



A Convenient Synthesis and Antibacterial Activity of Novel α -Aminophosphonic Acid Esters from Amino Acids/Esters (Kabachnik-Fields Reaction)

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Abstract: Synthesis of novel α -aminophosphonic acid esters (5a-n) were achieved with high yields through one-pot three component reaction process by Kabachnik-Fields reaction. It involves the reaction among amino acids/esters, substituted aromatic aldehydes and dialkyl phosphites in absolute ethanol at reflux temperature. Their structures were established by elemental analysis IR, ¹H, ¹³C, ³¹P NMR and mass spectral data. All the title compounds were screened for their antibacterial activity. Most of the compounds exhibited moderate antimicrobial activity.

Keywords: α -Amino phosphonic acid esters; Dialkyl phosphates; Aldehydes; Amino acid esters; Antibacterial activity.

Introduction

Kabachnik-Fields reaction¹ is used for the synthesis of α -amino phosphonic acid esters which have useful properties². They have vital role as that of the corresponding amino acid in biological system³⁻⁶. These are recognized as an important class of enzyme inhibitors either as transition state analogues⁷ or as non-hydrolysable phosphate surrogates⁸ and for the production of catalyst antibodies with esterases or amidase activity⁹. They also find use as potential antibiotics¹⁰, enzyme inhibitors¹¹ and pharmacological agents¹². α -Amino phosphonic acid esters, being phosphorus analogues of amino acid esters¹³ serve as building blocks for peptides. Their commercial applications are enzyme inhibitory neuroactive agents, HIV protease antagonists and collagenase inhibitors. Classical approach to their synthesis is the Kabachnik-Fields reaction, which is a one-pot three component¹⁴⁻¹⁶

operation involving amino acid ester, aldehyde and dialkyl phosphite. To the best of our knowledge, amino acid esters / acids were not used in the synthesis of α -amino phosphonates. We have used for the first time successfully and synthesized a series of novel α -amino phosphonates containing amino acids / esters under mild conditions without using any catalyst in high yields¹⁷ Antibacterial activity is also evaluated for the title compounds.

Experimental

Solvents were used after purifying them by the established procedure. Progress of the reaction and purity of the compounds were monitored by TLC using *n*-hexane and ethylacetate (1:1, by volume) as eluting system on silica gel and iodine as visualizing agent. Melting points were determined in an open capillary tube on Mel-temp apparatus. Micro analysis was performed at CDRI, Lucknow, India. IR spectra were recorded as KBr pellets on Nicolet 380 double beam spectrophotometer ($\bar{\nu}$ in cm^{-1}) in Environmental Engineering Lab, S.V.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 $\text{DMSO-}d_6$. The ^1H and ^{13}C chemical shifts were referenced to tetramethyl silane, and ^{31}P NMR chemical shifts to 85% H_3PO_4 . ^1H , ^{13}C and ^{31}P NMR spectral data were obtained from Indian Institute of Science, Bangalore, India. Mass spectra were recorded on a Jeol SX 102 DA/600 mass spectrometer using Argon / Xenon (6 keV, 10mA) as the FAB (fast atom bombardment) gas and also a Shimadzu QP-2000 GC-MS instrument.

Synthesis of 2-[[diethoxy-phosphoryl)-(4-methoxy-phenyl)-methyl]-amino} -3-methyl-butyrac acid methyl ester (4j)

L-Valine methyl ester prepared²⁸ (0.838 g, 0.005 mole) and 4-methoxy benzaldehyde (0.60 mL, 0.005 mole) and diethyl phosphite (0.64 mL, 0.005 mole) in dry ethanol (30 mL) was stirred for 30 minutes; then raised to reflux and continued for 5 h. Completion of the reaction was monitored by TLC analysis. After completion of the reaction, solvent was removed in a rota-evaporator. The residue was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and hexane and ethyl acetate (1:1) as an eluent to afford pure α -amino phosphonic acid ester (4j) as a solid, yield 1.43 g (74%), m.p. 116-118°C.

Results and Discussion

α -Aminophosphonic acid esters (4a-n) were synthesised by one-pot reaction of equimolar quantities of different amino acid esters/acids, substituted aromatic aldehydes and dimethyl / diethyl phosphite in absolute ethanol at reflux temperature for 4-5 hours in 74-81% yield (Table 1). Thin layer chromatography (TLC) was employed to monitor reaction progress and to determine the purity of the products. All the title compounds (4a-n) readily dissolve in polar solvents and melted in the range of 69-121°C (Scheme 1).

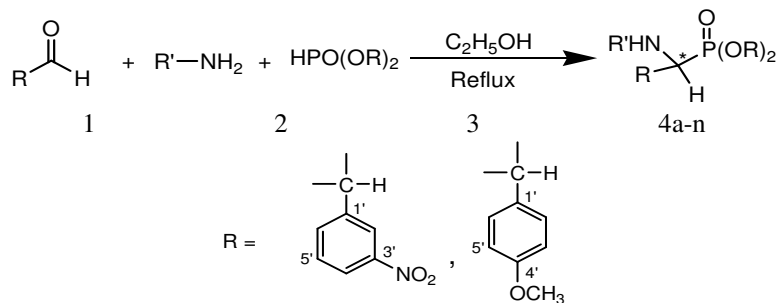
All the compounds (4a-n) showed absorption bands (Table 1) in the region 3200-3390, 1208-1251 and 731-757 cm^{-1} for $-\text{NH}$, $\text{P}=\text{O}$ and $\text{P-C}_{(\text{aliphatic})}$ respectively^{18,19}.

The ^1H NMR spectral data²⁰ of 4a-n are given in Table 2. The aromatic protons of α -amino phosphonic acid esters showed a complex multiplet at δ 6.15-8.69. The P-C-H proton resonated as a multiplet²¹ at δ 3.77-4.86 due to coupling with phosphorus and N-H. The N-H proton signals appeared at δ 5.38-6.90 as doublet ($J = 15-7.2$ Hz). These signals are confirmed by D_2O exchange spectral recording. The proton signals of $\text{P-OCH}_2\text{-CH}_3$ appeared as a quartet and $\text{P-OCH}_2\text{-CH}_3$ gave a triplet at δ 3.56-3.62 and δ 1.12-1.19 respectively.

Table 1. Physical, analytical, infrared and ^{31}P NMR spectral data of 4a-n

| Compd. | M.P., °C | Yield ^a , % | Molecular formula | Elemental Analysis Found (Calcd), % | | | IR λ_{max} cm ⁻¹ | | | ^{31}P NMR ^b |
|--------|----------|------------------------|--|-------------------------------------|-------------|-------------|--|------|----------------------------|----------------------------------|
| | | | | C | H | N | -NH | P=O | P-C _(aliphatic) | |
| 4a | 74-76 | 78 | C ₁₅ H ₂₃ N ₂ O ₇ P | 48.09 (48.13) | 6.15 (6.19) | 7.40 (7.48) | 3352 | 1209 | 739 | 19.32 |
| 4b | 69-71 | 80 | C ₁₇ H ₂₇ N ₂ O ₇ P | 50.67 (50.74) | 6.70 (6.76) | 6.91 (6.96) | 3250 | 1208 | 737 | 19.20 |
| 4c | 76-78 | 76 | C ₁₆ H ₂₅ N ₂ O ₇ P | 49.40 (49.48) | 6.41 (6.48) | 7.17 (7.21) | 3259 | 1210 | 752 | 19.60 |
| 4d | 73-75 | 79 | C ₁₈ H ₂₉ N ₂ O ₇ P | 51.84 (51.91) | 6.95 (7.01) | 6.67 (6.72) | 3257 | 1208 | 750 | 19.65 |
| 4e | 114-116 | 77 | C ₁₈ H ₂₁ N ₂ O ₇ P | 52.87 (52.94) | 5.14 (5.18) | 6.79 (6.86) | 3362 | 1211 | 735 | 19.61 |
| 4f | 111-113 | 78 | C ₂₀ H ₂₅ N ₂ O ₇ P | 54.96 (55.05) | 5.72 (5.77) | 6.38 (6.41) | 3390 | 1210 | 734 | 19.55 |
| 4g | 119-121 | 80 | C ₁₄ H ₂₁ N ₂ O ₇ PS | 42.80 (42.85) | 5.35 (5.39) | 7.11 (7.13) | 3268 | 1212 | 738 | 19.59 |
| 4h | 113-115 | 81 | C ₁₆ H ₂₅ N ₂ O ₇ PS | 45.63 (45.71) | 5.95 (5.99) | 6.59 (6.66) | 3269 | 1232 | 731 | 19.52 |
| 4i | 117-119 | 75 | C ₁₆ H ₂₆ O ₆ NP | 53.40 (53.47) | 7.24 (7.29) | 3.85 (3.89) | 3220 | 1242 | 752 | 21.52 |
| 4j | 116-118 | 74 | C ₁₈ H ₃₀ O ₆ NP | 55.85 (55.80) | 7.76 (7.80) | 3.58 (3.61) | 3200 | 1251 | 750 | 21.45 |
| 4k | 114-116 | 77 | C ₁₇ H ₂₈ O ₆ NP | 54.76 (54.68) | 7.49 (7.55) | 3.70 (3.75) | 3257 | 1228 | 757 | 21.42 |
| 4l | 115-117 | 78 | C ₁₉ H ₃₂ O ₆ NP | 56.78 (56.84) | 7.97 (8.03) | 3.44 (3.48) | 3258 | 1229 | 756 | 21.33 |
| 4m | 98-100 | 79 | C ₁₉ H ₂₄ O ₆ NP | 57.95 (58.01) | 6.10 (6.14) | 3.52 (3.56) | 3324 | 1220 | 745 | 22.39 |
| 4n | 99-101 | 80 | C ₂₁ H ₂₈ O ₆ NP | 59.78 (59.85) | 6.61 (6.69) | 3.27 (3.32) | 3325 | 1219 | 736 | 21.97 |

^aAfter one crystallization. ^bRecorded in DMSO-*d*₆



| Compd. | R | R' | (OR) ₂ |
|--------|---|---|-------------------------------|
| 4a | 3-NO ₂ -C ₆ H ₄ | (CH ₃) ₂ -CH-CH-COOCH ₃ | CH ₃ |
| 4b | 3-NO ₂ -C ₆ H ₄ | (CH ₃) ₂ -CH-CH-COOCH ₃ | C ₂ H ₅ |
| 4c | 3-NO ₂ -C ₆ H ₄ | H ₃ C-(CH ₂) ₂ -CH-COOC ₂ H ₅ | CH ₃ |
| 4d | 3-NO ₂ -C ₆ H ₄ | H ₃ C-(CH ₂) ₂ -CH-COOC ₂ H ₅ | C ₂ H ₅ |
| 4e | 3-NO ₂ -C ₆ H ₄ | C ₆ H ₅ -CH ₂ -CH-COOH | CH ₃ |
| 4f | 3-NO ₂ -C ₆ H ₄ | C ₆ H ₅ -CH ₂ -CH-COOH | C ₂ H ₅ |
| 4g | 3-NO ₂ -C ₆ H ₄ | SH ₃ C-CH ₂ -CH ₂ -CH-COOH | CH ₃ |
| 4h | 3-NO ₂ -C ₆ H ₄ | SH ₃ C-CH ₂ -CH ₂ -CH-COOH | C ₂ H ₅ |
| 4i | 4-CH ₃ O-C ₆ H ₄ | (CH ₃) ₂ -CH-CH-COOCH ₃ | CH ₃ |
| 4j | 4-CH ₃ O-C ₆ H ₄ | (CH ₃) ₂ -CH-CH-COOCH ₃ | C ₂ H ₅ |
| 4k | 4-CH ₃ O-C ₆ H ₄ | H ₃ C-(CH ₂) ₂ -CH-COOC ₂ H ₅ | CH ₃ |
| 4l | 4-CH ₃ O-C ₆ H ₄ | H ₃ C-(CH ₂) ₂ -CH-COOC ₂ H ₅ | C ₂ H ₅ |
| 4m | 4-CH ₃ O-C ₆ H ₄ | C ₆ H ₅ -CH ₂ -CH-COOH | CH ₃ |
| 4n | 4-CH ₃ O-C ₆ H ₄ | C ₆ H ₅ -CH ₂ -CH-COOH | C ₂ H ₅ |

Scheme 1

There is corresponding duplication of signals for the ethoxy group in ¹³C NMR spectra (Table 3). In fact CH₃ groups resonated as two doublets, one at δ 14.8 (*J* = 9.2 Hz), and the other doublet at δ 14.1 (*J* = 9.1 Hz), the OCH₂ groups also gave two doublets one at δ 62.3 (*J* = 7.0 Hz) and the other at δ 63.1 (*J* = 7.2 Hz). This indicates that the two ethoxy groups which are linked to phosphorus are not magnetically equivalent.

This may be due to restricted rotation at phosphorus centre²². The P-C-H chiral carbon gave a doublet in the range of δ 48.9-51.8 (d, *J*_{PC} = 143-145 Hz). The methoxy carbon (P-OCH₃) resonated as a doublet due to coupling with phosphorus at δ 55.0-53.4 (d, ²*J*_{POC} = 16.8-16.7 Hz). These values are in agreement with the literature²³ data ³¹P NMR chemical shifts²⁴ of these compounds (4a-n) appeared in the region 19.20-22.29 ppm as expected (Table 1).

Table 2. ^1H NMR Chemical Shifts^{a,b} of 4a-n

| Compd. | |
|--------|--|
| 4a | 8.28-7.66 (m, 4H, Ar-H), 1.14 (d, $J = 7.1$ Hz, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 2.50-2.48 (m, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.35 (d, $J = 7.2$ Hz, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.74 (s, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.92-3.90 (m, 1H, $P\text{-C-H}$), 6.56 (d, $J = 13$ Hz, 1H, -NH), 3.49 (s, 3H, -OCH ₃). |
| 4b | 8.29-7.66 (m, 4H, Ar-H), 1.14 (d, $J = 7.2$ Hz, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 2.51-2.47 (m, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.36 (d, $J = 7.2$ Hz, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.75 (s, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.93-3.91 (m, 1H, $P\text{-C-H}$), 6.59 (d, $J = 12$ Hz, 1H, -NH), 3.62 (q, $J = 6.5$ Hz, 2H, -OCH ₂ -CH ₃), 1.16 (t, $J = 7.2$ Hz, 3H, -OCH ₂ -CH ₃). |
| 4c | 8.61-7.41 (m, 4H, Ar-H), 1.13 (t, $J = 4.3$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.34-1.30 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.75-1.73 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 3.46 (t, $J = 4.8$ Hz, 1H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 4.12 (q, $J = 6.7$ Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COO-CH}_2\text{-CH}_3$), 1.30 (t, $J = 7.5$ Hz, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COO-CH}_2\text{-CH}_3$), 3.92-3.87 (m, 1H, $P\text{-C-H}$), 6.61 (d, $J = 15$ Hz, 1H, -NH), 3.39 (s, 3H, -OCH ₃). |
| 4d | 8.69-7.37 (m, 4H, Ar-H), 1.13 (t, $J = 4.4$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.33-1.30 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.76-1.74 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 3.45 (t, $J = 4.7$ Hz, 1H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 4.13 (q, $J = 6.8$ Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COO-CH}_2\text{-CH}_3$), 1.31 (t, $J = 7.4$ Hz, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COO-CH}_2\text{-CH}_3$), 3.91-3.89 (m, 1H, $P\text{-C-H}$), 6.57 (d, $J = 14$ Hz, 1H, -NH), 3.57 (q, $J = 6.6$ Hz, 2H, -OCH ₂ -CH ₃), 1.12 (t, $J = 7.5$ Hz, 3H, -OCH ₂ -CH ₃). |
| 4e | 8.47-7.11 (m, 9H, Ar-H), 2.91 (d, $J = 17.5$ Hz, 2H, -CH ₂ -CH-COOH), 3.88 (t, $J = 10.2$ Hz, 1H, -CH ₂ -CH-COOH), 10.51 (s, 1H, -CH ₂ -CH-COOH), 4.02-3.91 (m, 1H, $P\text{-C-H}$), 5.38 (d, $J = 7.4$ Hz, 1H, -NH), 3.35 (s, 3H, -OCH ₃). |
| 4f | 8.60-7.05 (m, 9H, Ar-H), 2.90 (d, $J = 17.4$ Hz, 2H, -CH ₂ -CH-COOH), 3.99 (t, $J = 10.1$ Hz, 1H, -CH ₂ -CH-COOH), 10.61 (s, 1H, -CH ₂ -CH-COOH), 4.03-3.92 (m, 1H, $P\text{-C-H}$), 5.39 (d, $J = 7.2$ Hz, 1H, -NH), 3.57 (q, $J = 6.6$ Hz, 2H, -OCH ₂ -CH ₃), 1.12 (t, $J = 7.5$ Hz, 3H, -OCH ₂ -CH ₃). |
| 4g | 8.49-7.37 (m, 4H, Ar-H), 2.08 (s, 3H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 2.44 (t, $J = 7.2$ Hz, 2H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 2.01-1.98 (m, 2H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 3.51 (t, $J = 7.4$ Hz, 1H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 10.53 (s, 1H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 3.91-3.89 (m, 1H, $P\text{-C-H}$), 5.51 (d, $J = 7.5$ Hz, 1H, -NH), 3.40 (s, 3H, -OCH ₃). |
| 4h | 8.29-7.39 (m, 4H, Ar-H), 2.09 (s, 3H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 2.45 (t, $J = 7.3$ Hz, 2H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 2.08-1.95 (m, 2H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 3.52 (t, $J = 7.4$ Hz, 1H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 10.54 (s, 1H, $\text{H}_3\text{CS-CH}_2\text{-CH}_2\text{-CH-COOH}$), 3.92-3.89 (m, 1H, $P\text{-C-H}$), 5.43 (d, $J = 7.4$ Hz, 1H, -NH), 3.56 (q, $J = 6.8$ Hz, 2H, -OCH ₂ -CH ₃), 1.12 (t, $J = 7.6$ Hz, 3H, -OCH ₂ -CH ₃). |

Contd...

| | |
|----|--|
| 4i | 7.52-6.89 (m, 4H, Ar-H), 1.12 (d, $J = 7.2$ Hz, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 2.70-2.68 (m, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.44 (d, $J = 7.3$ Hz, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.74 (s, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.91-3.89 (m, 1H, $P\text{-}\dot{C}\text{-H}$), 6.08 (d, $J = 13.2$ Hz, 1H, NH), 3.74 (s, 3H, -OCH ₃), 3.73 (s, 3H, Ar-OCH ₃). |
| 4j | 7.34-6.15 (m, 4H, Ar-H), 1.14 (d, $J = 7.2$ Hz, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 2.70-2.67 (m, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.35 (d, $J = 7.4$ Hz, 1H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.75 (s, 3H, $(\text{CH}_3)_2\text{-CH-CH-COOCH}_3$), 3.93-3.86 (m, 1H, $P\text{-}\dot{C}\text{-H}$), 6.08 (d, $J = 13.2$ Hz, 1H, -NH), 3.57 (q, $J = 6.6$ Hz, 2H, -OCH ₂ -CH ₃), 1.18 (t, $J = 6.4$ Hz, 3H, -OCH ₂ -CH ₃), 3.74 (s, 3H, Ar-OCH ₃). |
| 4k | 7.34-6.88 (m, 4H, Ar-H), 1.12 (t, $J = 4.2$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.35-1.32 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.76-1.74 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 3.49 (t, $J = 4.7$ Hz, 1H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 4.15 (q, $J = 6.8$ Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.61 (t, $J = 7.4$ Hz, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 4.85-4.83 (m, H, $P\text{-}\dot{C}\text{-H}$), 6.90 (d, $J = 10.7$ Hz, 1H, -NH), 3.34 (s, 3H, -OCH ₃), 3.74 (s, 3H, Ar-OCH ₃). |
| 4l | 7.34-6.89 (m, 4H, Ar-H), 1.11 (t, $J = 4.3$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.34-1.31 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.77-1.75 (m, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 3.48 (t, $J = 4.6$ Hz, 1H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 4.14 (q, $J = 6.9$ Hz, 2H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 1.60 (t, $J = 7.3$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH-COOC}_2\text{H}_5$), 4.86-4.83 (m, H, $P\text{-}\dot{C}\text{-H}$), 6.09 (d, $J = 10.8$ Hz, 1H, -NH), 3.56 (q, $J = 6.7$ Hz, 2H, -OCH ₂ -CH ₃), 1.19 (t, $J = 7.4$ Hz, 3H, -OCH ₂ -CH ₃), 3.75 (s, 3H, Ar-OCH ₃). |
| 4m | 7.34-6.75 (m, 9H, Ar-H), 2.86 (d, $J = 15.3$ Hz, 2H, -CH ₂ -CH-COOH), 3.87 (t, $J = 15.6$ Hz, 1H, -CH ₂ -CH-COOH), 10.90 (s, 1H, -CH ₂ -CH-COOH), 3.98-3.91 (m, 1H, $P\text{-}\dot{C}\text{-H}$), 6.08 (d, $J = 11.3$ Hz, 1H, -NH), 3.37 (s, 3H, -OCH ₃), 3.72 (s, 3H, Ar-OCH ₃). |
| 4n | 7.35-6.75 (m, 9H, Ar-H), 2.89 (d, $J = 15.4$ Hz, 2H, -CH ₂ -CH-COOH), 3.87 (t, $J = 15.2$ Hz, 1H, -CH ₂ -CH-COOH), 10.89 (s, 1H, -CH ₂ -CH-COOH), 3.87-3.80 (m, 1H, $P\text{-}\dot{C}\text{-H}$), 6.09 (d, $J = 11.2$ Hz, 1H, -NH), 3.59 (q, $J = 6.8$ Hz, 2H, -OCH ₂ -CH ₃), 1.17 (t, $J = 7.3$ Hz, 3H, -OCH ₂ -CH ₃), 3.75 (s, 3H, Ar-OCH ₃). |

^aChemical shifts in ppm from TMS and coupling constants J (Hz) in parenthesis ^bRecorded in DMSO-*d*₆.

In their FAB mass spectra²⁵ (Table 4), molecular ions were observed at m/z 409 (28), 394 (43), 385 (31), 402 (17.3) and 421 (9.3) corresponding to the compounds 4e, 4g, 4i, 4l and 4n respectively.

Antibacterial activity

Compounds 4a-n were screened for their antibacterial activity against gram positive bacteria, *Staphylococcus aureus*, *Bacillus faecalis* and gram negative bacteria, *Escherichia coli*, *Klebsiella pneumoniae* by the disc diffusion method^{26,27} in luria bertani nutrient agar medium at two concentrations (75, 100 $\mu\text{g/mL}$) 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 bacteria species was loaded to the discs by using micropipette. The plates were incubated at

35°C and examined for zone of inhibition around each disc after 24 h. Average value is taken out of three experimental results. The results (Table 5) were compared with the activity of the standard antibiotic *Penicillin* (75 µg/mL).

Table 3. ^{13}C NMR data^{a,b} of 4e, 4g, 4j and 4k

| Test compd. | Chemical shifts in ppm |
|-------------|--|
| 4e | 140.5 (C-1), 128.0 (C-2 & C-6), 128.5 (C-3 & C-5), 125.8 (C-4), 37.5 (-CH ₂ -CH-COOH), 63.3 (-CH ₂ -CH-COOH), 177.8 (-CH ₂ -CH-COOH), 48.9 (d, $J = 143$ Hz, 1C, $P-\dot{C}H$), 138.2 (C-1'), 124.9 (C-2'), 148.3 (C-3'), 122.2 (C-4'), 129.2 (C-5'), 135.3 (C-6'), 53.4 (d, $J = 16.8$ Hz, 1C, -OCH ₃). |
| 4g | 16.3 (H ₃ CS-CH ₂ -CH ₂ -CH-COOH), 29.7 (H ₃ CS-CH ₂ -CH ₂ -CH-COOH), 33.5 (H ₃ CS-CH ₂ -CH ₂ -CH-COOH), 63.5 (H ₃ CS-CH ₂ -CH ₂ -CH-COOH), 178 (H ₃ CS-CH ₂ -CH ₂ -CH-COOH), 50.2 (d, $J = 144$ Hz, 1C, $P-\dot{C}H$), 139.1 (C-1'), 122.9 (C-2'), 148.2 (C-3'), 122.9 (C-4'), 129.4 (C-5'), 134.7 (C-6'), 54.5 (d, $J = 16.7$ Hz, 1C, -OCH ₃). |
| 4j | 16.6 ((CH ₃) ₂ -CH-CH-COOCH ₃), 29.0 ((CH ₃) ₂ -CH-CH-COOCH ₃), 60.5 C(CH ₃) ₂ -CH-CH-COOCH ₃ , 172.8 ((CH ₃) ₂ -CH-CH-COOCH ₃), 50.6 (CH ₃) ₂ -CH-CH-COOCH ₃ , 51.8 (d, $J = 145$ Hz, 1C, $P-\dot{C}H$), 129.5 (C-1'), 129.2 (C-2' and C-6'), 113.8 (C-3' and C-5'), 156.4 (C-4'), 58.0 (Ar-OCH ₃), 62.3 (d, $J = 7.0$ Hz, 1C, -OCH ₂ -CH ₃), 14.1 (d, $J = 9.1$ Hz, 1C, -OCH ₂ -CH ₃), 63.1 (d, $J = 7.2$ Hz, 1C, -OCH ₂ -CH ₃), 14.8 (d, $J = 9.2$ Hz, 1C, -OCH ₂ -CH ₃). |
| 4k | 13.9 (CH ₃ -(CH ₂) ₂ -CH-COOC ₂ H ₅), 16.2 (CH ₃ -CH ₂ -CH ₂ -CH-COOC ₂ H ₅), 34.3 (CH ₃ -CH ₂ -CH ₂ -CH-COOC ₂ H ₅), 60.1 (CH ₃ -(CH ₂) ₂ -CH-COOC ₂ H ₅), 172.1 (CH ₃ -(CH ₂) ₂ -CH-COOC ₂ H ₅), 62.7 (CH ₃ -(CH ₂) ₂ -CH-COOC ₂ H ₅), 13.8 (CH ₃ -(CH ₂) ₂ -CH-COO-CH ₂ -CH ₃), 50.1 (d, $J = 144$ Hz, 1C, $P-\dot{C}H$), 129.8 (C-1'), 128.3 (C-2' & C-6'), 113.4 (C-3' & C-5'), 159.2 (C-4'), 63.0 (Ar-OCH ₃), 55 (d, $J = 16.8$ Hz, 1C, -OCH ₃). |

^aChemical shifts in ppm from TMS and coupling constants J (Hz) in parenthesis. ^bRecorded in DMSO-*d*₆.

Table 4. FAB mass spectral data of 4e, 4g, 4j, 4l and 4n

| Compd. | m/z, (%) |
|--------|--|
| 4e | 409 (28.1, M ⁺ +1), 363 (43.7), 335 (9.3), 288 (100), 258 (3.1), 242 (12.5), 83 (28.1). |
| 4g | 394 (42.8, M ⁺ +2), 352 (7.1), 318 (8.9), 207 (5.3), 141 (100). |
| 4j | 385 (31.4, M ⁺ -2), 370 (20), 334 (100), 309 (8.5), 238 (5.7), 105 (12.8). |
| 4l | 402 (17.3, M ⁺ +1), 376 (13), 316 (15.2), 298 (8.6), 257 (100), 121 (21.7). |
| 4n | 421 (9.3, M ⁺), 391 (7.8), 331 (59.3), 307 (100), 178 (5.2), 102 (81.2). |

The compound 4h showed higher activity against gram negative bacteria when compared to that of the standard. 4d showed higher activity against *Escherichia coli* when compared to that of the standard. The compound 4i exhibited more activity, against gram positive bacterium *Staphylococcus aureus* when compared to that of the *penicillin*. Majority of the compounds exhibited promising anti-bacterial activity.

Table 5. Antibacterial activity^a of new α -amino phosphonic acid esters (4a-n)

| Compd. | <i>Staphylococcus aureus</i> | | <i>Bacillus faecalis</i> | | <i>Escherichia coli</i> | | <i>Klebsiella pneumoniae</i> | |
|-------------------------|------------------------------|-------------------------|--------------------------|-------------------------|-------------------------|-------------------------|------------------------------|-------------------------|
| | 75 $\mu\text{g/mL}$ | 100 $\mu\text{g/mL}$ | 75 $\mu\text{g/mL}$ | 100 $\mu\text{g/mL}$ | 75 $\mu\text{g/mL}$ | 100 $\mu\text{g/mL}$ | 75 $\mu\text{g/mL}$ | 100 $\mu\text{g/mL}$ |
| 4a | 6 | 6 | 6 | 10 | 7 | 8 | 8 | 9 |
| 4b | - | - | 6 | 8 | 9 | 10 | 10 | 11 |
| 4c | 9 | 11 | 8 | 10 | - | - | 11 | 12 |
| 4d | - | - | 8 | 10 | 10 | 11 | 9 | 10 |
| 4e | 7 | 9 | - | - | 6 | 8 | 6 | 8 |
| 4f | - | - | 9 | 10 | 8 | 9 | 10 | 11 |
| 4g | 8 | 9 | 8 | 10 | 8 | 10 | 6 | 7 |
| 4h | 7 | 10 | - | - | 10 | 11 | 12 | 13 |
| 4i | 11 | 12 | 8 | 9 | 8 | 10 | 7 | 8 |
| 4j | - | - | 9 | 10 | 8 | 9 | 8 | 9 |
| 4k | 8 | 9 | 7 | 8 | 9 | 10 | 10 | 11 |
| 4l | 6 | 8 | 8 | 10 | 9 | 11 | 9 | 10 |
| 4m | 7 | 8 | 9 | 10 | 8 | 9 | 8 | 9 |
| 4n | 8 | 9 | 8 | 10 | 8 | 10 | 9 | 10 |
| Penicillin ^b | 9 | - | 8 | - | 7 | - | 11 | - |

^aConcentration in ppm ^b Standard antibacterial compound

Conclusion

Synthesis of α -amino phosphonic acid esters is achieved in high yields by one-pot three component reaction. Advantages of this synthetic procedure are the operational simplicity high yields and scope as it is applicable to various aldehydes and a variety of amino acids / esters. A few of these compounds exhibited high anti-bacterial activity than the representative compounds.

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