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Synthesis of new α-aminophosphonates by one pot reaction using tetramethyl guanidine (TMG)-as a catalyst

E. DADAPEER, S. SUBBA REDDY, V. KOTESWARA RAO and C. NAGA RAJU*

Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502 (India)

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ABSTRACT

The schiff's bases were prepared by reacting vaniline (4-hydroxy-3-methoxy benzaldehyde) with substituted aromatic amines in refluxing toluene. Dialkyl / diaryl phosphite undergoes addition readily with aromatic Schiff's bases to give α-aminophosphonates (Pudovik reaction) in presence of catalytic amount of tetramethyl guanidine. The structures of the title compounds were established by elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P NMR and LCMS mass spectral data. The anti-microbial activities of these compounds were evaluated and they exhibited significant antimicrobial activity.

Key words: Aromatic Schiff's bases, dialkyl/diaryl phosphite, tetramethyl guanidine, anti-microbial activity.

INTRODUCTION

α-Amino-phosphonates are important class of compounds since they are considered to be structural analogues of the corresponding α-aminoacids and find applications as enzyme inhibitors, antibiotics and pharmacological agents.[1] α-Aminophosphonates are key compounds in medicinal chemistry and pharmaceutical science[2]. In addition they have been used as antibacterial[3] and anti-HIV agents[4]. These also act as peptide mimics[5].

Out of available methods, one of the main routes to -aminophosphonates is the Pudovik reaction, consisting of the addition of dialkyl hydrogen phosphites to compounds containing C=N bonds[6]. A direct one pot synthesis of α-aminophosphonates has been reported via the reaction of an aldehyde with an amine and diakyl phosphite[7-9]. In this paper, we report a mild, convenient and simple procedure using a one-pot Pudovik reaction of an aldehyde, primary amine and dialkyl/diphenyl phosphite for the preparation of new α-amino phosphonates using tetramethyl guanidine (TMG) as a catalyst with high yields.

EXPERIMENTAL

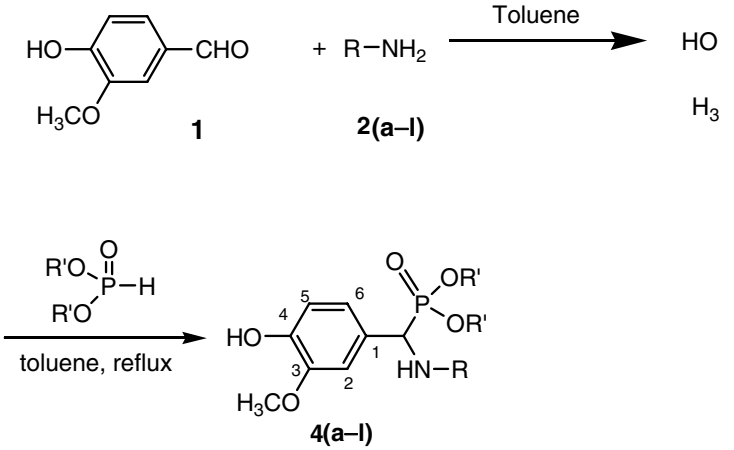
Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Microanalysis was performed at the University of Hyderabad, Hyderabad. IR spectra were recorded as KBr discs on a JASCO FT/IR 5300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF Supercon 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 MHz for ^{31}P. The compounds were dissolved in DMSO-d_6. The ^{1}H and ^{13}C chemical shifts were referenced to TMS. Ortho-phosphoric acid (85%) was used as an external reference for ^{31}P NMR spectra.

RESULTS AND DISCUSSION

The addition of diethyl/dimethyl/diphenyl phosphite to *in situ* prepared aldimines in refluxing toluene in the presence of TMG catalyst resulted in

the formation of new α-aminophosphonates in high yields (76-85%). The aldimines readily reacted with the three phosphites under similar reaction conditions to afford the corresponding.

α-aminophosphonates. In all cases, the reactions proceeded smoothly in refluxing toluene. The reactions, were clean and completed with in 5-6 h. The reaction conditions, were mild and the α-aminophosphonates formed exclusively without



Scheme

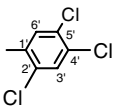
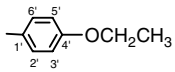
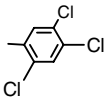
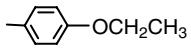
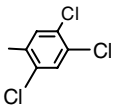
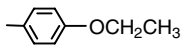
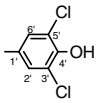
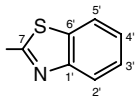
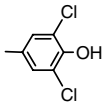
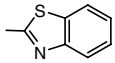
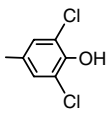
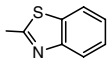
Compound	R	R'	Compound	R	R '
4a		Me	4g		Me
4b		Et	4h		Et
4c		Ph	4i		Ph
4d		Me	4j		Me
4e		Et	4k		Et
4f		Ph	4l		Ph

Table 1: Synthetic, analytical, infrared and ^{31}P NMR spectral data of α-aminophosphonates 4(a-l)

Compound	Molecular formula	M.p/°C	Yield %	Elemental analysis (%) Found (calculated.)			IR (cm^{-1})				(^{31}P)-NMR
				C	H	N	-OH	NH	P=O	P-C (aliphati)	[a,b]ppm
4a	$C_{16}H_{17}O_5Cl_3NP$	155-157	78	43.63 (43.58	3.84 3.88	3.18 3.17)	3366	3327	1260	755	22.66
4b	$C_{18}H_{21}O_5\ Cl_3NP$	160-162	76	46.09 (46.10	4.49 4.51	3.10 2.98)	3420	3368	1273	769	23.10
4c	$C_{26}H_{21}O_5Cl_3NP$	178-180	81	55.19 (55.27	3.78 3.75	2.53 2.48)	3528	3287	1207	763	21.16
4d	$C_{16}H_{18}O_6\ Cl_2NP$	150-152	85	45.54 (45.49	4.09 4.29	3.25 3.31)	3261	2966	1201	748	23.26
4e	$C_{18}H_{22}O_6Cl_2NP$	165-167	80	48.10 (48.00	5.01 4.92	3.01 3.11)	3508	3375	1226	736	21.48
4f	$C_{26}H_{22}O_6Cl_2NP$	170-172	77	57.28 (57.14	3.99 4.06	2.73 2.56)	3514	3371	1209	736	21.43
4g	$C_{18}H_{24}O_6NP$	130-132	82	56.57 (56.66	6.20 6.34	3.52 3.67)	3364	3294	1228	756	24.66
4h	$C_{20}H_{28}O_6NP$	140-142	78	58.68 (58.67	6.91 6.89	3.31 3.42)	3460	3368	1234	736	22.29
4i	$C_{28}H_{28}O_6NP$	180-182	76	66.58 (66.53	5.61 5.58	2.69 2.77)	3480	3280	1228	740	21.60
4j	$C_{17}H_{19}O_5N_2PS$	120-122	80	51.66 (51.77	4.86 4.86	6.97 7.10)	3327	3100	1203	752	22.45
4k	$C_{19}H_{23}O_5N_2PS$	145-147	77	54.13 (54.02	5.55 5.49	6.49 6.63)	3395	3202	1217	748	20.19
4l	$C_{27}H_{23}O_5\ N_2PS$	162-164	79	62.68 (62.54	4.46 4.47	5.29 5.40)	3394	3270	1215	754	22.19

[a] Recorded in $CDCl_3$ [b] Chemical shifts in ppm from 85% ortho-phosphoric acid.

Table 2: ^{1}H NMR Spectral data of α-aminophosphonates (4a-l)

Compd.	Ar-H	P-C-H	N-H	P-O-CH_3	P-OCH_2CH_3	P-OCH_2CH_3	Ar-O-CH_3	Ar-O-CH_2CH_3	Ar-O-CH_2CH_3	Ar-OH
4a	6.66-7.11 (m,5H)	5.31 (m, 1H)	3.49 (s, 1H)	3.87(d, *J*= 9.8Hz, 6H)	-	-	2.68 (s,3H)	-	-	9.23 (s, 1H)
4b	6.50-7.33 (m,5H)	5.12 (m, 1H)	3.60 (s, 1H)	-	3.82 (m,4H)	1.06 (t,6H)	2.40 (s,3H)	-	-	9.10 (s, 1H)
4c	6.61-7.16 (m, 15H)	4.74 (m, 1H)	3.48 (s, 1H)	-	-	-	2.17 (s,3H)	-	-	8.00 (s, 1H)
4d	6.38-7.26 (m, 5H)	4.72 (m, 1H)	3.12 (s, 1H)	3.40 (d, *J*= 12.0 Hz, 6H)	-	-	2.59 (s,3H)	-	-	9.55 (s, 1H)
4e	6.53-6.94 (m, 5H)	4.57 (m, 1H)	3.69 (s, 1H)	-	3.99 (m, 4H)	1.09 (t,6H)	2.17 (s,3H)	-	-	8.65 (s, 1H)
4f	6.45-7.2 (m, 15H)	4.01 (m, 1H)	3.08 (s, 1H)	-	-	-	2.49 (s,3H)	-	-	8.44 (s, 1H)
4g	6.51-6.86 (m, 7H)	4.80 (m, 1H)	3.52 (s, 1H)	3.41 (d, *J*= 13.0 Hz, 6H)	-	-	2.51 (s,3H)	3.35 (m,2H)	1.18 (t,3H)	8.20 (s, 1H)
4h	6.51-6.86 (m, 7H)	4.65 (m, 1H)	3.84 (s, 1H)	-	4.53 (m, 4H)	1.108 (t, 6H)	2.16 (s,3H)	3.84 (m,2H)	1.31 (t,3H)	9.01 (s, 1H)
4i	6.53-7.8 (m, 17H)	4.95 (m, 1H)	3.82 (s, 1H)	-	-	-	2.43 (s,3H)	3.88 (m,2H)	1.29 (t,3H)	8.91 (s, 1H)
4j	6.83-7.55 (m, 7H)	5.40 (m, 1H)	3.73 (s, 1H)	3.80 (d, *J*= 9.7 Hz, 6H)	-	-	2.17 (s,3H)	-	-	9.68 (s, 1H)
4k	6.70-7.50 (m, 7H)	5.58 (m, 1H)	3.34 (s, 1H)	-	3.98 (m, 4H)	1.12 (t,6H)	2.50 (s,3H)	-	-	8.84 (s, 1H)
4l	6.45-7.58 (m,17H)	5.01 (m, 1H)	3.49 (s, 1H)	-	-	-	2.48 (s,3H)	-	-	9.03 (s, 1H)

Table 3: ^{13}C NMR Spectral data of α-aminophosphonates (4a-l)

Carbonatom	Compounds											
	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l
C-1	128.91	129.01	129.83	128.18	126.75	129.49	126.87	127.55	135.82	129.03	130.75	129.87
C-2	112.33	112.55	112.31	110.56	110.23	113.93	110.52	110.47	110.99	110.28	112.49	112.01
C-3	151.32	151.23	151.02	146.94	147.10	147.28	151.88	152.05	151.30	151.03	151.68	150.98
C-4	142.77	143.89	142.89	145.94	145.81	143.88	145.81	145.65	144.02	145.60	146.31	143.72
C-5	116.88	115.89	115.99	114.53	114.69	115.29	115.42	115.62	115.90	118.96	117.77	116.82
C-6	120.66	120.72	120.84	120.58	121.04	120.63	120.71	121.00	120.01	120.03	120.85	120.59
C-7	-	-	-	-	-	-	-	-	-	167.33	166.50	170.82
C-1^{1}	143.44	142.99	143.10	142.91	140.77	143.10	139.97	140.38	139.33	125.66	126.31	124.17
C-2^{1}	121.82	121.52	121.39	114.22	114.08	114.84	115.25	114.62	114.00	121.73	121.33	121.35
C-3^{1}	132.88	132.60	132.98	126.31	126.71	126.18	115.42	115.37	115.29	126.07	125.59	126.00
C-4^{1}	123.10	123.22	123.37	139.50	140.47	140.16	147.24	147.08	145.82	125.01	125.44	124.97
C-5^{1}	132.10	132.32	132.08	126.31	126.71	125.16	115.42	115.37	115.29	120.88	121.00	121.23
C-6^{1}	117.82	616.54	118.98	114.22	114.08	115.13	115.25	114.62	114.00	150.09	147.37	148.89
Ar-O$\underline{C}H_3$	56.04	56.18	56.06	56.04	56.00	56.65	55.82	55.90	56.50	56.11	54.99	55.92
Ar-O-$\underline{C}H_2CH_3$	-	-	-	-	-	-	63.77	64.00	64.32	-	-	-
Ar-O-$CH_2\underline{C}H_3$	-	-	-	-	-	-	14.77	14.97	14.79	-	-	-
P-O-$\underline{C}H_3$	53.02 (d, (d, *J*=7.4 Hz)	-	-	53.16 (d, *J*=7.4 Hz)	-	-	-	53.56(d, *J*=7.3 Hz)	-	-	55.9 *J*=7.3 Hz)	
P-O-$\underline{C}H_2CH_3$	-	62.43(d, *J*=6.8 Hz)	-	-	63.39(d, *J*=6.7 Hz)	-	-	63.22(d, *J*=6.9 Hz)	-	-	62.62 (d, *J*=6.8 Hz)	-
P-O-$CH_2\underline{C}H_3$	-	15.00 (d, *J*=12.6 Hz)	-	-	16.28(d, *J*=12.7 Hz)	-	-	16.23 (d, *J*=12.8 Hz)	-	-	16.30 (d, *J*=12.6 Hz)	-
N-$\underline{C}$-C/P	55.98	56.03	56.01	55.40	54.82	55.72	55.82	55.34	54.72	55.90	55.73	55.61
P-O-Ar Carbon												
C-1^{11}	-	-	149.82	-	-	147.26	-	-	150.30	-	-	149.33
C-2^{11}&6^{11}	-	-	115.02	-	-	115.27	-	-	115.80	-	-	115.20
C-3^{11}&5^{11}	-	-	130.19	-	-	129.41	-	-	130.01	-	-	129.87
C-4^{11}	-	-	121.39	-	-	122.47	-	-	121.86	-	-	121.35

noticeable formation of undesired side products. The important feature of this reaction is the robustness of functional groups, such as chloro, ethoxy, and hydroxy groups under the reaction conditions. T.M.G. is found to be more effective than other catalysts in terms of yields, reaction time and cost of the catalyst[10].

The synthetic, analytical, IR and ^{31}P NMR spectral data of compounds (4a-l) are given in Table 1. The IR spectral data showed P=O stretching frequencies in the region 1201-1260 $cm.^{-1}$ Characteristic absorption bands for P-$C_{(aliphatic)}$ and N-H stretching vibrations were observed in the regions 736-769 and 2928 – 3368 cm^{-1} respectively.[11]

The ^{31}P NMR signals appeared in the range of 20.19 – 24.66 ppm[12].

^{1}H NMR Spectral data

The proton NMR spectral data of 4a-l are furnished in Table 2. The aromatic protons showed a complex multiplet in the region δ 6.38-7.80. The chemical shift of the proton of methyne (P-C-H) resonated as multiplet in the region δ 4.01- 5.88 due to its coupling with ^{31}P and the neighboring proton of N-H[13].

Aromatic –OH proton signal appeared as a singlet in the range of δ 8.00 - 9.68 which was confirmed by D_2O exchange experiment. The N-H proton signal of the compounds appeared at δ 3.12-3.82 as a singlet which was confirmed by D_20

Table 4: Mass spectral data of α-aminophosphonates 4c, 4d, 4h and 4k

Compound	m/z (% relative abundance)
4c	566 ($M^{+\cdot}$, 100), 530 (1), 479 (5), 444 (15), 360(6), 338 (10), 259 (8), 40(2).
4d	423 ($M^{+\cdot}$, 100), 405 (5), 389 (20), 376 (5), 301 (10), 270 (11), 239 (10), 181 (10), 139 (5).
4h	410 ($M^{+\cdot}$, 50), 391 (20), 363 (2), 316 (10), 273 (98), 272 (100), 272 (100), 151 (5), 138 (10).
4k	423 ($M^{+\cdot}$, 100), 37.8 (5), 299 (10), 285 (40), 167 (4), 151 (30), 137 (2), 121 (2), 106 (5).

Table 5: Antibacterial activity of α-aminophosphonates 4a-l

Compound	Zone of inhibition /mm					
	***Escherichia coli*μg/disc**			***Staphylococcus aureus*μg/disc**		
	100[a]	50[a]	25[a]	100[a]	50[a]	25[a]
4a	14	8	4	11	8	6
4b	10	7	5	8	6	-
4c	13	8	4	10	8	6
4d	12	6	6	6	5	4
4e	15	12	8	12	9	5
4f	15	12	7	15	10	8
4g	9	8	4	7	4	
4h	10	6	5	10	8	5
4i	10	5	3	12	11	8
4j	12	8	6	11	8	5
4k	8	5	5	-	-	-
4l	8	7	6	9	7	5
Penicillin[b]	12	8	-	9	6	-

[a] In DMF concentration in ppm. [b] Reference compound

exchange experiment. The P-O-CH_3 proton signal appeared as a doublet in the region δ 3.40-3.87 (d, *J* = 9.7-13.00 Hz)[14]. The proton signal of P-O*CH*$_2$ *CH*$_3$ showed a multiplet and P-O*CH*$_2$ *CH*$_3$ gave a triplet in the region δ 3.82-3.99 and δ1.06-1.12 respectively. The proton signal of Ar-O-$\underline{CH}_3$ appeared as a singlet in the region δ 2.16 - 2.68. The Ar-O$\underline{CH}_2CH_3$ proton signal appeared as multiplet at δ 3.35-3.88 and Ar-OCH$_2\underline{CH}_3$ proton resonated as triplet at δ 1.18 - 1.31.

Carbon-13 NMR spectra

The ^{13}C NMR spectral data of 4a-l are presented in Table 3. The carbon chemical shifts for Ar-O-CH_3 is observed in the region at δ 54.99 – 56.65. The carbon chemical shifts for Ar-O-$\underline{CH}_2CH_3$ and Ar-O-CH$_2\underline{CH}_3$ are observed in the region at δ 63.77-64.32 and 14.77-14.79 respectively. The carbon chemical shift for P-O-$\underline{CH}_3$ is observed as doublet in the region at δ 53.02 – 54.90 (d, *J* = 7.3-7.4 Hz). The carbon chemical shifts for P-O-$\underline{CH}_2CH_3$ and P-O-CH$_2\underline{CH}_3$ are observed as doublet in the region at δ 62.43-63.39 (d, *J* = 6.7-6.9 Hz) and 15.00-16.30 (d, *J* = 12.62-12.8 Hz) respectively.

The chemical shifts for N-$\underline{C}$-C/P is observed in the region at δ 54.72-56.03 and the aromatic carbons in the title compounds are observed in the expected regions[15,16a,b,c,17].

Antimicrobial Activity

Antibacterial activity

Antibacterial activity of all the title compounds 4a-l was assayed[18] against the growth of *Staphylococcus aureus* (gram +Ve) and *Escherichia coli* (gram -Ve) at three different concentrations (100, 50, 25 ppm) (Table 5). Highlight is that majority of the compounds exhibited high activity against both the bacteria and two compounds 4e and 4f were more effective than that of the standard compound.

Penicillin was tested as a standard reference to compare the activity of these compounds.

Antifungal activity

The Compounds 4a-l were screened for their antifungal activity (Table 6) against *Aspergillus niger* and *Helminthosporium oryzae* species along with standard fungicide Griseofulvin at three different concentrations (100, 50, 25 ppm).[19]

Table 6: Antifungal activity of α-aminophosphonic acid esters 4a-l

Compound	Zone of inhibition / mm					
	*Aspergillus niger*µg/disc^{-1}			*Helminthosporium oryzae*µg/disc^{-1}		
	100[a]	50[a]	25[a]	100[a]	50[a]	25[a]
4a	10	7	5	11	6	5
4b	11	8	4	11	9	5
4c	13	9	6	13	10	7
4d	12	10	8	15	9	4
4e	10	7	5	12	8	7
4f	9	5	3	13	11	9
4g	10	6	4	9	8	-
4h	9	8	6	11	9	5
4i	14	10	9	13	12	8
4j	8	9	6	9	7	4
4k	13	9	8	10	9	7
4l	13	10	8	11	9	5
Griseofulvin[b]	12	10	5	12	10	5

[a] In DMF concentration in ppm. [b] Reference compound

It is gratifying to observe that all the compounds 4a-l were exhibited moderate to high antifungal activity when compared to that of the reference compound. The highlight is that majority of the compounds exhibited high activity against fungi and the compound 4d is more effective against *H. oryzae* and 4i showed higher activity against *A. niger* when compared to that of the standard.

CONCLUSIONS

In conclusion, we have developed a convenient method for the synthesis of new α-aminophosphonates by reacting various aryl amines and vaniline with diethyl, dimethyl and diphenyl phosphites involving Pudovik reaction using tetramethyl guanidine as a catalyst in high yields. These compounds exhibited significant antibacterial and antifungal activity.

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