S. Afr. J. Chem., 2007, **60**, 125–128,
<http://journals.sabinet.co.za/sajchem/>.

Tetramethylguanidine (TMG)-catalysed Synthesis of α-Aminophosphonates by a One-pot Reaction

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Received 19 April 2007; revised 6 September 2007; accepted 2 November 2007.

ABSTRACT

Aldimines (Schiff's bases) undergo nucleophilic addition with diethyl/dimethyl/diphenylphosphite (Pudovik reaction) in the presence of a catalytic amount of tetramethylguanidine (TMG) at ambient temperature to afford the corresponding α-aminophosphonates in high yields. The Schiff's bases were prepared by reacting cinnamaldehyde with substituted amines in refluxing absolute alcohol. The structures of the title compounds were established by elemental analysis and IR, ^{1}H, ^{13}C, ^{31}P NMR and FAB mass spectral data. The antimicrobial activities of these compounds were evaluated and they exhibited significant antimicrobial activity.

KEYWORDS

Imines, α-aminophosphonates, tetramethylguanidine (TMG), dialkyl- and arylphosphites, antimicrobial activity.

1. Introduction

One of the main routes to α-aminophosphonates is the Pudovik reaction, consisting of the addition of dialkyl hydrogen phosphites to compounds containing C=N bonds.[1] α-Aminophosphonates are an 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.[2] As building blocks of peptides, α-aminophosphonic acids seem to be even closer analogues of the α-aminocarboxylic acids than their α-aminophosphonic counterparts, due to their monobasic/acidic character, and the higher stability of the P-C bond of phosphonic acids compared with the P-O.[3] A direct one-pot synthesis of α-aminophosphonates has been reported via the reaction of an aldehyde with an amine and dialkyl phosphite.[4–7] In this paper, we report a mild, convenient and simple procedure using a one-pot Pudovik reaction of an aldehyde, primary amine and dialkylphosphite/diphenylphosphite for the preparation of novel α-aminophosphonates in the presence of tetramethylguanidine (TMG) as a catalyst with high yields.

2. Results and Discussion

The addition of diethyl/dimethyl/diphenylphosphite to aldimines (prepared) in the presence of tetramethylguanidine in refluxing absolute ethanol resulted in the formation of novel α-aminophosphonates in high yields (75–90%). 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 ethanol. The reactions were clean and completed within 4–5 h. The reaction conditions were very mild and the α-aminophosphonates formed exclusively without the noticeable formation of undesired side-products. The present method does not require any additives or promoters for the reaction to proceed. Another important feature of this reaction is the robustness of functional groups, such as chloro and hydroxyl groups under the reaction conditions. Tetramethylguanidine[8] is found to be more effective than other catalysts in terms of yields, reaction time and cost of the catalyst.

The synthetic and analytical data of compounds **3a–l** are given in Table 1. Compounds **3a–l** exhibited P=O stretching frequencies in the region 1205–1256 cm^{-1}. Characteristic absorption bands (Table 1) for P-C$_{(aliphatic)}$ and N-H stretching vibrations were observed in the regions 733–787 and 3372–3448 cm^{-1}, respectively.[9]

The proton NMR spectral data of **3a–l** are furnished in Table 2. The aromatic protons showed a complex multiplet in the region δ 6.87–7.42 ppm. The P-C*-H proton signal appeared as a multiplet[10] in the region δ 4.32–4.52 ppm, due to its coupling with ^{31}P and the neighboring proton of N-H. The N-H proton gave a singlet signal in the region δ 4.82–4.96 ppm. The proton signal of POC*H*$_2$CH$_3$ showed a multiplet and POCH$_2$C*H*$_3$ gave a triplet in the regions δ 3.33–3.56 ppm and δ 1.18–1.24 ppm, respectively.[10a]

The ^{13}C NMR spectral data for a few members (**3a**, **e**, **i** and **l**) are presented in Table 3. The ^{13}C chemical shifts for P-C*-H appeared in the region δ 37.02–39.77 ppm as a doublet[10b] (d, ^1J = 151.8–153.0 Hz, 1C). The diethyl phosphite moiety gave two doublets[10c] one at δ 61.14 ppm (J = 6.9 Hz, P-O-CH$_2$) and the other at δ 15.08 ppm (d, J = 12.6 Hz, P-OCH$_2$-CH$_3$).

^{31}P NMR signals for **3a–l** appeared in the region δ 21.01–26.88 ppm.[11]

3. Experimental

Melting points were determined in open capillary tubes on a Mel-temp apparatus and were uncorrected. Microanalyses were performed at the Indian Institute of Science, Bangalore, and the Central Drug Research Institute, Lucknow. IR spectra were recorded as KBr discs on a Nicolet 380 FT-IR spectrophotometer in the Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 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 tetramethylsilane and the ^{31}P chemical shifts to 85% H_3PO_4. Mass spectra were recorded on a Jeol SX 102 DA/600 mass

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Table 1 Physical, elemental, IR and ^{31}P NMR spectral data for compounds **3a–l**.

Compound	Molecular formula	M.p./°C	Yield/%	Elemental analysis % Found (calcd.)			IR $\bar{\nu}$/cm^{-1}			^{31}P NMR
				C	H	N	NH	P=O	P-C$_{ali}$	δ/ppm
3a	$C_{19}H_{22}NO_3ClP$	210–212	87	60.20 (60.24	5.82 5.85	3.65 3.69)	3410	1256	736	24.83
3b	$C_{17}H_{18}NO_3ClP$	260–262	90	58.19 (58.21	5.13 5.17	3.94 3.99)	3448	1205	746	26.78
3c	$C_{27}H_{22}NO_3ClP$	280–282	85	68.21 (68.28	4.61 4.66	2.89 2.94)	3440	1229	733	21.01
3d	$C_{18}H_{23}N_2O_3P$	274–276	79	62.32 (62.41	6.62 6.69	8.04 8.08)	3408	1220	741	25.44
3e	$C_{16}H_{19}N_2O_3P$	235–237	80	62.00 (62.04	6.14 6.18	9.00 9.04)	3404	1214	736	23.22
3f	$C_{26}H_{23}N_2O_3P$	244–246	75	70.52 (70.58	5.20 5.23	6.29 6.33)	3440	1222	740	24.95
3g	$C_{17}H_{23}N_2O_4P$	265–267	84	58.23 (58.28	8.01 8.04)	7.94 7.99)	3412	1210	745	23.76
3h	$C_{15}H_{19}N_2O_4P$	252–254	89	55.85 (55.90	5.91 5.94	8.63 8.69)	3372	1236	756	24.85
3i	$C_{25}H_{23}N_2O_4P$	236–238	90	67.21 (67.255	5.1 5.19	6.25 6.27)	3390	1256	757	23.52
3j	$C_{19}H_{24}NO_4P$	222–224	78	63.10 (63.15	6.62 6.69	3.84 3.87)	3423	1239	743	25.10
3k	$C_{17}H_{20}NO_4P$	276–278	69	61.19 (61.25	6.00 6.04	4.18 4.20)	3389	1246	787	26.74
3l	$C_{27}H_{24}NO_4P$	229–231	82	70.84 (70.89	5.25 5.28	3.02 3.06)	3390	1238	739	26.88

Table 2 ^{1}H NMR spectral data [a] for compounds **3a–l**.

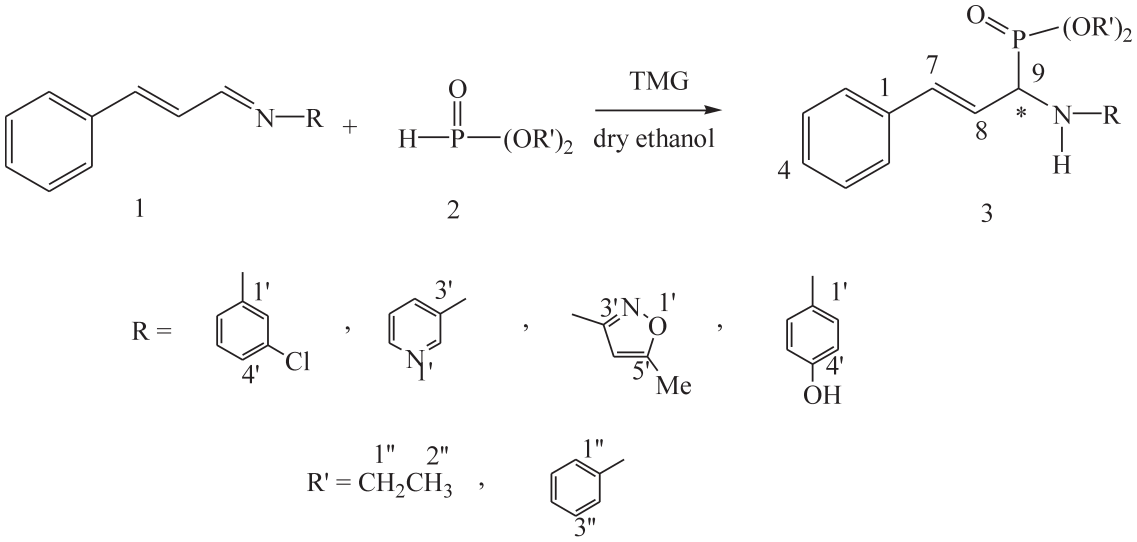
Compound	Ar-H	P-C*H	NH (s, 1H)	POC*H*$_2$CH$_3$/C*H*$_3$	POCH$_2$C*H*$_3$	Ph-C*H* = CH [b]	Ph-CH = C*H* [b]	Other H
3a	6.92–7.31 (m, 9H)	4.38–4.42 (m, 1H)	4.82	3.42–3.47 (m, 2H)	1.24 (t, 3H)	6.48 (d, J = 13.8)	6.17 (d, J = 13.3)	–
3b	6.97–7.42 (m, 9H)	4.36–4.43 (m, 1H)	4.91	3.27 (s, 3H)	–	6.44 (d, J = 14.2)	6.08 (d, J = 13.5)	–
3c	6.89–7.28 (m,19H)	4.38–4.44 (m, 1H)	4.89	–	–	6.42 (d, J = 14.3)	6.02 (d, J = 13.4)	–
3d	6.96–7.31 (m, 9H)	4.48–4.41 (m, 1H)	4.84	3.38–3.46 (m, 2H)	1.22 (t, 3H)	6.53 (d, J = 14.1)	6.19 (d, J = 13.6)	–
3e	6.94–7.28 (m, 9H)	4.32–4.39 (m, 1H)	4.97	3.41 (s, 3H)	–	6.48 (d, J = 13.9)	6.12 (d, J = 13.5)	–
3f	6.87–7.29 (m,19H)	4.47–4.41 (m, 1H)	4.92	–	–	6.46 (d, J = 14.2)	6.17 (d, J = 13.3)	–
3g	6.95–7.31 (m, 5H)	4.41–4.49 (m, 1H)	4.96	3.44–3.51 (m, 2H)	1.19 (t, 3H)	6.41 (d, J = 13.8)	6.15 (d, J = 13.7)	2.39 (s, 3H) (N-O-C-CH$_3$)
3h	6.98–7.36 (m, 5H)	4.39–4.44 (m, 1H)	4.86	3.47 (s, 3H)	–	6.47 (d, J = 14.4)	6.18 (d, J = 13.4)	2.41 (s, 3H) (N-O-C-CH$_3$)
3i	6.92–7.34 (m,15H)	4.41–4.48 (m, 1H)	4.89	–	–	6.44 (d, J = 14.1)	6.13 (d, J = 13.2)	2.44 (s, 3H) (N-O-C-CH$_3$)
3j	6.94–7.28 (m, 9H)	4.44–4.51 (m, 1H)	4.86	3.48–3.56 (m, 2H)	1.18 (t, 3H)	6.43 (d, J = 13.9)	6.14 (d, J = 13.6)	9.05 (br s) (OH)
3k	6.96–7.29 (m, 9H)	4.46–4.52 (m, 1H)	4.94	3.52 (s, 3H)	–	6.49 (d, J = 14.5)	6.19 (d, J = 13.3)	9.08 (br s) (OH)
3l	6.92–7.26 (m,19H)	4.39–4.43 (m, 1H)	4.87	–	–	6.51 (d, J = 14.2)	6.14 (d, J = 13.5)	9.08 (br s) (OH)

[a] Recorded in DMSO-d_6; δ in ppm.
[b] Coupling constants in Hz in parentheses.

Table 3 ^{13}C NMR spectral data[a] for the compounds **3a–l**.

Compound	δ/ppm
3a	126.2 (C-1), 129.5 (C-2), 129.2 (C-3), 129.5 (C-4), 126.2 (C-5), 135.9 (C-6), 129.5 (C-7), 123.2 (C-8), 39.7 (C*-9, d, J = 151.4 Hz), 137.0 (C-1′), 128.5 (C-2′), 134.8 (C-3′), 125.6 (C-4′), 130.0 (C-5′), 127.5 (C-6′), 61.1 (C-1′′, d, J = 6.8 Hz), 15.0 (C-2′′, d, J = 6.8 Hz)
3e	126.4 (C-1), 128.8 (C-2), 128.6 (C-3), 128.8 (C-4), 126.4 (C-5), 137.4 (C-6), 129.6 (C-7), 121.4 (C-8), 37.0 (C*-9, d, J = 150.6 Hz), 151.6 (C-2′),), 144.5 (C-3′), 135.0 (C-4′), 125.8 (C-5′), 152.8 (C-6′),55.4 (C-1′′, d, J = 6.5 Hz)
3i	124.2 (C-1), 126.7 (C-2), 126.4 (C-3), 126.8 (C-4), 124.2 (C-5), 135.1 (C-6), 128.0 (C-7), 121.5 (C-8), 37.1 (C*-9, d, J = 151.2 Hz), 158.0 (C-3′), 128.0 (C-4′), 169.0 (C-5′), 13.1 (C-4′, CH_3), 149.0 (C-1′′), 129.1 (C-2′′ & 6′′), 128.8 (C-3′′& 5′′), 125.6 (C-4′′)
3l	126.2 (C-1), 128.8 (C-2), 128.4 (C-3), 128.8 (C-4), 126.3 (C-5), 134.9 (C-6), 129.7 (C-7), 122.9 (C-8), 39.7 (C*-9, d, J = 151.8 Hz), 118.1 (C-2′ & 6′), 116.2 (C-3′& 5′), 147.3 (C-4′),138.4 (C-1′′), 129.0 (C-2′′ & 6′′), 128.0 (C-3′′& 5′′), 126.0 (C-4′′)

[a] Recorded in DMSO-d_6; coupling constants in parentheses.



Compound	R	R'	Compound	R	R'
3a	3-Cl-C_6H_4	C_2H_5	3g	5-CH_3-C_3HNO	C_2H_5
3b	3-Cl-C_6H_4	CH_3	3h	5-CH_3-C_3HNO	CH_3
3c	3-Cl-C_6H_4	C_6H_5	3i	5-CH_3-C_3HNO	C_6H_5
3d	3-C_5H_4N	C_2H_5	3j	4-OH-C_6H_4	C_2H_5
3e	3-C_5H_4N	CH_3	3k	4-OH-C_6H_4	CH_3
3f	3-C_5H_4N	C_6H_5	3l	4-OH-C_6H_4	C_6H_5

Scheme 1

spectrometer using argon/xenon (6 kV, 10 mA) as the FAB carrier gas.

3.1. General Procedure

A mixture of aldimine (**1**) (0.005 mol), which was generated *in situ* by reacting the corresponding amine with cinnamaldehyde, diethyl/dimethyl/diphenylphosphite (**2**, 0.005 mol) and tetramethylguanidine (10 mol %) in dry ethanol (40 mL) was stirred at reflux temperature for an optimum time (4–5 h) (see Scheme 1). After completion of the reaction, as identified by TLC (silica gel) using n-hexane and ethyl acetate (8:2 by volume) as a mobile phase, the solvent was removed in a rota-evaporator and the crude product was purified by column chromatography on silica-gel (60–120 mesh) using n-hexane and ethyl acetate (8:2) as an eluent to afford the α-aminophosphonates (**3a–l**).

3.2. Antimicrobial Activity

The antibacterial activities of all the title compounds (**3a–l**) were assayed[12] against the grout of *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) at three different concentrations, namely 500, 250 and 100 ppm (Table 4). Note that the majority of the compounds exhibited high activity against both bacteria, and three compounds, **3f**, **3c** and **3h** were equally effective as the standard. Penicillin was used as a standard reference compound to compare the activities of these compounds.

3.3. Antifungal Activity

The compounds **3a–l** (Table 5) were screened for their antifungal activities against *Aspergillus niger* and *Helminthosporium oryzae* along with the standard fungicide Griseofulvin. The disc diffusion method[13] was followed for screening the compounds at three different concentrations (500, 250 and 100 ppm).

It is gratifying to observe that all the compounds **3a–l** exhibited significant antifungal activity compared with that of the reference compound.

Acknowledgements

The authors express their thanks to Prof C.D. Reddy, Department of Chemistry, Sri Venkateswara University, Tirupati, for his

Table 4 Antibacterial activities of α-aminophosphonic acid esters **3a–l**.

Compound	Zone of inhibition/mm					
	Escherichia coli			*Staphylococcus aureus*		
	500 ppm	250 ppm	100 ppm	500 ppm	250 ppm	100 ppm
3a	24	11	6	26	11	7
3b	23	10	4	25	11	6
3c	24	12	5	21	10	6
3d	22	10	5	22	9	5
3e	22	11	6	26	12	6
3f	21	13	7	21	10	5
3g	23	10	5	20	10	6
3h	20	12	6	24	12	7
3i	21	10	5	23	13	6
3j	25	9	4	22	9	4
3k	24	9	4	20	10	5
3l	22	10	5	21	12	6
Penicillin	20	12	5	22	14	8

Table 5 Antifungal activities of α-aminophosphonic acid esters **3a–l**.

Compound	Zone of inhibition/mm					
	Aspergillus niger			*Helminthosporium oryzae*		
	500 ppm	250 ppm	100 ppm	500 ppm	250 ppm	100 ppm
3a	21	12	5	19	10	7
3b	19	13	6	19	9	6
3c	19	10	5	18	8	5
3d	20	12	4	19	8	5
3e	18	14	4	20	10	5
3f	24	13	5	17	9	6
3g	21	12	5	20	12	7
3h	22	12	3	19	11	6
3i	19	13	4	16	9	6
3j	20	12	6	17	8	6
3k	24	14	5	19	12	6
3l	23	13	4	18	11	5
Griseofulvin	22	16	5	20	18	8

helpful guidance and discussions and to Dr K. Vijayalakshmi, Department of Applied Microbiology, Sri Padmavathi Mahila University, India, for assistance with the biological studies. We extend our thanks to the Director, CDRI, Lucknow, and SIF, IISC, Bangalore, for providing elemental and spectral data.

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