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An efficient one-pot synthesis of α-aminophosphonic acid esters from Schiff bases using sodium ethoxide as a catalyst (Pudovik reaction) and their bio-activity

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Synthesis of novel α-aminophosphonic acid esters was achieved through a one-pot two-step reaction process (Pudovik reaction). In the first step tryptophan methyl ester is reacted with substituted aromatic aldehydes in absolute ethanol to form Schiff bases. In the second step, these are treated with dialkyl/diaryl phosphites *in situ* using sodium ethoxide as a catalyst at refluxing temperature. The structures of these compounds were established by elemental analyses IRS, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data. All the title compounds exhibited moderate antimicrobial activity.

Key words: α-aminophosphonic acid esters, dialkyl/diaryl phosphites, aldehydes, tryptophan methyl ester, sodium ethoxide, antimicrobial activity.

INTRODUCTION

α-Aminophosphonic acid esters are an important class of compounds since they are structural analogues of the corresponding α-aminoacids [1]. Recently they have been receiving considerable attention due to their wide applications in the synthesis of phosphanopeptides [2]. The utilization of α-aminophosphonic acid esters as peptide mimics [3], haptens of catalytic antibodies [4], enzyme inhibitors [5], antibiotics and pharmacological agents [6] is also well established. Even though few synthetic approaches are available [7] for α-aminophosphonic acid esters, nucleophilic addition of dialkyl/diaryl phosphites to imines (Pudovik reaction) [8] is one of the most convenient methods. This method has been successfully used for the synthesis of title compounds.

Tryptophan itself is an important bio-active aminoacid [9], which undergoes enzymatic decarboxylation to tryptamine. It plays an important role in nerve functioning. Its hydroxy derivative is a well known antimigraine drug. Tryphtophan is phosphorylated in the present investigation to increase its bioactivity [10, 11].

RESULTS AND DISCUSSION

The synthesis of the title compounds (**5a**–**l**) was accomplished by the conversion of tryptophan methyl ester to the corresponding Schiff's base (**3**) by the reaction with the respective aldehydes. Compound **3** upon treatment with diphenyl/diethyl/dimethyl phosphite in the presence of catalytic amount of sodium ethoxide in absolute ethanol at reflux temperature for 4–5 hours afforded α-aminophosphonic acid esters (**5a**–**l**) in 72–82% yield. Thin layer chromatography was employed to monitor the reaction progress and to determine the purity of the products. All the title compounds (**5a**–**l**) were readily soluble in polar solvents and melted in the temperature range of 90–302ºC.

Absorption bands were present in the regions 3354–3413, 1200–1250, 951–957, 1175–1191, 737–748 and 1039–1094 cm^{-1} for –NH, P=O, P–O, O–C, P–C$_{(aliphatic)}$ and P–O–C$_{(aliphatic)}$ respectively [12], in compound **5a**–**l** (Table 1).

The ^{1}H NMR spectral data of compound **5a**–**l** are given in Table 2. The aromatic protons [13] of α-aminophosphonic acid esters showed a complex multiplet at δ 6.67–8.85. The P–C–H protons resonated as a multiplet [14] at δ 3.58–3.74 due to coupling with phosphorus and N–H. The N–H proton signals appeared at δ 2.94–3.75 (J = 6.5–8.8 Hz) as doublets and aromatic NH appeared at δ 10.73–10.90 as a singlet. These signals are confirmed by D_2O exchange spectral recording. The –CH_2 protons showed a doublet at δ 2.93–3.61 (J = 7.1–8.7 Hz) and –CH proton appeared at δ 3.55–3.64 as a multiplet and –COO–$\underline{CH_3}$ as a singlet at δ 2.30–2.85. The proton signal of P–$\underline{OCH_2}$–CH_3 appeared as a multiplet and P–OCH_2–$\underline{CH_3}$ gave a triplet at δ 3.61–3.68 and 1.08–1.20 (J = 6.9–7.0 Hz) respect-ively. The P–$O\underline{CH_3}$ appeared as a singlet at δ 2.31–2.50.

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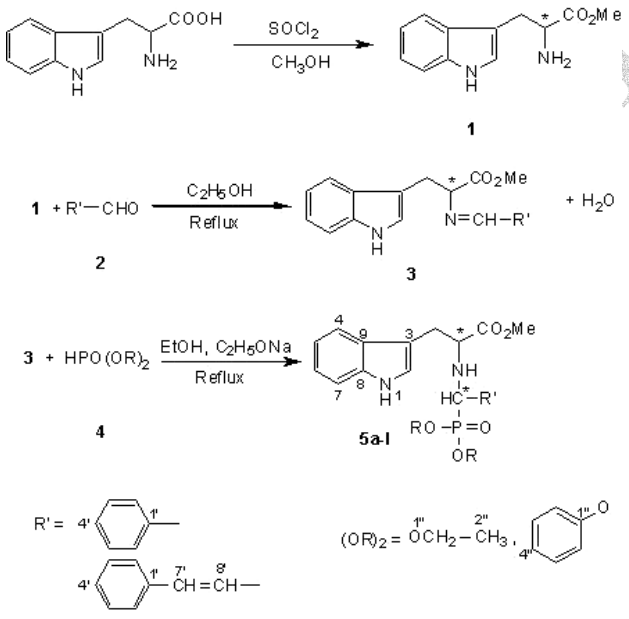
Table 1. Physical, analytical, infrared and ^{31}P NMR spectral data of **5a–l**.

Comp.	m. p., °C	Yield [a], %	Molecular formula	Elemental Analysis Found (Calc.), %			IRS λ_{max}, cm^{-1}						^{31}P NMR[b]
				C	H	N	–NH	P=O	P–O–C$_{aryl}$		P–C$_{(aliphatic)}$	P–O–C$_{(aliphatic)}$	
									P–O	O–C			
5a	249–251	72	$C_{21}H_{24}N_2O_5PCl$	55.89 (55.96)	5.26 (5.30)	6.15 (6.20)	3413	1203	-	-	745	1078	2.44
5b	278–280	76	$C_{23}H_{28}N_2O_5PCl$	57.60 (57.68)	5.81 (5.89)	5.78 (5.84)	3404	1230	-	-	746	1094	1.62
5c	300–302	74	$C_{31}H_{28}N_2O_5PCl$	64.65 (64.71)	4.87 (4.90)	4.77 (4.82)	3412	1227	951	1180	-	-	5.14
5d	115–117	80	$C_{21}H_{24}N_3O_7P$	54.58 (54.61)	5.18 (5.24)	9.07 (9.10)	3408	1201	-	-	747	1054	2.79
5e	120–122	82	$C_{23}H_{28}N_3O_7P$	56.37 (56.42)	5.70 (5.76)	8.47 (8.53)	3413	1208	-	-	737	1079	2.31
5f	109–111	79	$C_{31}H_{28}N_3O_7P$	63.47 (63.51)	4.76 (4.82)	7.12 (7.17)	3410	1203	957	1175	-	-	5.19
5g	117–119	79	$C_{21}H_{25}N_2O_6P$	58.25 (58.30)	5.77 (5.82)	6.40 (6.47)	3389	1211	-	-	746	1054	2.30
5h	114–116	80	$C_{23}H_{29}N_2O_6P$	59.91 (59.99)	6.25 (6.34)	6.01 (6.08)	3354	1250	-	-	747	1039	2.96
5i	120–122	78	$C_{31}H_{29}N_2O_6P$	66.86 (66.90)	5.19 (5.25)	4.97 (5.03)	3351	1249	955	1182	-	-	5.14
5j	95–97	78	$C_{23}H_{28}N_2O_5P$	62.22 (62.29)	6.29 (6.36)	6.25 (6.31)	3401	1220	-	-	743	1077	2.96
5k	90–92	77	$C_{25}H_{32}N_2O_5P$	63.55 (63.60)	6.78 (6.83)	5.83 (5.90)	3395	1200	-	-	746	1075	2.43
5l	91–93	76	$C_{33}H_{32}N_2O_5P$	69.75 (69.83)	5.60 (5.68)	4.87 (4.93)	3392	1219	954	1191	-	-	5.17

a - After one crystallization; b - Recorded in DMSO-d_6.



Comp.	R’	$(OR)_2$	Comp.	R’	$(OR)_2$
5a	4-Cl–C_6H_4	CH_3	**5g**	2-OH–C_6H_4	CH_3
5b	4-Cl–C_6H_4	C_2H_5	**5h**	2-OH–C_6H_4	C_2H_5
5c	4-Cl–C_6H_4	C_6H_5	**5i**	2-OH–C_6H_4	C_6H_5
5d	3-NO_2–C_6H_4	CH_3	**5j**	C_6H_5–CH=CH	CH_3
5e	3-NO_2–C_6H_4	C_2H_5	**5k**	C_6H_5–CH=CH	C_2H_5
5f	3-NO_2–C_6H_4	C_6H_5	**5l**	C_6H_5–CH=CH	C_6H_5

Sheme 1.

There is corresponding doubling of signals of the ethoxy group in ^{13}C NMR spectra (Table 3).

In fact, P–O–CH_2–$\underline{CH_3}$ group resonated [15] as a doublet at δ 13.2–13.5 ($^3J_{P–O–C–C}$ = 8.2–9.1 Hz) and at δ 14.2–15.6 ($^3J_{P–O–C–C}$ = 8.2–9.2 Hz), the P–O–$\underline{CH_2}$–CH_3 group gave two doublets one at δ 62.3–63.1 ($^2J_{P–O–C}$ = 6.9–7.0 Hz) and the other one at δ 63.1–64.2 ($^2J_{P–O–C}$ = 7.0–7.1 Hz) and –COO–$\underline{CH_3}$ resonated at δ 50.2–50.9. The chiral carbon of tryptophan methyl ester (–$\underline{C}$H–CO_2CH_3) resonated in the region δ 60.5–63.4. The chiral carbon of P–C–H gave a doublet in the range of δ 39.5–49.2 (d, $J_{P–C}$ = 143–147 Hz). The methoxy carbon (P–$\underline{OCH_3}$) resonated as a doublet due to coupling with phosphorus at δ 51.8 (d, $^2J_{P–O–C}$ = 16.9 Hz). These values are in agreement with the literature data [16, 17].

^{31}P NMR chemical shifts [14, 18] (Table 1) of these compounds (**5a**–**l**) appeared in the down field region 1.62–5.19 ppm.

In the FAB mass spectra [19] (Table 4), compounds **5a, 5d, 5e, 5g** and **5i** exhibited their respective molecular ions at m/z 450 (**7**), 461 (**11**), 489 (**7**), 432 (**10**) and 528 (**10**).

ANTIBACTERIAL ACTIVITY

Compounds **5a**–**l** were screened in regard to their antibacterial activity against gram positive bacteria,

Staphylococcus aureus, Bacillus faecalis and gram negative bacteria, *Escherichia coli*, *Klebsiella pneumoniae* by the disc diffusion method [20, 21], in luria bertani nutrient agar medium at various concentrations (75, 100 μg/ml) in DMSO. These solutions containing 10^6 cells/ml were added to each Whatmann No.1 (made in UK) filter paper disc (6 mm diameter) and DMSO was used as the control. The freshly prepared agar medium containing the bacteria species was loaded on the discs by using micropipette. The plates were incubated at 35ºC and examined for zone of inhibition around each disc after 24 h. The results were compared with the activity of the standard antibiotic *Penicillin* (75 μg/ml).

EXPERIMENTAL

Solvents were used after purifying them by the established procedure. The progress of the reaction and purity of the compounds were monitored by thin layer chromatography (TLC) using *n*-hexane and ethylacetate (2:1, by volume) as eluating system on silica gel and iodine as visualizing agent. Melting points were determined in open capillary tubes on Mel-temp apparatus and were uncorrected. Microanalysis was performed at Indian Institute of Science, Bangalore, India.

IR spectra were recorded using KBr pellets on Nicolet 380 double beam spectrophotometer ($\bar{\nu}$ in cm^{-1}) in Environmental Engineering Lab, Sri Venkateswara University, Tirupati. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C, 161.9 MHz for ^{31}P NMR as solutions in DMSO-d_6. The ^1H and ^{13}C chemical shifts were referenced with respect to tetramethyl silane, and ^{31}P chemical shifts to 85% H_3PO_4 (*ortho*-phosphoric acid). The techniques of double heteronuclear resonance were used while recording ^1H NMR spectra. ^1H, ^{13}C and ^{31}P NMR spectral data were obtained by Indian Institute of Science, Bangalore, India. Mass spectra were recorded on a Jeol SX 102 DA/600 mass spectrometer using Argon/Xenon (6 kV, 10 mA) as the fast atom bombardment (FAB) gas and also a Shimadzu QP-2000 GC-MS (gas chromatography-mass spectroscopy) instrument.

Table 2. ^1H NMR chemical shifts [a,b] of **5a–l**.

Comp.	Ar–H	–CH_2 (d, 2H)	–CH (m, 1H)	P–C–H (m, 1H)	N–H (d, 1H)	–COO–CH_3 (s, 3H)	P–OCH_2–CH_3 (m, 2H)	P–OCH_2–CH_3/OCH_3 (3H)	Ar–NH (s, 1H)	Other H′s
5a	7.85–6.91 (m, 9H)	2.93 (J = 7.1)	3.61–3.58	3.70–3.68	3.01 (J = 6.5)	2.32	-	2.31 (s)	10.80	-
5b	7.83–6.95 (m, 9H)	2.94 (J = 7.0)	3.60–3.57	3.69–3.67	2.94 (J = 8.3)	2.32	3.65–3.61	1.08 (t, J = 6.9)	10.87	-
5c	8.52–6.87 (m, 19H)	2.94 (J = 6.8)	3.58–3.55	3.74–3.70	2.98 (J = 6.8)	2.30	-	-	10.90	-
5d	7.86–6.90 (m, 9H)	3.12 (J = 8.1)	3.60–3.58	3.72–3.68	3.13 (J = 8.4)	2.31	-	2.30 (s)	10.90	-
5e	7.84–6.95 (m, 9H)	3.06 (J = 8.2)	3.60–3.57	3.71-3.69	3.12 (J = 8.5)	2.31	3.67–3.64	1.09 (t, J = 7.0)	10.87	-
5f	8.85–7.22 (m, 19H)	3.36 (J = 8.3)	3.59–3.55	3.62–3.59	3.35 (J = 8.1)	2.50	-	-	10.88	-
5g	7.44–6.68 (m, 9H)	3.03 (J = 7.9)	3.61–3.58	3.64–3.63	3.71 (J = 8.3)	2.85	-	2.49 (s)	10.74	10.42 (s, 1H, OH)
5h	7.43-6.67 (m, 9H)	3.30 (J = 7.9)	3.60–3.58	3.63–3.61	3.72 (J = 8.4)	2.49	3.68–3.64	1.18 (J = 6.9)	10.75	10.41 (s, 1H, OH)
5i	8.13–6.76 (m, 19H)	3.28 (J = 8.2)	3.60–3.59	3.61–3.58	3.75 (J = 8.2)	2.51	-	-	10.73	10.40 (s, 1H, OH)
5j	7.87–6.95 (m, 10H)	3.60 (J = 8.6)	3.62–3.59	3.70–3.67	3.33 (J = 8.8)	2.61	-	2.50 (s)	10.81	7.45 (–CH=CH_2, t, J = 11.4 Hz, 1H), 6.65 (–CH=CH_2, d, J = 13.3 Hz, 1H)
5k	7.85–6.93 (m, 10H)	3.60 (J = 8.5)	3.61–3.57	3.71–3.68	3.34 (J = 8.6)	2.49	3.67–3.62	1.20 (t, J = 7.0)	10.80	7.44 (–CH=CH_2, t, J = 11.2, 1H), 6.64 (–CH=CH_2, d, J = 13.1, 1H)
5l	8.15–6.73 (m, 19H)	3.61 (J = 8.7)	3.64–3.60	3.71–3.67	3.35 (J = 8.2)	2.71	-	-	10.82	7.46 (–CH=CH_2, t, J = 11.5 Hz, 1H), 6.60 (–CH=CH_2, d, J = 13.5, 1H)

- No such type of protons present; a - Chemical shifts in ppm from TMS and coupling constants J in Hz in parenthesis; b - Recorded in DMSO-d_6.

Table 3. ^{13}C NMR spectral data[a,b] of compounds **5b**, **5e**, **5g** and **5l**.

Comp.	Chemical shifts in ppm
5b	128.6 (C-2). 115.8 (C-3), 127.5 (C-4), 128.4 (C-5), 119.7 (C-6), 111.0 (C-7), 136.4 (C-8), 131.9 (C-9), 30.9 (–$\underline{CH_2}$–CHCOOCH$_3$), 64.3 (–CH$_2$–$\underline{CH}$COOCH$_3$), 171.2 (–CH$_2$–CH$\underline{CO}$OCH$_3$), 50.3 (–CH$_2$–CHCOO$\underline{CH_3}$), 48.9 (d, J_{P-C} = 143 Hz, 1C, P–C–$\underline{H}$), 136.1 (C-1′), 129.5 (C-2′&C-6′), 128.7 (C-3′&C-5′), 132.4 (C-4′), 62.3 (d, $^2J_{P-O-C}$ = 6.9 Hz, IC, –$\underline{OCH_2}$–CH$_3$), 14.5 (d, $^3J_{P-O-C-C}$ = 8.2 Hz, IC, –OCH$_2$–$\underline{CH_3}$), 63.1 (d, $^2J_{P-O-C}$ = 7.0 Hz, IC, –$\underline{OCH_2}$–CH$_3$), 15.6 (d, $^3J_{P-O-C-C}$ = 8.2 Hz, IC, –OCH$_2$–$\underline{CH_3}$).
5e	128.9 (C-2). 115.9 (C-3), 127.8 (C-4), 128.5 (C-5), 119.7 (C-6), 111.0 (C-7), 136.7 (C-8), 132.1 (C-9), 31.3 (–$\underline{CH_2}$–CHCOOCH$_3$), 63.4 (–CH$_2\underline{CH}$COOCH$_3$), 172.3 (–CH$_2$CH$\underline{CO}$OCH$_3$), 50.5 (–CH$_2$CHCOO$\underline{CH_3}$), 42.3 (d, J_{P-C} = 145 Hz, 1C, P–C–$\underline{H}$), 138.2 (C-1′), 123.3 (C-2′), 148.3 (C-3′), 121.9 (C-4′), 129.2 (C-5′), 134.2 (C-6′), 63.1 (d, $^2J_{P-O-C}$ = 7.0 Hz, IC, –$\underline{OCH_2}$–CH$_3$), 13.2 (d, $^3J_{P-O-C-C}$ = 9.1 Hz, IC, –OCH$_2$–$\underline{CH_3}$), 64.2 (d, $^2J_{P-O-C}$ = 7.1 Hz, IC, –$\underline{OCH_2}$–CH$_3$), 14.2 (d, $^3J_{P-O-C-C}$ = 9.2 Hz, IC, –OCH$_2$–$\underline{CH_3}$).
5g	128.7 (C-2). 115.7 (C-3), 127.4 (C-4), 128.4 (C-5), 118.4 (C-6), 111.2 (C-7), 136.2 (C-8), 133.4 (C-9), 28.9 (–$\underline{CH_2}$–CHCOOCH$_3$), 60.5 (–CH$_2\underline{CH}$COOCH$_3$), 172.8 (–CH$_2$CH$\underline{CO}$OCH$_3$), 50.5 (–CH$_2$CHCOO$\underline{CH_3}$), 39.5 (d, J_{P-C} = 147 Hz, 1C, P–C–H), 120.8 (C-1′), 156.4 (C-2′), 117.5 (C-3′), 129.1 (C-4′), 126.5 (C-5′), 129.4 (C-6′), 51.8 (d, $^2J_{P-O-C}$ = 16.9 Hz, IC, –O–$\underline{CH_3}$).
5l	128.5 (C-2). 116.0 (C-3), 127.9 (C-4), 128.6 (C-5), 119.6 (C-6), 111.0 (C-7), 136.5 (C-8), 131.7 (C-9), 31.5 (–$\underline{CH_2}$–CHCOOCH$_3$), 63.4 (–CH$_2\underline{CH}$COOCH$_3$), 172.3 (–CH$_2$CH$\underline{CO}$OCH$_3$), 50.2 (–CH$_2$CHCOO$\underline{CH_3}$), 49.2 (d, J_{P-C} = 147 Hz, 1C, P–C–H), 135 (C-1′), 126.3 (C-2′&C-6′), 128.3 (C-3′&C-5′), 127.3 (C-4′), 127.4 (C-7′), 123.3 (C-8′), 157.3 (C-1″), 115.8 (C-2″ & C-6″), 129.2 (C-3″ & C-5″, 121.2 (C-4″) .

a - Chemical shift in ppm from TMS and coupling constants *J* (Hz) in parenthesis; b - Recorded in DMSO-d_6.

Table 4. FAB Mass spectral data of compounds **5a**, **5d**, **5e**, **5g** and **5i**.

Comp.	m/z (%)
5a	450 (7.1, $M^{+\bullet}$), 417 (81.2), 335 (100), 193 (19.2), 146 (18.2), 118 (20.3), 64 (14.2).
5d	461 (10.7 $M^{+\bullet}$), 428 (17.8), 339 (100), 215 (7.5), 118 (10.8), 64 (7.1).
5e	489 (7.3, $M^{+\bullet}$), 431 (5.2), 399 (10.7), 359 (14.2), 327 (71.4), 255 (78.5), 118 (100), 64 (71.4).
5g	432 (10.0, $M^{+\bullet}$), 390 (14.2), 309 (25.7), 249 (100), 231 (17.1), 203 (11.4), 188 (77.1).
5i	528 (9.8, $M^{+\bullet}$), 492 (7.8), 419 (17.1), 235 (65.2), 118 (100), 64 (31.2).

Table 5. Antibacterial activity[a] of some new α-aminophosphonic acid esters (**5a**–**l**).

Comp.	*Staphylococcus aureus*		*Bacillus faecalis*		*Escherichia coli*		*Klebsiella pneumoniae*	
	75 µg/ml	100 µg/ml	75 µg/ml	100 µg/ml	75 µg/ml	100 µg/ml	75 µg/ml	100 µg/ml
5a	-	-	8	9	-	-	7	8
5b	6	8	-	-	10	12	10	12
5c	-	-	10	11	9	12	-`	-
5d	-	-	9	10	-	-	6	8
5e	7	9	-	-	8	10	9	10
5f	13	16	12	14	16	18	10	12
5g	8	10	-	-	10	11	12	15
5h	12	13	-	-	11	12	10	11
5i	8	11	-	-	8	10	-	-
5j	-	-	6	8	8	10	-	-
5k	7	8	10	12	8	9	6	9
5l	8	11	14	15	6	10	-	-
Penicillin[b]	9		8		7		11	

a - Concentration in ppm; b - Standard antibacterial compound.

Synthesis of 2-{[hydroxy-phenyl-methyl-2-dimethoxy-phosphoryl)-methyl]amino}-3-(1H-indol-3-yl)-propionic acid methyl ester (**5g**). Tryptophan-methyl ester was prepared using the reported procedure [22].

Tryptophan methyl ester (1.09 g, 0.005 mol) and *o*-hydroxybenzaldehyde (**2**) (0.52 g, 0.005 mol) in dry ethanol (20 ml) were refluxed upon stirring for 2 hours to form the imine (**3**). A solution of dimethylphosphite (**4**) (0.53 ml, 0.005 mol) was added slowly at room temperature, in the presence of catalytic amount of sodium ethoxide without isolating the imine. The reaction temperature was raised to reflux value and maintained for 4 h. Completion of the reaction was monitored by TLC analysis. After completion of the reaction, solvent was removed in a rotary evaporator. The residue was purified by column chromatography using silica gel (60–120 mesh) as adsorbent and hexane and ethylacetate (2:1) as an eluent to afford pure α-aminophosphonic acid ester (5 g) as a solid phase, yield 1.16 g (79%), m. p. 117–119°C.

The results indicate that the compounds **5b**, **5e**, **5f** and **5h** exhibited promising antibacterial activity. The compound 5a showed the same activity against gram positive bacteria *Bacillus faecalis* when compared to that of the standard. The compound **5l** exhibited more activity against gram positive bacteria *Bacillus faecalis* when compared to that of *Penicillin*. It is gratifying to note that the nitro compound **5f** exhibited very high activity against both gram positive and negative bacteria, since it contains nitro-group.

CONCLUSION

In conclusion, synthesis of α-aminophosphonic acid esters is achieved in good yields in a two-step reaction process in the presence of sodium ethoxide as a catalyst. The advantages are smaller reaction time intervals, low cost of the reactant chemicals, simple experimental procedure.

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ЕФИКАСНА СИНТЕЗА В ЕДИН СЪД НА ЕСТЕРИ НА α-АМИНОФОСФОРНАТА КИСЕЛИНА С ШИФОВИ БАЗИ С ИЗПОЛЗВАНЕ НА НАТРИЕВ ЕТОКСИД КАТО КАТАЛИЗАТОР (РЕАКЦИЯ НА ПУДОВИК) И ТЯХНАТА БИОЛОГИЧНА АКТИВНОСТ

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(Резюме)

Осъществена е синтеза на нови естери на α-аминофосфорната киселина чрез двустадийна реакция в един съд (Реакция на Пудовик). В първия стадий метилов естер на триптофан реагира със заместени ароматни алдехиди в абсолютен етанол до образуване на Шифови бази. Във втория стадий те взаимодействат *in situ* с диалкил/диарилфосфит с използване на натриев етоксид като катализатор и при нагряване с обратен хладник. Структурата на тези съединения е определена с елементен анализ, ИЧС, ^{1}H, ^{13}C, ^{31}P ЯМР и масспектрометрия. Всички споменати съединения показаха умерена антимикробна активност.