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ONE-POT SYNTHESIS AND SPECTRAL CHARACTERIZATION OF NEW α-AMINOPHOSPHONATES

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ABSTRACT

A simple, efficient and catalyst-free method for the synthesis of α-amino phosphonates is developed via three-component Kabachnik-Fields reaction by reacting nor-valine ethyl ester **(1)** / Phenyl glycine ethyl ester **(4)**, various substituted aromatic aldehydes **(2_{a-i})** and dialkyl/aryl phosphite in dry ethanol/toluene under reflux conditions. The structures of all the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P-NMR and Mass spectral data.

Key words : α-Aminophosphonates, Catalyst-free method, Kabachnik-Fields reaction, Spectral analysis.

INTRODUCTION

α-Aminophosphonates, structural analogues of natural aminoacids[1] have received significant importance in medicinal, bioorganic and organic chemistry owing to their unique physicochemical and biological properties. Their design as reagents and potential synthons in organic synthesis is gaining increased attention[2]. The applications of α-aminophosphonates have ranged from agriculture to medical uses as anti-cancer agents[3], enzyme-inhibitors[4], peptide-mimetics[5], antibiotics and pharmacological agents[6]. In view of all this information, substituted α-aminophosphonates are often synthesized in an organic solvent via a traditional Kabachnik-Fields reaction[7], in which an aldehyde, an amine and dialkyl phosphite in one-pot set-up. In some reports, this reaction was carried out in straight forward one-pot procedures without any catalysts[8, 9] and are benign and do not call for any drastic work-ups. While, in most cases, it was performed using catalysts, such as $LiClO_4$[10], $TaCl_5$-SiO_2[11], $In Cl_3$[12] lanthanide-triflates[13] and CF_3COOH[14]. However,

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many of these catalysts are expensive and have to be used in stoichiometric amount. The catalyst-free synthesis of α–aminophosphonates is rather limited[15]. The key step in this synthesis is the nucleophillic addition of amine to carbonyl compound followed by the addition of a dialkyl or diphenyl phosphites to produce α-aminophosphonates by the elimination of water.

Herein, we report an easy one pot synthesis of new α-aminophosphonates by Kabachnik-Fields reaction under mild conditions without any catalyst.

EXPERIMENTAL

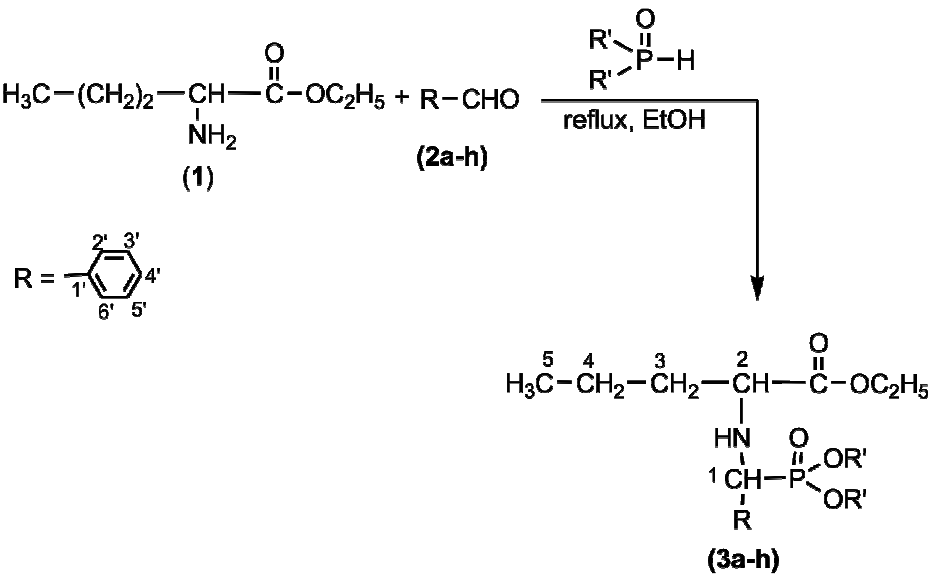
The IR spectra (KBr pellets and Nujol mulls) were recorded on a Perkin-Elmer 283 unit. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 on a AMX 400MHz spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) with TMS as internal standard. ^{31}P NMR spectra were recorded using 85% H_3PO_4 as external reference. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. Mass-spectra was recorded on Jeol 5X102DA/600 mass-spectrometer using Argon/Xenon (6 KeV, 10 mA) as the fast atom bombardment (FAB) gas. Melting points were determined in an open capillary tubes on Mel-temp apparatus, Tempo Instruments, India and were uncorrected. The following abbreviations were used while presenting the NMR data s = singlet, d = doublet, t = triplet and m = multiplet.

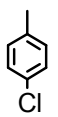
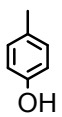
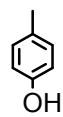
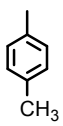
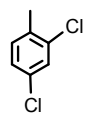
General procedure for preparation of α-aminophosphonates

A mixture of nor-valine ethyl ester **(1)** (0.54 g, 0.003 mole), 4-hydroxybenzaldehyde **(2f)** (0.366 g, 0.003 mole) was stirred in dry ethanol (15 mL) at room temperature for 1 hr. Diethylphosphite (0.38 mL) (0.003 mole) in dry ethanol (15 mL) was added dropwise. Stirring was continued at room temperature for another 0.5 hr, after which the mixture was heated under reflux for 4 hrs. The progress of the reaction was monitored by TLC analysis on silica gel using hexane-ethyl acetate (2 : 1 v/v). After completion of the reaction, the solvent was removed by rota-evaporator and the resulting residue was purified by column chromatography on silica gel (100-200 mesh, ethyl acetate / hexane 1 : 4) as eluent to afford pure α-aminophosphonate **(3f)**, yield 1.72 g, 77%. Synthesis of other compounds **(3a-3e)**, **(3g)**, **(3h)** and **(5a-5d)** was accomplished by adopting the above procedure.

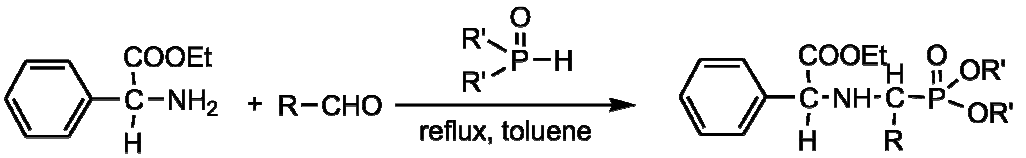
RESULTS AND DISCUSSION

The synthetic route involves reaction of equimolar quantities of nor-valine ethyl ester **(1)**/ phenyl glycine ethyl ester **(4)**, various aromatic aldehydes **(2a-i)** and dimethyl/diethyl/ dibutyl/ diphenyl phosphite in dry ethanol / toluene at reflux temperature **(Schemes 1 and 2)**.

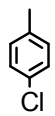
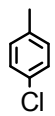
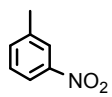
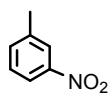


Compd.	R	R'	Compd.	R	R'
2a and 3a		Me	2e and 3e		Et
2b and 3b		Me	2f and 3f		Et
2c and 3c		Me	2g and 3g		Et
2d and 3d		Me	2h and 3h		Et

Scheme 1



(4) **(2a-l)** **(5a-d)**

Compd.	R	R'
2a and 5a		Butyl
2a and 5b		Phenyl
2i and 5c		Butyl
2i and 5d		Phenyl

Scheme 2

All compounds **(3a-h)** exhibited characteristic IR absorption bands (Table 1) for P=O, C=O, P—C and N-H groups in the regions 1201-1236, 1737-1745, 758-792 and 3361-3431cm^{-1} and for **(5a-d)** in the regions 1215-1232, 1738-1745, 780-786, 3260-3283 cm^{-1} [16].

In ^{1}H NMR spectra, aromatic protons of **(3a-h)** showed complex multiplets in the region δ 6.46 -7.93. The N-H proton signal of the compounds appeared at δ 4.70-4.84 as a singlet. The two methoxy group protons, which are attached to phosphorus (P-O-C-H) resonated as two doublets at δ 3.53-3.59 (d, J = 13 Hz) (Table 3) and at δ 3.20-3.59 due to coupling with phosphorus atom respectively[17, 18]. The aromatic protons of the benzene ring of α-aminophosphonic acid esters **(5a-d)** showed a complex multiplets in the region δ 6.57-8.03. The N-H proton signal resonated at δ 5.03-5.12 as a singlet (Table 4)[19].

Table 1. Physical, IR and ^{31}P NMR spectral data of α-aminophosphonates (3a-h)

Comp.	Yield (%)	M. P. (°C)	Molecular formula	Calcd / (found)			IR (cm^{-1})				^{31}P NMR
				C	H	N	P=O	C=O	P-C	N-H	
3a	80	Semi solid	$C_{16}H_{25}ClNO_5P$	50.78 (50.87)	6.60 (6.70)	3.65 (3.71)	1210	1739	781	3392	24.03
3b	75	Semi solid	$C_{16}H_{26}NO_6P$	53.39 (53.48)	7.20 (7.30)	3.84 (3.90)	1215	1737	763	3409	24.45
3c	74	Semi solid	$C_{15}H_{25}N_2O_5P$	52.24 (52.32)	7.30 (7.30)	8.08 (8.14)	1218	1743	773	3411	23.18
3d	69	Semi solid	$C_{17}H_{28}NO_5P$	57.04 (57.13)	7.80 (7.90)	3.85 (3.92)	1215	1741	764	3396	25.43
3e	73	Semi solid	$C_{17}H_{29}N_2O_5P$	54.74 (54.83)	7.80 (7.90)	7.45 (7.52)	1201	1744	780	3394	24.06
3f	77	Semi solid	$C_{18}H_{30}NO_6P$	55.74 (55.81)	7.70 (7.80)	3.56 (3.62)	1217	1743	788	3361	22.23
3g	76	Semi solid	$C_{18}H_{29}BrNO_5P$	47.92 (48.01)	6.40 (6.50)	3.04 (3.11)	1225	1745	758	3262	23.24
3h	67	Semi solid	$C_{18}H_{28}Cl_2NO_5P$	49.01 (49.10)	6.30 (6.40)	311.00 (3.18)	1236	1743	792	3413	24.86

[a]Recorded in $CDCl_3$

Table 2. Physical, IR and ^{31}P NMR spectral data of a-aminophosphonates (5a-d)

Comp.	Yield (%)	M. P. (°C)	Molecular formula	Calcd /(found)			IR(cm^{-1})				^{31}P NMR
				C	H	N	P=O	C=O	P-C	N-H	
5a	78	Semi solid	$C_{25}H_{35}ClNO_5P$	60.45 (60.54)	7.1 (7.10)	2.75 (2.82)	1235	1745	786	3280	20.08
5b	77	Semi solid	$C_{29}H_{27}ClNO_5P$	64.83 (64.91)	5.00 (5.10)	2.54 (2.61)	1230	1742	781	3360	21.12
5c	75	Semi solid	$C_{25}H_{35}N_2O_7P$	59.20 (59.28)	6.90 (7.00)	5.47 (5.53)	1215	1738	780	3282	22.88
5d	76	Semi solid	$C_{29}H_{27}H_2O_7P$	63.64 (63.73)	4.90 (5.00)	5.07 (5.13)	1218	1739	783	3283	21.97

[a]Recorded in $CDCl_3$

Table 3. ^{1}**H NMR spectral data of α-aminophosphonates (3a-h)**

Comp.	Ar-H	P-C-H	N-H	C-O-$\underline{CH_2}$-CH_3/C-O-CH_2-CH_3	P-OCH_3/P-OCH_3	P-O-CH_2-CH_3/P-O-CH_2-CH_3	= -CH_3	= -$\underline{CH_2}$-$\underline{CH_3}$	-CH	Ar-OH
3a	6.46 -7.89 (m, 4H)	5.74-5.81 (d, J = 11 Hz)	4.73-4.81 (d, J = 11 Hz)	4.08-4.25 (m, 4H) 1.54-1.58 (t, 6H, J = 7 Hz)	3.55-3.57 (d, 3H, J = 13 Hz) 3.20-3.31 (d, 3H, J = 13 Hz)	-	0.93 (s, 3H)	1.35-1.83 (m, 4H)	3.23-3.67 (m, 1H)	
3b	6.70-7.75 (m, 4H)	5.71-5.83 (d, J = 11 Hz)	4.72-4.84 (d, J = 11 Hz)	3.83-391 (m, 4H) 1.64-1.16 (t, 6H, J = 7.1 Hz)	3.53-3.55 (d, 3H, J = 13 Hz) 3.25-3.29 (d, 3H, J = 13 Hz)	-	1.02 (s, 3H)	1.34-1.84 (m, 4H)	3.24-3.68 (m, 1H)	9.81 (s, 1H)
3c	7.80-7.93 (m, 4H)	5.73-5.58 (d, J = 11 Hz)	4.74-4.82 (d, J = 11 Hz)	3.62-3.78 (m, 4H) 1.28-1.14 (t, 6H, J = 7.1 Hz)	3.54-3.58 (d, 3H, J = 13 Hz) 3.28-3.36 (d, 3H, J = 13 Hz)	-	0.92 (s, 3H)	1.36-1.81 (m, 4H)	3.30-3.68 (m, 1H)	
3d	7.02-7.28 (m, 4H)	5.75-5.84 (d, J = 11 Hz)	4.79-4.82 (d, J = 11 Hz)	3.82-3.92 (m, 4H) 1.64-1.18 (t, 6H, J = 7 Hz)	3.56-3.59 (d, 3H, J = 13 Hz) 3.27-3.30 (d, 3H, J = 13 Hz)	-	0.89 (s, 3H)	1.42-1.83 (m, 4H)	3.21-3, 67 (m, 1H)	
3e	6.58-7.48 (m, 4H)	5.76-5.82 (d, J = 11 Hz)	4.73-4.83 (d, J = 11 Hz)	3.62-3.93 (m, 4H) (t, 6H, J = 7 Hz)	-	4.13-4.32 (m, 4H) 1.12-1.15 (t, 6H, J = 10.5 Hz)	0.91 (s, 3H)	1.41-1.82 (m, 4H)	3.20-3.68 (m, 1H)	
3f	6.70-7.73 (m, 4H)	5.76-5.88 (d, J = 11 Hz)	4.74-4.77 (d, J = 11 Hz)	3.81-3.93 (m, 4H) 1.65-1.18 (t, 6H, J = 7.0 Hz)	-	4.09-4.21 (m, 4H) 1.14-1.18 (t, 6H, J = 10 Hz)	0.93 (s, 3H)	1.40-1.81 (m, 4H)	3.22-3.34 (m, 1H)	9.78 (s, 1H)
3g	6.51- 7.46 (m, 4H)	5.74-5.80 (d, J = 11 Hz)	4.70-4.79 (d, J = 11 Hz)	3.64-3.76 (m, 4H) 1.82-1.14 (t.6H, J = 7.0 Hz)	-	4.11-4.32 (m, 4H) 1.13-1.26 (t, 6H, J = 10 Hz)	0.96 (s, 3H)	1.44-1.87 (m, 4H)	3.22-3.34 (m, 1H)	
3h	7.41-7.82 (m, 3H)	5.71-5.79 (d, J = 11 Hz)	4.71-4.84 (d, J = 11 Hz)	3.91-3.99 (m, 4H) 1.81-1.12 (t, 6H, J = 7.0 Hz)	-	4.12-4.35 (m, 4H) 1.12-1.41 (t, 6H, J = 10 Hz)	0.98 (s, 3H)	1.42-1.83 (m, 4H)	3.23-3.34 (m, 1H)	

[a]Recorded in $CDCl_3$

Table 4. ^{1}H NMR spectral data of α-aminophosphonates (5a-d)

Compd.	Ar-H /P-O-C_6H_5	P-C-H	N-H	C-O-$\underline{CH_2}$-CH_3/C-O-CH_2-CH_3	P-O-$\underline{CH_2}$-CH_2-CH_2-CH_3	P-O-CH_2-CH_2-$\underline{CH_2}$-CH_3	P-O-CH_2-CH_2-CH_2-$\underline{CH_3}$	Ar-$\underline{CH}$-NH
5a	7.16-7.88 (m, 9H)	4.84-4.90 (d, J = 12 Hz)	5.09 (s, 1H)	3.82-3.92 (q, 4H, J = 14 Hz) 1.42-1.48 (t, 6H, J = 12 Hz)	3.96-4.01 (m, 4H)	1.14-1.26 (m, 4H)	0.73-0.80 (t, 6H, J = 14 Hz)	2.5 (d, 1H, J = 6 HZ)
5b	7.10-7.71 (m, 19H)	4.82-4.87 (d, J = 12 Hz)	5.03 (s, 1H)	3.86-3.94 (q, 4H, J = 14 Hz) 1.44-1.48 (t, 6H, J = 12 Hz)	-	-	-	2.52 (d, 1H, J = 7 Hz)
5c	7.14-8.03 (m, 9H)	4.79-4.92 (d, J = 12 Hz)	5.12 (s, 1H)	3.85-3.92 (q, 4H, J = 14 Hz) 1.43-1.47 (t, 6H, J = 12 Hz)	3.97-4.08 (m, 4H)	1.16-1.24 (m, 4H)	0.75-0.83 (t, 6H, J = 14 Hz)	2.45 (d, 1H, J = 6 Hz) 2.63 (d, 1H, J = 6 Hz)
5d	6.57-7.81 (m, 19H)	4.89-4.98 (d, J = 12 Hz)	5.05 (s, 1H)	3.90-3.98 (q, 4H, J = 14 Hz) (t, 6H, J = 12 Hz)	-	-	-	

[a]Recorded in $CDCl_3$

The [1]3C NMR chemical shifts in the title compounds (Table 5) were observed in the expected regions[20]. Phosphorus resonance signals in the compounds **(3a-h)** (Table 1) appeared in the region δ 23.18-25.43 and for **(5a-d)** (Table 2) in the region 21δ 20.08-22.88.

Table 5. ^{13}C NMR Spectral data of α-aminophosphonates (3a, 3d, 3f and 3h)

Compd.	3a	3d	3f	3h
C – 1	51.63	52.68	52.7	51.95
C – 5	20.63	19.91	20.85	20.15
C – 4	32.63	32.31	32.24	32.27
C – 3	45.69	45.32	45.56	45.5
C - 2	69.91	68.92	69.98	66.21
C - 1'	135.42	134.52	135.48	134.72
C - 2'	128.42	128.2	129.44	135.72
C - 3'	127.54	127.54	128.54	133.6
C - 4'	135.36	134.23	138.55	132.89
C - 5'	127.54	127.54	128.54	128.85
C - 6'	128.42	128.2	129.44	127.57
O-$\underline{CH_2}$-CH_3	62.57	62.49	62.37	62.66
O-CH_2-$\underline{CH_3}$	39.94	39.92	39.89	39.91
P-O-CH_2-$\underline{CH_3}$	-	-	16.07 (d, *J*=12.6 Hz)	16.28 (d, *J*=12.8 Hz)
P-O-$\underline{CH_2}$-CH_3	-	-	62.35 (d, J=6.8 Hz)	62.37 (d, J=6.8 Hz)
P-O-CH_3	16.26 (d, J=12.4 Hz)	16.4 (d, J=12.4 Hz)	-	-
>C=O	169.74	169.71	169.73	169.72

[a]Recorded in $CDCl_3$

FAB Mass spectra of **(3f)** and **(5a)** showed MH^{2+}, $M^{+\bullet}$ ions and respective

characteristic daughter ions (Table 6).

Table 6. Mass Spectral data of α-aminophosphonates (3f and 5a)

Compound	m/z (% relative abundance)
3f	388(58.8, MH^{+2}), 341(8.8), 313(44.1), 299 (11.7), 285(52.14) 154(26.4), 146(88.2), 136(26.4), 102(100).
5a	495(48.1, $M^{+\bullet}$), 480(11.1), 463(12.1), 459(48.11), 406(14.8), 371(9.2), 198(100), 108(37).

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