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Uncatalyzed three component synthesis and anti-microbial activity of α-amino phosphonates

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Abstract

*A series of new α-amino phosphonates have been synthesised via one-pot reaction by reacting 2-hydroxy aniline with aromatic aldehydes and dimethyl phosphite in dry toluene under reflux conditions in the absence of catalyst. All the newly synthesized α-amino phosphonates **(4a-j)** were established by elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and Mass spectrometry. They were found to possess significant anti-microbial activity.*

Keywords: α-amino phosphonates, Kabachnik-Fields reaction, Anti microbial activity.

INTRODUCTION

α -amino phosphonates , due to their structural analogy to α -amino acids, have been the subject of considerable interest. One of the most general, straightforward and widely applied method for the synthesis of α-amino phosphonates is Kabachnik-Fields reaction[1]. It is the most familiar method for the formation of C-P bonds involves nucleophilic addition of organophosphorus compounds containing labile P-H bond to aldehydes and amines in an one-pot three component reaction affording α-amino phosphonates. The main interest in phosphonyl compounds and related derivatives resides in their important biological activity as antibiotics[2], herbicides[3], insecticides[4], fungicides[5], anti viral agents[6], and in their wide range of applications with respect to enzyme inhibition[7] including HIV protease[8]. Hence a large variety of substances can be employed for the synthesis of phosphonyl compounds and their related derivatives[9].

For this purpose, Lewis acids and bases have been conveniently used as promoters of such a phosphonylation[10]. However these methods show a few limitations since these catalysts are expensive or somewhat difficult to prepare. Now a days organic synthesis involving world wide

due to stringent environment and economic regulations. Hence we made an attempt to synthesis α-amino phosphonates in high yields under catalyst free conditions and evaluated their anti microbial activity.

RESULTS AND DISCUSSION

Synthesis of α-amino phosphonates were accomplished by the reaction of equimolar quantities of different aldehydes, 2-hydroxy aniline and dimethyl phosphite in dry toluene at reflux temperature for 6-8h without using any catalyst. The progress of the reaction was monitored by thin-layer chromatography and the reaction was proceeded smoothly and afforded α-amino phosphonates in high yield (75-85%).

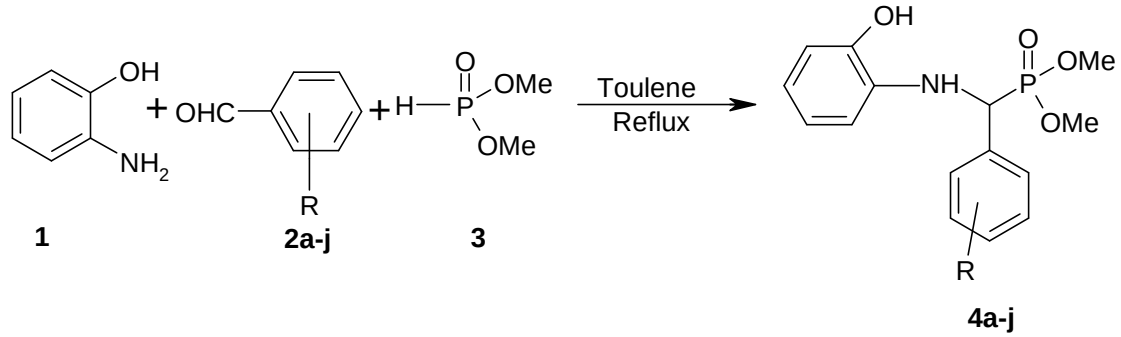
All the compounds (**4a-j**) were readily soluble in polar solvents and melted in the range of 125-275ºC. It is worth mentioning that some of the synthesized α-amino phosphonates are novel compounds and in accessible to preparation by other methods. All the structures of the synthesized α-amino phosphonates (**4a-j**) were established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectroscopy and Mass spectrometry.

All the compounds **(4a-j)** showed absorption bands in the region 3304-3392, 1199-1260 and 746-766 cm^{-1} for –NH, -P=O and P-$C_{(aliphatic)}$ respectively[11]. The aromatic protons of the benzene rings of the α-amino phosphonates **(4a-j)** showed a complex multiplets at δ 6.36-7.91 ppm. The P-C-H proton signal appeared as a multiplet[12] at δ 5.09-5.54ppm due to its coupling with both phosphorus and the N-H proton. The exo cyclic N-H proton signal appeared at δ 4.42-4.82 ppm as a singlet. The methoxy protons of the dimethyl phosphite moiety resonated as two distinct doublets in the range of δ 3.69-3.78 ppm (^{3}J P-H= 10.2-10.5 Hz) and δ 3.44-3.56 ppm (^{3}J P-H= 10.2-10.6 Hz)[13] indicating their magnetic non equivalence. The Phenolic –OH group present in **(1)** give signal at downfield region δ 8.96-9.77 ppm.

The carbon chemical shifts for methine carbon (CH-P) resonated at δ 50.12-54.24ppm (d, J_{p-c} =148.2-151.0 Hz)[14]. The P-OCH_3 groups also gave a doublet at δ 53.72-54.91 ppm ($^{2}J_{P-C}$ = 7.0 Hz)[15]. The ^{31}P-NMR signals[16] appeared in the region δ 23.16-28.30 ppm for these compounds. FAB mass spectra of 4a, 4b, 4c, 4d and 4e showed expected $M^{+\cdot}$ ions and characteristic daughter ions.

Biological Activity

The antibacterial and antifungal activities of the test compounds were evaluated by the disc diffusion method[17] and their effect was compared to the standard antibiotic *Ampicillin* and anti fungal agent *Nystatin.* The anti bacterial role of all the title compounds **(4a-j)** were assayed against the growth of *Escherichia coli* and *Pseudomonas aeuroinosa* at two different concentrations: 100 μg/disc, 250 μg/disc (Table 1). The majority of the compounds exhibited moderate activity against both bacteria. *Ampicillin* was used as a standard reference compound to compare the activities of these compounds. The compounds **(4a-j)** (Table 1) screened for their anti fungal activities against *Aspergillus niger* and *Fusarium moniliforme* along with the standard fungicide *Nystatin.* It is gratifying to observe that all the compounds **(4a-j)** exhibited moderate anti fungal activity compared with that of the reference compound.



1 **2a-j** **3** **4a-j**

Scheme 1

Compd.	R
2a&4a	3'-NO_2
2b&4b	4'-Cl
2c&4c	2'-OH
2d&4d	4'-OCH_3
2e&4e	2'-NO_2

Compd.	R
2f&4f	4'-F
2g&4g	4'-OH
2h&4h	4'-CH_3
2i&4i	4'-NO_2
2j&4j	3'-Cl

Table 1. Antimicrobial Activity of compounds 4a-j

Compound	Zone of inhibition/mm							
	Antibacterial activity				Antifungal activity			
	Escherichia coli		*Pseudomonas aeuroinosa*		*Aspergillus niger*		*Fusarium moniliforme*	
	100 µg/dis	250 µg/disc	100 µg/disc	250µg/disc	100 µg/disc	250µg/disc	100 µg/disc	250µg/disc
4a	8	10	11	15	11	19	12	17
4b	9	12	10	14	12	20	13	16
4c	11	14	7	11	13	18	13	15
4d	9	13	9	13	14	17	13	14
4e	9	11	9	16	19	27	20	29
4f	8	8	5	14	14	17	16	25
4g	7	10	7	9	18	27	19	23
4h	8	9	7	11	21	26	15	27
4i	7	10	6	10	11	18	12	17
4j	8	9	8	12	10	15	12	15
Ampicillin	20	-	21	-	-	-	-	-
Nystatin	-		-	-	25	-	23	-

MATERIALS AND METHODS

General procedure

The chemicals procured were of commercial quality or chemically pure. All solvents were dried, deoxygenated and redistilled before use. The IR spectra (KBr pellets and Nujol mulls) were recorded on a Perkin-Elmer 283 unit. ^{1}H and ^{13}C spectra were recorded on a Bruker spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) with TMS as internal standard. ^{31}P NMR spectra were measured using 85 % H_3PO_4 as external reference. Elemental analyses were recorded on a Carlo Erba 1108 Elemental Analyser, Central Drug Research Institute, Lucknow, India. Mass spectra were recorded on Jeol 5 x 102 DA/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 tube on Mel-temp apparatus, Tempo instruments, India and were uncorrected.

Typical procedure for the synthesis of compound (4a)

A mixture of 2-amino-phenol **1** (0.72 g, 0.005 mol) and 3-nitrobenzaldehyde **2a** (0.005 mol) was stirred in anhydrous toluene (15 mL) at room temperature for 1 h. Dimethylphosphite **3** (0.7 mL, 0.005 mol) in anhydrous toluene (15 mL) was added dropwise. Stirring was continued at room temperature for another 30 min, after which the mixture was heated under reflux for 6-8 h. The reaction was monitored by TLC on silica gel using petroleum ether and ethyl acetate (1:2 v/v). After completion of the reaction, the solvent was removed by rotaevaporator and the resulting residue was purified by column chromatography on silica gel (100-200 mesh, ethyl acetate/hexane) as eluent to afford pure α-amino-phosphonate (**4a**). The other compounds **4b** to **4j** were prepared employing a procedure similar to that described for compound **4a**.

Physical, analytical and spectral data for the compounds (4a-j)

Dimethyl(2-hydroxyphenylamino)(3'-nitrophenyl)methylphosphonite **4a**:
Yield: 78%; M.p: 126-128ºC; IR (KBr): 3375 (-NH), 1260 (P=O), 766 (P-C) cm^{-1}; ^{1}H-NMR (500MHz, DMSO-d_6): δ 9.77 (s, 1H, Ar-OH), 6.50-7.9 (m, 8H, Ar-H), 5.52-5.54 (m, 1H, *J*=15.2Hz, P-C-H), 4.45 (s, 1H, NH). 3.73 (d, 3H, ^{3}J=10.5Hz, P-OCH_3), 3.55ppm (d, 3H, ^{3}J =10.4Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 24.5 ppm; FAB MS: m/z (%): (352, 65%) [MH^+]; Anal. Calcd.(%) for $C_{15}H_{17}N_2O_6P$: C 51.14, H 4.86 N 7.95; Found: C 51.03, H 4.79, N 7.84.

Dimethyl(2-hydroxyphenylamino)(4'-chlorophenyl)methylphosphonite **4b**:
Yield: 75%; M.p: 181-182ºC; IR (KBr): 3304 (-NH), 1239 (P=O), 750 (P-C) cm^{-1}; ^{1}H- NMR (500MHz, DMSO-d_6): δ 9.08 (s, 1H, Ar-OH), 6.43-7.91 (m , 8H, Ar-H), 5.54-5.56 (m, 1H, *J*=15.8Hz, P-C-H), 4.43 (s, 1H, NH), , 3.76 (d, 3H, ^{3}J =10.6Hz, P-OCH_3), 3.54 ppm (d, 3H, ^{3}J =10.3Hz, P-OCH_3); ^{13}C-NMR (125MHz, DMSO-d_6): δ139.86 (C-1), 145.18 (C-2), 118.56 (C-3), 119.91 (C-4), 130.71 (C-5), 115.67 (C-6), 54.24 (C-7), 135.46 (C-1'), 131.70 (C-2'), 148.25 (C-3'), 120.69 (C-4'), 133.64 (C-5'), 134.78 (C-6'), 53.93 (P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 26.60 ppm; FAB MS: m/z (%): (341, 45%) [MH^+]; Anal. Calcd (%) for $C_{15}H_{17}ClNO_4P$: C 52.72, H 5.01, N 4.10; Found: C 52.61, H 4.90, N 4.00.

Dimethyl(2-hydroxyphenylamino)(2'-hydroxyphenyl)methylphosphonite **4c**:
Yield: 82%; M.p: 210-212ºC; IR (KBr): 3314 (-NH), 1230 (P=O), 752 (P-C) cm^{-1}; ^{1}H- NMR (500MHz, DMSO-d_6): δ 9.52 (s, 1H, Ar-OH), 8.96 (s, 1H, Ar-OH), 6.37-7.62 (m, 8H, Ar-H), 4.53 (s, 1H, NH), 5.48-5.51 (m, 1H, *J*=15.8Hz, P-C-H), 3.78 (d, 3H, ^{3}J =10.4Hz, P-OCH_3), 3.56

ppm (d, 3H, ^{3}J =10.3Hz, P-OCH_3); ^{13}C-NMR (125MHz, DMSO-d_6): δ144.43 (C-1), 149.34 (C-2), 118.14 (C-3), 118.96 (C-4), 132.96 (C-5), 115.90 (C-6), 53.82 (C-7), 132.50 (C-1'), 129.42 (C-2'), 128.38 (C-3'), 134.46 (C-4'), 128.38 (C-5'), 129.42(C-6'), 54.91 ppm (P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 27.52 ppm; FAB MS: m/z (%): (323, 58%) $[MH]^+$. Anal. Calcd.(%) for $C_{15}H_{18}NO_5P$: C 55.73, H 5.61, N 4.33; Found: C 52.62, H 5.59, N 4.27.

Dimethyl(2-hydroxyphenylamino)(4'-methoxyphenyl)methylphosphonite **4d**:
Yield: 85%; M.p: 180-182ºC; IR (KBr): 3373 (-NH), 1199 (P=O), 757 (P-C) cm^{-1}; ^{1}H- NMR (500MHz, DMSO-d_6): δ 9.62 (s, 1H, Ar-OH), 6.44-7.36 (m, 8H, Ar-H), 5.09-5.12 (m, 1H, *J*=15.6Hz, P-C-H), 4.48 (s, 1H, NH), , 3.69 (d, 3H, ^{3}J =10.5Hz, P-OCH_3), 3.44 (d, 3H, ^{3}J =10.1Hz, P-OCH_3), 2.50 ppm (s, 3H); ^{13}C-NMR (125MHz, DMSO-d_6): δ 144.45 (C-1), 149.35 (C-2), 117.15 (C-3), 119.97 (C-4), 133.29 (C-5), 114.91 (C-6), 50.22 (C-7), 128.51 (C-1'), 151.58 (C-2'), 116.90 (C-3'), 142.40 (C-4'), 128.44 (C-5'), 136.92(C-6'), 53.96 ppm (P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 25.93 ppm; FAB MS (m/z, %): (337, 48%) $[MH]^+$. Anal. Calcd.(%) for $C_{16}H_{20}NO_5P$: C 56.97, H 5.98, N 4.15; Found: C 56.86, H 5.93, N 4.10.

Dimethyl(2-hydroxyphenylamino)(2'-nitrophenyl)methylphosphonite **4e**:
Yield: 76%; M.p: 272-274ºC; IR (KBr): 3360 (-NH), 1255 (P=O), 746 (P-C) cm^{-1};^{1}H-NMR (500MHz, DMSO-d_6): δ 9.85 (s, 1H, Ar-OH), 6.49-7.8 (m, 8H, Ar-H), 4.82 (s, 1H, NH), 5.48-5.51 (m, 1H, *J*=15.4Hz, P-C-H), 3.74 (d, 3H, ^{3}J =10.6Hz, P-OCH_3), 3.57 ppm (d, 3H, ^{3}J =10.4Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 23.9 ppm; FAB MS m/z (%): (297, 56%) $[MH]^+$. Anal. Calcd.(%) for $C_{15}H_{17}N_2O_6P$: C 51.14, H 4.86, N 7.95; Found: C 51.04, H 4.62, N 7.76.

Dimethyl(2-hydroxyphenylamino)(4'-fluorophenyl)methylphosphonite **4f**:
Yield: 81%; M.p: 186-188ºC; IR (KBr): 3343 (-NH), 1245 (P=O), 761 (P-C) cm^{-1}; ^{1}H-NMR (500MHz, DMSO-d_6): δ 9.76 (s, 1H, Ar-OH), 6.51-7.9 (m, 8H, Ar-H), 5.51-5.53 (m, 1H, *J*=15.2Hz, P-C-H), 4.46 (s, 1H, NH), 3.75 (d, 3H, ^{3}J =10.6Hz, P-OCH_3), 3.54 ppm (d, 3H, ^{3}J =10.5Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 27.04 ppm; Anal. Calcd.(%) for $C_{15}H_{17}FNO_4P$: C 55.39, H 5.27, N 4.31; Found: C 55.28, H 5.21, N 4.25.

Dimethyl(2-hydroxyphenylamino)(4'-hydroxyphenyl)methylphosphonite **4g**:
Yield: 79%; M.p: 218-220ºC; IR (KBr): 3392 (-NH), 1217 (P=O), 751 (P-C) cm^{-1};^{1}H-NMR (500MHz, DMSO-d_6): δ 9.74 (s, 1H, Ar-OH), 6.44-7.89 (m, 8H, Ar-H), 5.53-5.55 (m, 1H, *J*=15.4Hz, P-C-H), 4.42 (s, 1H, NH), 3.78 (d, 3H, ^{3}J =10.7Hz, P-OCH_3), 3.56 ppm (d, 3H, ^{3}J =10.4Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 27.98 ppm; Anal. Calcd.(%) for $C_{15}H_{18}NO_5P$: C 55.73, H 5.61, N 4.33; Found: C 55.62, H 5.55, N, 4.27.

Dimethyl(2-hydroxyphenylamino)(4'-methylphenyl)methylphosphonite **4h**:
Yield: 82%; M.p: 210-212ºC; IR (KBr): 3342 (-NH), 1212 (C-N), 754 (P-C) cm^{-1}; ^{1}H-NMR (500MHz, DMSO-d_6): δ 9.74 (s, 1H, Ar-OH), 6.36-7.64 (m, 8H, Ar-H), 5.39-5.41 (m, 1H, *J*=15.6Hz, P-C-H), 4.52 (s, 1H, NH), 3.75 (d, 3H, ^{3}J =10.4Hz, P-OCH_3), 3.56 ppm (d, 3H, ^{3}J =10.2Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 27.52 ppm; Anal. Calcd.(%) for $C_{16}H_{20}NO_4P$: C 59.81, H 6.27 N 4.36; Found: C 59.70, H 6.22, N 4.31.

Dimethyl(2-hydroxyphenylamino)(4'-nitrophenyl)methylphosphonite **4i**:
Yield: 85%; M.p: 208-210ºC; IR (KBr): 3346 (-NH), 1242 (P=O), 755 (P-C) cm^{-1}; ^{1}H-NMR (500MHz, DMSO-d_6): δ 9.24 (s, 1H, Ar-OH), 6.44-7.36 (m, 8H, Ar-H), 5.46 (m, 1H, *J*=16.2Hz, P-C-H), 4.48 (s, 1H, NH), 3.76 (d, 3H, ^{3}J =10.4Hz, P-OCH_3), 3.54 ppm (d, 3H, ^{3}J =10.4Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 28.04 ppm; Anal. Calcd.(%) for $C_{15}H_{17}N_2O_6P$: C 51.14, H 4.86, N 7.95; Found: C 51.03, H 4.80, N 7.89.

Dimethyl(2-hydroxyphenylamino)(3'-chlorophenyl)methylphosphonite **4j**:
Yield: 88%; M.p: 176-178ºC; IR (KBr): 3353 (-NH), 1215 (P=O), 752 (P-C) cm^{-1}; ^{1}H-NMR (500MHz, DMSO-d_6): δ 9.26 (s, 1H, Ar-OH), 6.37-6.74 (m, 8H, Ar-H), 5.31 (m, 1H, *J*=15.4Hz, P-C-H), 4.81 (s, 1H, NH), 3.72 (d, 3H, ^{3}J =10.4Hz, P-OCH_3), 3.55 ppm (d, 3H, ^{3}J =10.5Hz, P-OCH_3); ^{31}P-NMR (202MHz, DMSO-d_6): δ 28.30 ppm; Anal. Calcd.(%) for $C_{15}H_{17}ClNO_4P$: C 52.72, H 5.01, N 4.10; Found: C, 52.62, H 4.99, N 4.04.

CONCLUSION

In our endeavour, a simple procedure for the synthesis of new α-aminophosphonates (**4a-j)** in high yields by Kabachnik-Fields reaction without using any catalyst is described.

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