(III) halides were obtained by acylation with 4-chlorobenzoic acid chloride and condensation with 1,3,3-trimethyl-2-(formylmethylene)indoline (Fischer's aldehyde), respectively.

Organic solvents were purchased from Merck and Aldrich. All manipulations with moisture-sensitive compounds were performed under an inert atmosphere of dry argon, standard Shlenk's techniques being used. Solvents were purified and dewatered by conventional procedures. The ^{31}P and ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (121.4 and 300 MHz, respectively) for $CDCl_3$ and DMSO-d_6 solutions with tetramethylsilane. Chemical shifts were reported relative to internal tetramethylsilane (^{1}H) or to external 85% H_3PO_4 (^{31}P). Reactions accompanied by any changes on phosphorus atom were monitored by ^{31}P NMR spectroscopy.

[1] National University of Food Technologies
68, Volodymyrska St., 01601 Kyiv, Ukraine
[*] *sval_kov@ukr.net*

2.2.1. Synthesis of compound 1.3

A solution of compound **1.1** (0.01 mol) in pyridine (10 ml) was cooled to 283 K, and phosphorus tribromide (0.011 mol) was added dropwise. The reaction mixture was stirred at 293 K for 24 h and then evaporated to dryness in vacuo. The residue was dissolved in benzene (15 ml), followed by addition of triethylamine (0.02 mol), filtration of the mixture, and evaporation of the filtrate to dryness in vacuo. The compound **1.3** was used without further purification.

2.2.2. Synthesis of compound 1.4

Compound **1.3** (0.01 mol) was dissolved in benzene (15 ml), stirred and cooled to 283 K; then diethylamine (0.01 mol) and triethylamine (0.01 mol) were added dropwise. The mixture was stirred at 298 K for 2 h and then filtered. The filtrate was evaporated to dryness in vacuo. The compound **1.4** was used without further purification.

2.2.3. Synthesis of compound 1.5

To a solution of compound **1.4** (0.01 mol) in benzene (20 ml), sulfur (0.01 mol) was added. The mixture was stirred for 24 h. Then it was evaporated to dryness in vacuo. Solid residue obtained was washed with hexane. The product was purified by crystallization from an *iso*-propanol/hexane mixture.

2.2.4. Synthesis of compound 2.1

A mixture of 5-amino-2-methoxycarbonylthiophene (0.05 mol), Fischer's aldehyde (0.05 mol) and one drop of pyrolidine in *iso*-propanol (70 ml) was refluxed for 4 h. The reaction mixture was cooled to the room temperature. The precipitate formed was filtered and dried in vacuo.

2.2.5. Synthesis of compound 2.2

A solution of compound **2.1** (0.01 mol) in pyridine (10 mL) was cooled to 283 K, and phosphorus tribromide (0.01 mol) was added dropwise. The reaction mixture was stirred at 298 K for 24 h, then diluted with benzene (10 ml), followed by addition of triethylamine (0.02 mol), filtration of the mixture, and evaporation of the filtrate to dryness in vacuo. The product **2.2** was used without further purification.

2.2.6. Synthesis of compound 2.3

A solution of compound **2.2** (0.01 mol) in benzene (20 mL) was cooled to 283 K and stirred; then morpholine (0.01 mol) and triethylamine (0.01 mol) were added dropwise consistently. The mixture was stirred at 298 K for 2 h and then filtered. The filtrate was evaporated to dryness in vacuo. The compound **2.3** was used without further purification.

2.2.7. Synthesis of compound 2.4a

To a solution of compound **2.3** (0.01 mol) in pyridine (20 ml), pounded sulfur (0.01 mol) was added. The mixture was stirred for 24 h. Then it was evaporated to dryness in vacuo.

2.2.8. Synthesis of compound 2.4b

To a solution of compound **2.3** (0.01 mol) in pyridine (20 ml), a solution of 4-bromophenylazide (0.01 mol) in benzene (20 ml) was added. The mixture was stirred at 323 K for 1 h. Then, after cooling, the mixture was filtered. The precipitate was washed consistently with 2–3 ml of alcohol and 5 ml of water.

3. Results and Discussion

The *N*-substituted derivatives of 5-amino-2-methoxycarbonylthiophene **1.1** and **2.1** are phosphorylated easily at the endocyclic nucleophilic center and at position 4 of the thiophene ring when they react with phosphorus(III) halides in pyridine at room temperature to lead to formation of new fused heterocyclic compounds – 1*H*-thieno[3,2-*c*][1,5,2]oxazaphosphinine and 1,2-dihydrothieno[2,3-*b*][1,4]azaphosphinine. Despite the weak activating effect of the *N*-substituted amino group at position 5 on the reactivity of the position C-3 and the presence of the electron acceptor group at position 5 of the thiophene moiety, probably, phosphorilation under the mild conditions is promoted by the high nucleophilicity of the exocyclic O- and C-reactive centres of the initial compounds as well as the formation of energetically advantageous six-membered rings as a result of the reaction.

3.1. Synthesis of 1*H*-Thieno[3,2-*c*][1,5,2]oxazaphosphinine Derivatives

Due to the high activity of amide group in respect to phosphorus(III) halides, it is expected that the reaction between compound **1.1** and PBr_3 proceeds through the formation of intermediate **1.2**. Then as a result of intra molecular attack of PBr_2 group on the nucleophilic C-3-centre of thiophene ring, six-membered [1,5,2] oxazaphosphinine cycle is formed. One of the factors contributing to O-phosphorylation followed by attack on C3 position of thiophene can be considered, the participation of the imidate fragment in the cyclization process [23, 24]. The structure of methyl 1-bromo-3-(4-chlorophenyl)-1λ^3-1*H*-thieno [3,2-*c*] [1,5,2]oxazaphosphinine-6-carboxylate (**1.3**) was confirmed by NMR ^{31}P spectroscopy (Table 2) and its chemical transformations. The ^{31}P NMR spectrum of compound **1.3** is characterized by a signal at 130 ppm and the chemical shift determined is in according to the data for analogous pyrazole derivatives [25]. Three- and four-coordinated phosphorus derivatives (**1.4** and **1.5**, respectively) were synthesized on the basis of the bromide **1.3** (Scheme 1).

Table 1

NMR ^{1}H spectroscopy data for compounds 1.1–2.4

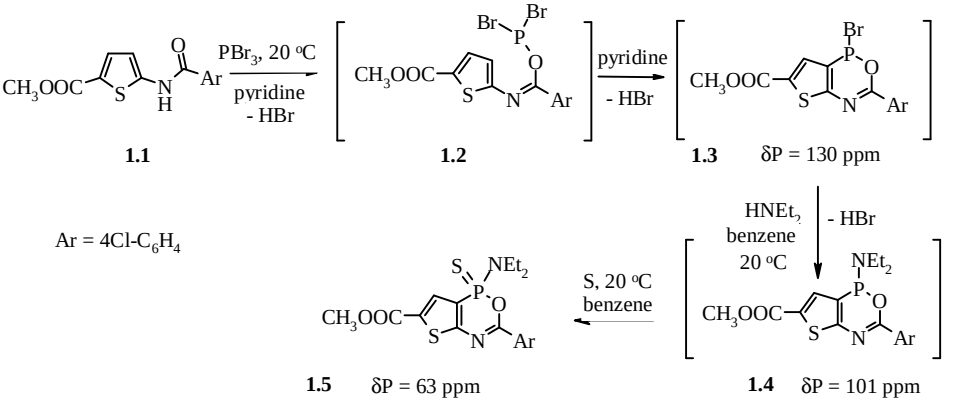
Compound	*d*P, ppm	*d*H, ppm
1.1[1]	-	3.81 (s, 3H, CH_3O), 6.99 (d, 1H, J_{HH} = 4.2 Hz, C^3-H), 7.67 (d, 1H, J_{HH} = 4.2 Hz, C^4-H), 7.68 (d, 2H, J_{HH} = 8.3 Hz, 4-ClC_6H_4), 8.06 (d, 2H, J_{HH} = 8.3 Hz, 4-ClC_6H_4), 12.11 (s, 1H, NH)
1.3	130.3 (C_6H_5N)	the compound was not isolated from the reaction mixture
1.4	101.0 (C_6H_5N)	the compound was not isolated from the reaction mixture
1.5[2]	62.7 (DMSO)	1.10 (t, 3H, J_{HH} = 7.2 Hz, CH_3CH_2N), 3.24 (m, 2H, J_{HH} = 7.2 Hz, CH_2-N), 3.92 (s, 3H, CH_3O), 7.68 (d, 2H, J_{HH} = 8.7 Hz, 4-ClC_6H_4), 7.84 (d, 1H, J_{HH} = 5.7 Hz, C^4-H), 8.11 (d, 2H, J_{HH} = 8.7 Hz, 4-ClC_6H_4)
2.1[1]	-	3.83 (s, 3H, CH_3O), 6.77 (d, 1H, J_{HH} = 3.9 Hz, C^3-H), 6.62 (d, 1H, J_{HH} = 10.6 Hz, CH=C(N)), 7.65 (d, 1H, J_{HH} = 3.9 Hz, C^4-H), 8.62 (d, 1H, J_{HH} = 10.6 Hz, N=CH-), indole moiety: 1.63, 2.12 (s, 6H. CH_3-C), 3.35 (s, 1H, CH_3-N), 7.03 (d, 1H, J_{HH} = 7.3 Hz), 7.09 (t, 1H, J_{HH} = 7.3 Hz), 7.29 (t, 1H, J_{HH} = 7.3 Hz), 7.42 (d, 1H, J_{HH} = 7.3 Hz)
2.2	69.2 (C_6H_5N)	the compound was not isolated from the reaction mixture
2.3	22.4 (C_6H_5N)	the compound was not isolated from the reaction mixture
2.4a[1]	32.2 (C_6H_5N)	2.85 – 3.09 (4H, m, N($\underline{CH_2}CH_2$)O), 3.35 – 3.59 (m, 4H, N($CH_2\underline{CH_2}$)O), 3.98 (s, 3H, CH_3O), 7.73 (d, 1H, J_{HH} = 5.8 Hz, C^4-H), 8.29 (d, 1H, J_{HH} = 25 Hz, N=CH-), indole moiety: 1.51, 1.81 (s, 6H. CH_3-C), 3.83 (s, 1H, CH_3-N), 7.37 - 7.51 (m, 3H), 7.63 (d, 1H, J_{HH} = 7.3 Hz)
2.4b[1]	-2.6 (DMSO)	2.95 – 3.27 (4H, m, N($\underline{CH_2}CH_2$)O), 3.37 – 3.58 (m, 4H, N($CH_2\underline{CH_2}$)O), 3.93 (s, 3H, CH_3O), 6.17 (d, 2H, J_{HH} = 8.7 Hz, 4-BrC_6H_4), 6.87 (d, 2H, J_{HH} = 8.7 Hz, 4-BrC_6H_4), 7.60 (d, 1H, J_{HH} = 4.8 Hz, C^4-H), 8.27 (d, 1H, J_{HH} = 23 Hz, N=CH-), indole moiety: 1.51, 1.66 (s, 6H, CH_3-C), 3.79 (c, 1H, CH_3-N), 7.32 (m, 1H), 7.40 - 7.42 (m, 2H), 7.50 (d, 1H, J_{HH} = 7.3 Hz)

Notes: [1] $CDCl_3$; [2] DMSO-d_6

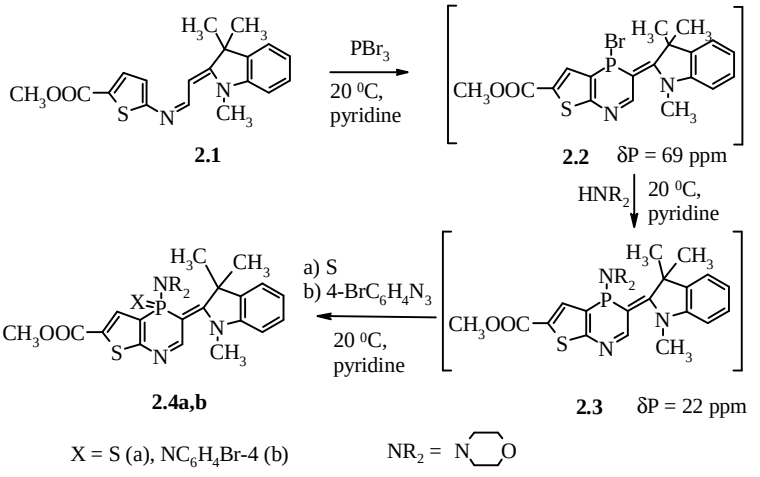
Table 2

Physico-chemical characteristics of compounds 1.1–2.4

Compound	Empirical formula	T_{melt}, K	Yield, %	Found, %			Calculated, %		
				N	P	S	N	P	S
1.1	$C_{13}H_{10}ClNO_3S$	415–416	70	4.82	–	10.92	4.74	–	10.84
1.3	$C_{13}H_8BrClNO_3PS$	–	–	–	–	–	–	–	–
1.4	$C_{17}H1_8ClN_2O_3PS$	–	–	–	–	–	–	–	–
1.5	$C_{17}H_{18}ClN_2O_3PS_2$	444–445	22	6.59	7.13	15.12	6.53	7.22	14.95
2.1	$C_{19}H_{20}N_2O_2S$	398–399	80	8.30	–	9.32	8.23	–	9.42
2.2	$C_{19}H_{18}BrN_2O_2PS$	–	–	–	–	–	–	–	–
2.3	$C_{23}H_{26}N_3O_3PS$	–	–	–	–	–	–	–	–
2.4a	$C_{23}H_{26}N_3O_3PS_2$	508–509	65	8.65	6.29	13.31	8.62	6.35	13.15
2.4b	$C_{29}H_{30}BrN_4O_3PS$	502–503	74	8.88	5.00	5.23	8.96	4.95	5.13



Scheme 1



Scheme 2

The compound **1.5** is a highly melting crystalline substance. Its physical constants and the data of ^{31}P, ^{1}H NMR spectroscopy are given in Tables 1 and 2. In the ^{1}H NMR spectrum of compound **1.5**, the chemical shift at 6.77 ppm corresponding to the H atom at C3 position of the initial thiophene derivative **1.1** is not observed. In the low-field region, only the signal of the H atom at C4 position of the thiophene cycle is represented at 7.85 ppm as a doublet ($^{3}J_{HP}$ = 5.7 Hz). The ratio of the integrated intensities of the signals of the C4-H proton of thiophene and protons of the fragment $N(CH_2CH_3)_2$ is 1:4:6, which corresponds to the presence of only one diethylamine substituent at the phosphorus atom and confirms the formation of [1,5,2]oxazaphosphinine ring.

3.2. Synthesis of 1,2-Dihydrothieno[2,3-*b*][1,4]azaphosphinine Derivatives

The compound **2.1** contains an enamine fragment with exocyclic C-nucleophilic centre. Phosphorylation of compound **2.1** with phosphorous tribromide also proceeds with the participation of two nucleophilic C-centres, exactly, the endocyclic C3-thiophene atom and the exocyclic CH-centre, to form a new phosphorus-containing fused system – 1,2-dihydro-1λ^{3}-thieno[2,3-b][1,4]azaphosphinine (**2.2**, Scheme 2). The structure of 1-bromo-1,2-dihydro-1λ^{3}- thieno[2,3-b][1,4]azaphosphinine (**2.2**) was confirmed by ^{31}P NMR spectroscopy (Table 1) and its chemical transformations. The chemical shift in the ^{31}P NMR spectrum of compound **2.2** is located at 69 ppm. Derivatives of three- (**2.3**) and four-coordinated phosphorus (**2.4a,b**) are synthesized on the basis of compound **2.2** (Scheme 2).

^{31}P and ^{1}H NMR spectroscopy data, physical constants and elemental analysis data of compounds **2.4a,b** are shown in Tables 1 and 2. Chemical shifts at 6.77 and 5.70 ppm corresponding to the H-atom on C3 position of thiophene and one of the exocyclic H atoms at the C-C double bond in the original imine **2.1** are absent in the NMR spectra of compounds **2.4a,b**. Signals of H atom at the N=C double bond of compounds **2.4a,b** are represented by doublets at 8.29 ppm ($^{3}J_{HP}$ = 25.2 Hz) and 8.27 ppm ($^{3}J_{HP}$ = 23 Hz). Chemical shifts of H-atoms at C4 thiophene position are observed at 7.73 ppm ($^{3}J_{HP}$ = 5.8 Hz) and 7.59 ppm ($^{3}J_{HP}$ = 4.8 Hz), respectively.

4. Conclusions

Derivatives of earlier unknown bicyclic systems – 1*H*-thieno[3,2-*c*][1,5,2]oxazaphosphinine and 1,2-dihydrothieno[2,3-*b*][1,4]azaphosphinine have been obtained by phosphorylation of *N*-substituted 5-amino-2-carbomethoxythiophene derivatives with phosphorus tribromide under mild conditions. Easily available reagents were used. The compounds obtained are stable under normal conditions, contain an ester group and can be used as starting material for different reactions. Obtained heterocycles contain endocyclic P and N or P, O and N atoms in the same ring, so multifunctional ligands can be created on the basis of these compounds to solve problems of coordination chemistry.

References

[1] Mathey F.: Phosphorus-Carbon Heterocyclic Chemistry. Pergamon Press, Oxford 2001.
[2] Ishii A., Yoshioka R., Nakayama J., Hoshino M.: Tetrahedron Lett., 1993, **34**, 8259. https://doi.org/10.1016/S0040-4039(00)61405-3
[3] Uchiyama Y., Kawaguchi T., Kuroda K.: Heteroatom. Chem., 2014, **25**, 326. https://doi.org/10.1002/hc.21163
[4] Kondo R., Yasuda T., Yang Y., Kim J. Y., Adachi C.: J. Mater. Chem., 2012, **22**, 16810. https://doi.org/10.1039/C2JM33526C

[5] Dienes Y., Durben S., Karpati T. *et al.*: Chem.-Eur. J., 2007, **13**, 7487. https://doi.org/10.1002/chem.200700399
[6] Neumann T., Dienes Y., Baumgartner T.: Org. Lett., 2006, **8**, 495. https://doi.org/10.1021/ol052911p
[7] Baumgartner T., Bergmans W., Karpati T. *et al.*: Chem.-Eur. J., 2005, **11**, 4687. https://doi.org/10.1002/chem.200500152
[8] Ishii A., Takaki I., Nakayama J., Hoshino M.: Phosphorus Sulfur, 1993, **77**, 149. https://doi.org/10.1080/10426509308045639
[9] Yasuike S., Nakashima F, Kurita J., Tsuchiya T.: Heterocycles, 1997, **45**, 1899. https://doi.org/10.3987/COM-97-7930
[10] Fenske D., Longer K., Heymann M., Becher H.-J.: Chem. Ber., 1976, **109**, 359. https://doi.org/10.1002/cber.19761090137
[11] Lampin J., Mathey F.: J. Organomet. Chem., 1974, **71**, 239. https://doi.org/10.1016/S0022-328X(00)93116-4
[12] Ishii A., Tsuchiya T., Nakayama J., Hoshino M.: Tetrahedron Lett., 1993, **34**, 2347. https://doi.org/10.1016/S0040-4039(00)77610-6
[13] Ishii A., Takaki I., Nakayama J., Hoshino M.: Tetrahedron Lett., 1993, **34**, 8255. https://doi.org/10.1016/S0040-4039(00)61404-1
[14] Ishii A., Yoshioka R,, Nakayama J., Hoshino M.: Tetrahedron Lett., 1993, **34**, 8259. https://doi.org/10.1016/S0040-4039(00)61405-3
[15] Combes C., Plenat F., Cristau H.-J.: Phosphorus, Sulfur, Silicon. Relat. Elem., 1996, 111, 33. https://doi.org/10.1080/10426509608054662
[16] Yasuike S., Nakashima F., Kurita J., Tsuchiya T.: Heterocycles, 1997, **45**, 1899. https://doi.org/10.3987/COM-97-7930
[17] Yasuike S., Kurita J., Tsuchiya T.: Heterocycles, 1997, **45**, 1891. https://doi.org/10.3987/COM-97-7911
[18] Dotz K., Tiriliomis A., Harms K.: Tetrahedron, 1993, **49**, 5577. https://doi.org/10.1016/S0040-4020(01)87270-7
[19] Ren Y., Linder T., Baumgartner T.: Can. J. Chem., 2009, **87**, 1222. https://doi.org/10.1139/V09-108
[20] Ren Y., Baumgartner T.: Chem.-Asian J., 2010, **5**, 1918. https://doi.org/10.1002/asia.201000196
[21] Kovaleva S., Chubaruk N., Tolmachov A., Pinchuk A.: Khim. Heterocycl. Soed., 2001, **9**, 1287.
[22] Kovaleva S., Simurova N., Mayboroda E.: Ukr. Khim. Zh., 2016, **82**, 91.
[23] Schmidpeter A., Gross J., Schrenk E., Sheldrick N.: Phosphorus Sulfur, 1982, **14**, 49. https://doi.org/10.1080/03086648208073110
[24] Fluck E., Vargaus M.: Zeitschrift für anorganische und allgemeine Chemie., 1977, **437**, 53. https://doi.org/10.1002/zaac.19774370107
[25] Volochnuk D., Pushechnikov A., Krotko D. *et al.*: Synthesis, 2003, **6**, 906.

Received: November 21, 2017 / Revised: January 25, 2018 / Accepted: May 23, 2018

СИНТЕЗ АНЕЛЬОВАНИХ ГЕТЕРОЦИКЛІВ, ЩО МІСТЯТЬ P- І N-АТОМИ, НА ОСНОВІ ПОХІДНИХ 5-АМІНО-2-МЕТОКСИКАРБОНІЛТІОФЕНУ

Анотація. *Синтезовані похідні нових біциклічних систем – 1H-тієно[3,2-c][1,5,2]оксазофосфініну і 1,2-дігідротієно[2,3-b][1,4] азафосфініну за реакцією фосфорилювання N-заміщених похідних 2-аміно-5-метоксикарбонілтіофену з трибромідом фосфору(III). Показано, що гетероциклізація може бути проведена в основному середовищі і за м'яких умов. Методами хімічного аналізу, ^{1}H і ^{31}P ЯМР спектроскопії вивчено кінцеві продукти реакції.*

Ключові слова: *тіофен, азафосфінін, оксазафосфінін, анельовані цикли, гетероцикл, фосфорилювання.*