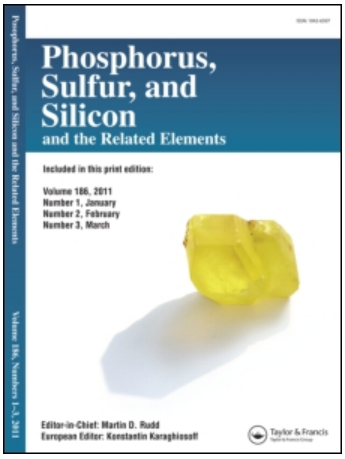

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Synthesis and Biological Activity of Heterocyclic Aminophosphonates

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A variety of synthetic methods for preparation of heterocyclic aminophosphonates is presented; which are concerning furyl, thienyl, pyrryl and pyridyl derivatives of aminomethanephosphonic acid and also phosphonic analogues of proline and homoproline. The obtained heterocyclic aminophosphonates were used as starting materials for synthesis of some peptidyl phosphonates. The compounds were evaluated as inhibitors of serine proteases. Most of the obtained heterocyclic aminophosphonates were preliminary tested as potential herbicides against selected plants, and some of them showed the herbicidal activity.

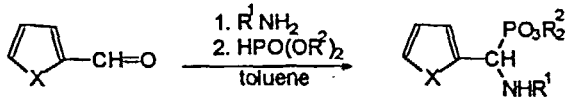
INTRODUCTION

α-Aminoalkanephosphonic acids (named briefly aminophosphonic acids) are important compounds, with a broad application in many areas of agriculture and medicine. The best example is "glyphosate", the herbicide widely applied in agriculture [1]. At present, a literature concerning synthesis and application of aminophosphonates is very extensive, comprising more than five thousand publications [2].

In the contrary, aminophosphonic acids bearing heterocyclic moiety are considerably little known. However, the heterocyclic aminophosphonates are becoming a subject of a growing interest. A number of papers concerning synthesis of various heterocyclic aminophosphonic acids have been published, lately [3-6,11-13]. Some of the obtained heterocyclic aminophosphonates showed an interesting biological activity [7,8,21-23].

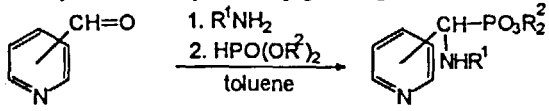
RESULTS AND DISCUSSION

According to last findings, the best method of synthesis of the furan, thiophene, pyrrole (and other five-membered heterocycles) derivatives of α-aminomethanephosphonic acid is a thermal addition of dialkyl (diaryl) phosphonates to the aldimines, formed *in situ* from the corresponding aldehydes and amines [3,4,10,11]. The method, which is depicted below, allowed to obtain a large number of heterocyclic derivatives of α-aminomethanephosphonic acid [3,4,11].



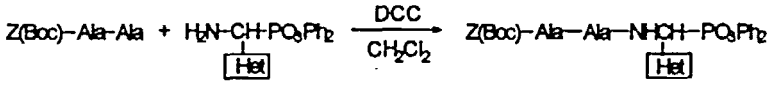
X = O, S, NH
R^1 = Bu, $PhCH_2$
R^2 = Et, Ph, $PhCH_2$

The majority of pyridine derivatives of α-aminomethanephosphonic acid have been also synthesized, by this way [4-6,19]:



R^1 = Bu, $PhCH_2$
R^2 = Et, Ph

The above reaction can be also carried out in the absence of solvent [20].
Some of 2-pyridyl derivatives were obtained in 1969, by an addition of diethyl phosphite to Schiff bases, formed from aniline and pyridine-2-carboxaldehyde [17,18].
In the case of thienyl, pyrazolyl, imidazolyl and 3-pyridyl aldehydes, the N-blocked aminophosphonic derivatives can be obtained in the course of amidoalkylation reaction [3,4]. Additionally, the free phosphonic acids can be achieved in a *one-pot* synthesis, using a mixture of the aldehyde, benzhydrylamine and diethyl phosphite [3-5].
The phosphonic analogues of proline and homoproline were synthesized in the reaction of dialkyl phosphites [14,16] or diaryl phosphites [7] with cyclic trimers, formed *in situ* from the cyclic imines. Another way to obtain the phosphonic analogue of proline was the cyclization of γ-chloro-α-aminobutanephosphonate in a basic condition [15].
Some of diphenyl esters of heterocyclic aminophosphonic acids were used for synthesis of peptidyl derivatives, containing terminal diphenyl phosphonate moiety. The peptides were synthesized easily by the coupling of diphenyl phosphonate with N-blocked amino acid, using the DCC method. For example, diphenyl esters of phosphonic analogue of proline and homoproline were coupled with the selected N-protected amino acids (Ala, Phe, Lys) to give peptidyl phosphonates, which resulted to be specific, moderate inhibitors of the Dipeptidyl Peptidase IV[7,8]. Other serine proteases were not inhibited by the above dipeptides [7,8].
Coupling of other heterocyclic diphenyl phosphonates with N-protected dipeptide (Z-Ala-Ala), it allowed to obtain a series of new heterocyclic peptidyl phosphonates [9], according to the scheme:



Het : 2-furyl, 2,3-thienyl, 2,3-pyridyl

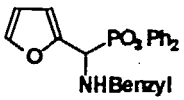
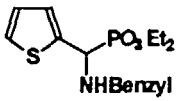
The obtained heterocyclic peptidyl phosphonates have been tested as irreversible inhibitors of chymotrypsin (ChT), human neutrophil elastase (HNE), porcine pancreatic elastase (PPE) and others. The compounds, which showed inhibitory potency are reported in Table 1.

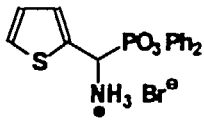
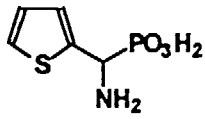
Table 1. Rate constants (k_{ob}/[I]) of inhibition of chymotrypsin, PPE and HNE by phosphono-peptides [9]

Inhibitor	ChT	PPE	HNE
Z-Ala-Ala-2-FurylGly^P(OPh)$_2$	28	159	370
Boc-Ala-Ala-2-FurylGly^P(OPh)$_2$	NI	600	135
Z-Ala-Ala-2-ThienylGly^P(OPh)$_2$	152	253	140
Boc-Ala-Ala-2-ThienylGly^P(OPh)$_2$	17	856	41
Z-Ala-Ala-3-ThienylGly^P(OPh)$_2$	26	25	13
Boc-Ala-Ala-3-ThienylGly^P(OPh)$_2$	5	124	13
Z-Ala-Ala-2-PirydylGly^P(OPh)$_2$	8	NI	NI
Z-Ala-Ala-3-PirydylGly^P(OPh)$_2$	26	4	NI

Most of the obtained heterocyclic α-aminophosphonic acids and esters were tested as potential herbicides against selected plants (*Lepidium sativum L., Cucumis sativus*) [22,23]. Examples of the compounds showing herbicidal activity are given in Table 2.

Table 2. Effect of selected heterocyclic aminophosphonates on the growth of test plant *Lepidium sativum*, measured as percentage change in root and shoot weight, compared with that of control [23]

	R	-59	-66	-50	-85
	S	-28	-30	-37	-65
	R	N	N	N	-90
	S	-11	-22	-46	--86

	R	N	-79	-87	-100
	S	N	-60	-45	-100
	R	N	-49	-69	-82
	S	N	N	N	-24

ACKNOWLEDGEMENT

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References

[1] E. Grossbard and D. Atkinson eds., *The Herbicide Glyphosate,* Butterworth, London 1985.

[2] P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon,* **63,** 193 (1991).

[3] B. Boduszek, *Phosphorus, Sulfur and Silicon,* **104,** 63, (1995).

[4] B. Boduszek, *Phosphorus, Sulfur and Silicon,* **113,** 209, (1996).

[5] B. Boduszek, *Tetrahedron,* **52,** 12483, (1996).

[6] B. Boduszek, *Phosphorus, Sulfur and Silicon,* **122,** 27, (1997).

[7] B. Boduszek, J. Oleksyszyn, C.M. Kam, J. Selzler, R.E. Smith and J.C. Powers, *J. Med. Chem.,* **37,** 3969, (1994).

[8] J.C. Powers, B. Boduszek and J. Oleksyszyn, *USA Pat.,* No. **5,543,396** (1996).

[9] A. T. Mauricio, B. Boduszek and J.C. Powers, *to be published.*

[10] J. Lukszo, J. Kowalik and P. Mastalerz, *Chem. Lett.,* **1978,** 1103.

[11] C. Hubert, B. Qussaid, G. Etemad-Moghadam, M. Koenig and B. Garrigues, *Synthesis,* **1994,** 51.

[12] L. Cottier, and others, *Phosphorus, Sulfur and Silicon,* **116,** 93 (1996).

[13] L. Cottier, and others, *Phosphorus, Sulfur and Silicon,* **118,** 181 (1996).

[14] E.W. Petrillo, E.R. Spitzmiller, *Tetrahedron Lett.,* **1979,** 4929.

[15] W. Subotkowski, R. Tyka and P. Mastalerz, *Pol. J. Chem.,* **54,** 503, (1980).

[16] V.A. Solodenko, V.P. Kukhar, *Zh. Obsh. Chim.,* **57,** 2392, (1987).

[17] B.P. Lugovkin, *Khim. Geter. Soiedin.,* **1968,** 117.

[18] B.P. Lugovkin, *Zh. Obsh. Chim.,* **40,** 562 (1970).

[19] G.H. Hakimelahi, A.R. Sardarian, *Helv. Chim. Acta,* **73,** 180, (1990).

[20] S.W.A. Bligh, C.M. McGrath, S. Failla and P. Finocchiaro, *Phosphorus, Sulfur and Silicon,* **118,** 189, (1996).

[21] D. Redmore, *United States Patent No.* **3,770,750** (1973).

[22] G. Forlani, and others, *Phosphorus, Sulfur and Silicon,* **109–110,** 353, (1996).

[23] B. Boduszek, P. Kafarski, *unpublished results.*