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Novel Heterocyclic Aminophosphonic Acids Derived from Furan and Thiophene

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Heterocyclic derivatives of aminomethylphosphonic acid were obtained in a one-pot procedure, by treatment of the corresponding heterocyclic aldimines with a mixture of trimethyl phosphite and bromotrimethylsilane (BrTMS). A reagent for phosphorylation of the imines in this case was the tris(trimethylsilyl)phosphite, formed *in situ* in a reaction mixture. The silylated esters formed were hydrolyzed to the final aminophosphonic acids.

Key words: furyl derivatives of aminomethylphosphonic acid, thienyl derivatives of aminophosphonic acid, silylation, trimethyl phosphite, bromotrimethylsilane

Aminophosphonates and aminophosphonic acids are recognized as a very interesting class of compounds, due to their biological activity [1,2]. In the last decades an intensive synthetic work was performed in preparation of various aminophosphonic acids, first of all, for such aminophosphonic acids, which were analogues of the natural amino acids, or analogues of some important non-natural amino acids, as well [3]. Aminophosphonic acids possessing a heterocyclic moiety are suprisingly little known. Recently, there is a growing interest for the heterocyclic derivatives of aminophosphonic acids, due to promising expected biological properties of these compounds. A main difficulty with obtaining of the heterocyclic derivatives of aminophosphonic acids is an inapplicability of the known, typical procedures used for synthesis of the most of the common aminophosphonates. Therefore, there is a need to search for new methods, which could be more efficient in preparation of the desired heterocyclic aminophosphonic acids.

Recently, some heterocyclic derivatives of aminomethylphosphonic acid were prepared; thus, for example; the furan derivatives [8–11], thiophene derivatives [13], imidazole and pyrazole derivatives [9], and pyridine derivatives [7,12]. The prevailing synthetic procedure used for preparation of the above derivatives was the known, slightly modified method, depending mainly on the addition of dialkyl phosphite to the corresponding heterocyclic imine. This method is not useful as a general procedure for the synthesis of the majority of heterocyclic and other delicate aminophosphonic acids, since, in some cases the products were not available, due to the decomposition of the heterocyclic moieties in reaction conditions, or, because of a cleavage of some heterocyclic aminophosphonic acids in an acidic medium [6,7].

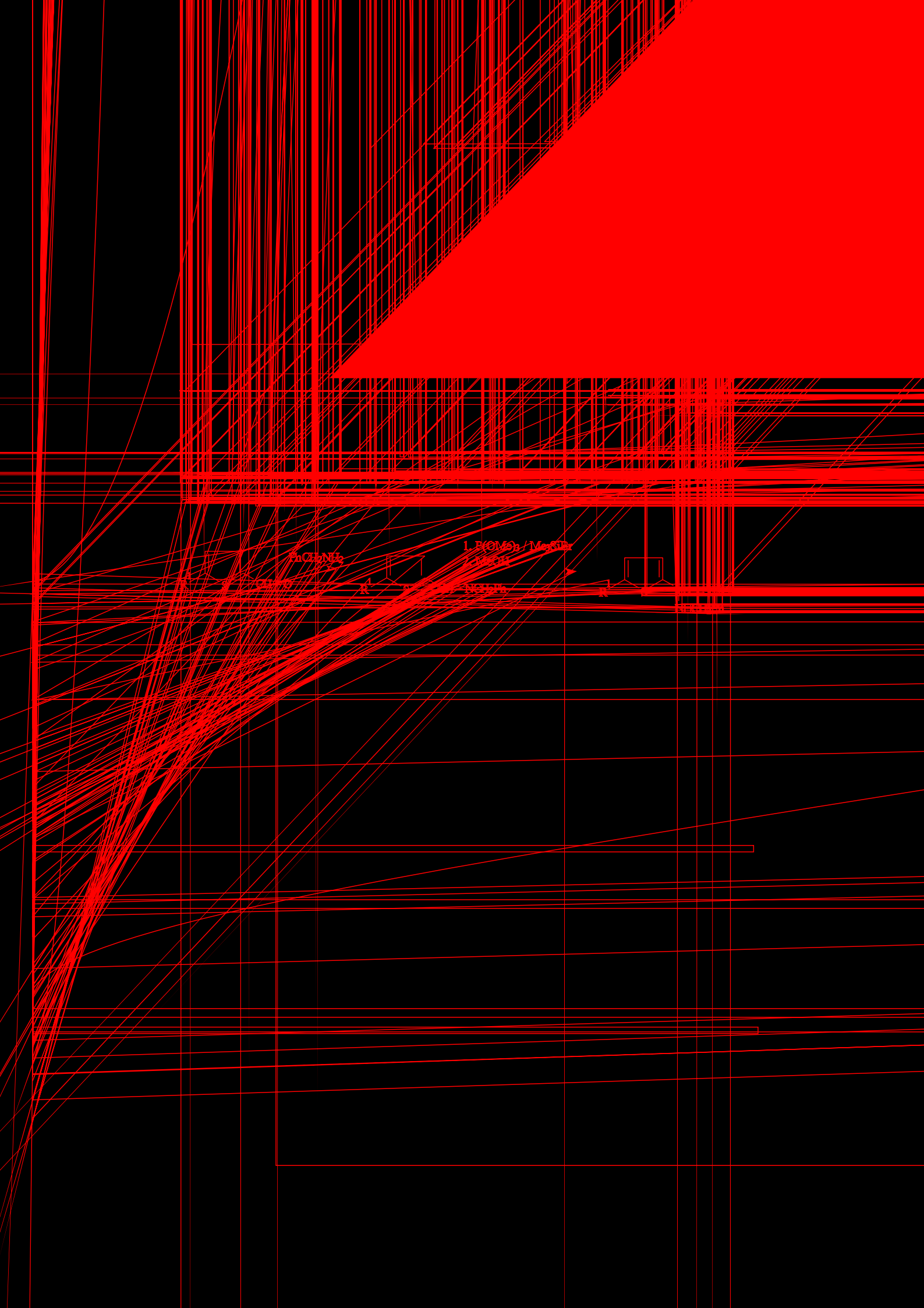
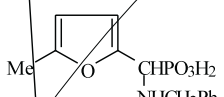
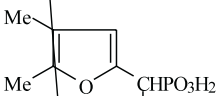
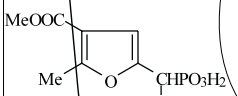
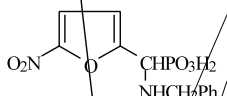
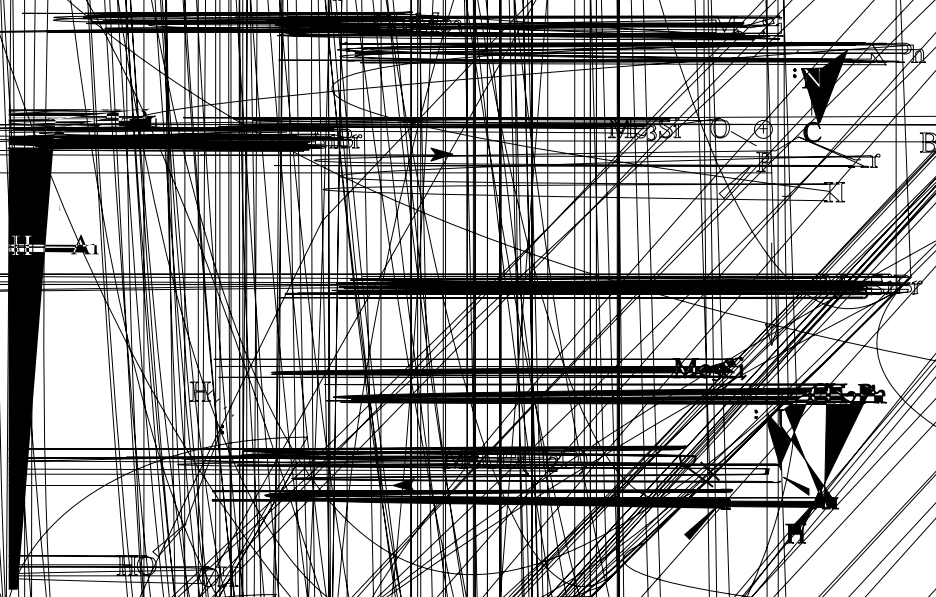

BnCH2NH2
1. P(OMe)3 / Me3SiBr
2. MeOH

Table. Analytical data of the aminophosphonic acids **3a–e** and **6a–d**.

Compound	Yield %	M.p. °C	^{1}H NMR, (D_2O + D_2SO_4) δ, ppm	^{31}P NMR, δ, ppm
 **3a**	36	199–201 (dec.) (tars)	7.57(m, 5H, Ph), 6.82(bs, 1H, furyl-3), 6.36(bs, 1H, furyl-4), 4.90(d, 1H, CHP, J = 18.5 Hz), 4.40(dd, 2H, CH_2N, J = 12 Hz), 2.49(s, 3H, CH_3).	9.279(s)
3b	51	201–203 (dec.) (tars)	7.22–7.01(m, 5H, Ph), 6.35(bs, 1H, furyl-3), 5.87(bs, 1H, furyl-4), 4.45(d, 1H, CHP, J = 18.6 Hz), 3.87(dd, 2H, CH_2N, J = 13.3 Hz), 2.35(q, 2H, CH_2**CH_3**), 0.92 (t, 3H, CH_2**CH_3**).(spectrum in D_2O).	9.026(s)
 **3c**	62	170–173 (dec).	7.21–7.09(m, 5H, Ph), 6.23(s, 1H, furyl-3), 4.31(d, 1H, CHP, J = 18.0 Hz), 3.94(dd, 2H, CH_2N, J = 13.2 Hz), 1.96 (s, 3H, CH_3), 1.67(s, 3H, CH_3).	9.770(s)
 **3d**	75	156–159	7.17–7.11(m, 5H, Ph), 6.59(s, 1H, furyl-3), 4.38(d, 1H, CHP, J = 18.0 Hz), 4.00(bs, 2H, CH_2N), 3.57(s, 3H, OCH_3), 2.25(s, 3H, CH_3).	8.419(s)
 **3e**	80	dec. > 155 (tars) lit.[14].	7.57(bs, 1H, furyl-4), 7.50(m, 5H, Ph) 7.04(bs, 1H, furyl-3), 5.05(d, 1H, CH-P, J = 19.8 Hz), 4.49(bs, 2H, NCH_2Ph)	5.684(s)
6a	52	219–220	7.36(m,5H, Ph), 7.14(s, 1H, thienyl-3), 6.86(s, 1H, thienyl-4), 4.80(d, 1H, CHP, J = 18.0 Hz), 4.20(dd, 2H, CH_2N, J = 13.2 Hz), 2.50(s, 3H, CH_3).	10.466(s)
Et S CHP **6b**	23	184–185	7.20–7.10(m, 5H, Ph), 6.93(s, 1H, thienyl-3, 6.64(s, 1H, thienyl-4), 4.62(d, 1H, CHP, J = 15.3 Hz), 4.05–3.81(m, 2H, CH_2N), 2.55(q, 2H, **CH_2**CH_3), 1.05 (t, 3H, CH_2**CH_3**).	10.144(s)
6c	54	179–183	7.20–7.09(m, 5H, Ph), 6.92(s, 1H, thienyl-4), 6.78(s, 1H, thienyl-3), 4.58 (d, 1H, CHP, J = 18.3 Hz), 3.98(dd, 2H, CH_2N, J = 13.5 Hz).	8.963(s)
6d	60	dec. > 165 (tars) lit.[14].	8.00(bs, 1H, thienyl-4), 7.42(m, 6H, Ph and thienyl-3), 4.97(d, 1H, CH-P, J = 18.6 Hz), 4.36(m, 2H, NCH_2Ph).	6.939(s)

Addition of the partially silylated esters of phosphorous acid to a double bond in imines has been studied [15]. From the literature data and our results we can propose a general mechanistic picture of the addition of a fully silylated ester of H_3PO_3 to a double bond of the imine (Scheme 2). In this case the nucleophile taking part in the reaction is the tris(trimethylsilyl) phosphite [$P(OSiMe)_3$], produced in a reaction medium from the Me_3SiBr and $P(OMe)_3$. The observed electronic demand of the imine bond suggests, that in the first stage of the reaction, a transient iminium cation is formed by action of the BrTMS on imine nitrogen. Addition of the silyloxy P(III) species to this cation, accompanied by valency expansion at phosphorus, gives the *N*- and *O*-silylated phosphonate, in which after treatment with methanol (or another protic solvent) undergoes a process of removing of the silyl groups from the intermediate with simultaneous formation of the corresponding aminophosphonic acid (Scheme 2).



EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance DPX 300 MHz in D_2O–D_2SO_4 (1:1) solutions, using 300.13 MHz for ^1H NMR and 121.49 MHz for ^{31}P NMR spectra, respectively.

Melting points were determined on a Digital Melting Point Apparatus Electrothermal 9200, and were uncorrected. Elemental analyses were done in the Laboratory of Instrumental Analysis, in the Institute.

According to the

***Procedure for preparation of aminophosphonic acids* 3a–e *and* 6a–d**: Syntheses of the all aminophosphonic acids were carried out in the equipment, protected against moisture. To the earlier prepared solution of imine (**2** or **5**), trimethyl phosphite (0.15 g, 1.2 mmol) was added, and then, (after 15 min.), to this stirred solution the bromomethylsilane (0.68 g, 4.5 mmol) was added dropwise. The whole mixture was stirred for 24 hrs at room temp. and evaporated. The resulting oil was treated with methanol (3–5 mL) and refrigerated. Usually, after diluting of this mixture with some diethyl ether, the product **3** (or **6**) separated out as a white, crystalline solid. The product was filtered, washed with diethyl ether and dried. Analytical data of the compounds obtained are given in the table.

Elemental analyses for the new obtained compounds: 3a–d and 6a–c:

Anal. for **3a**; $C_{13}H_{16}NO_4P$ (281.239): Calc. N, 4.98; P, 11.01; found: N, 4.79; P, 10.92. Anal. for **3b**; $C_{14}H_{18}NO_4P$ (295.265): Calc. N, 4.74; P, 10.49; found: N, 4.59; P, 10.54. Anal. for **3c**; $C_{14}H_{18}NO_4P$ (295.265): Calc. N, 4.74; P, 10.49; found: N, 4.61; P, 10.47. Anal. for **3d**; $C_{15}H_{18}NO_6P$ (339.275): Calc. N, 4.13; P, 9.13; found: N, 4.07; P, 9.15. Anal. for **6a**; $C_{13}H_{16}NO_3PS$ (297.305): Calc. N, 4.71; P, 10.42; found: N, 4.52; P, 10.42. Anal. for **6b**; $C_{14}H_{18}NO_3PS$ (311.331): Calc. N, 4.50; P, 9.95; found: N, 4.39; P, 9.91. Anal. for **6c**; $C_{12}H_{13}NO_3PSCl$ (317.725): Calc. N, 4.41; P, 9.75; found: N, 4.35; P, 9.72.

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