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TMG catalysed one pot-synthesis of α-Aminophosphonates

Bitragunta Siva Kumar

Department of Chemistry, Vel Tech Technical University, Avadi, Chennai, T. N., India

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ABSTRACT

*α-Aminophosphonates (**4a-j**) were synthesized in one-pot simultaneous reaction of p-anisidine(**1**), dimethylphosphite(**3**), and different aromatic aldehydes (**2a-j**) by Kabachnik–Fields reaction in the presence of tetramethylguanidine(TMG) (10 mole%) as catalyst in toluene at reflux temperature afforded **4a-j** in good yields. All these compounds were found to exhibit moderate to good antimicrobial activity.*

Keywords: Aminophosphonate, tetramethylguanidine, antimicrobial activity.

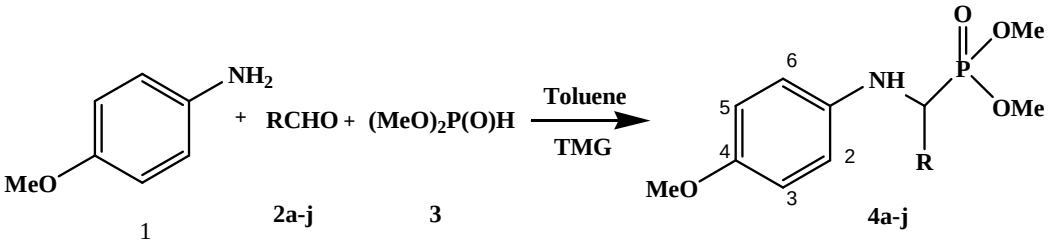
INTRODUCTION

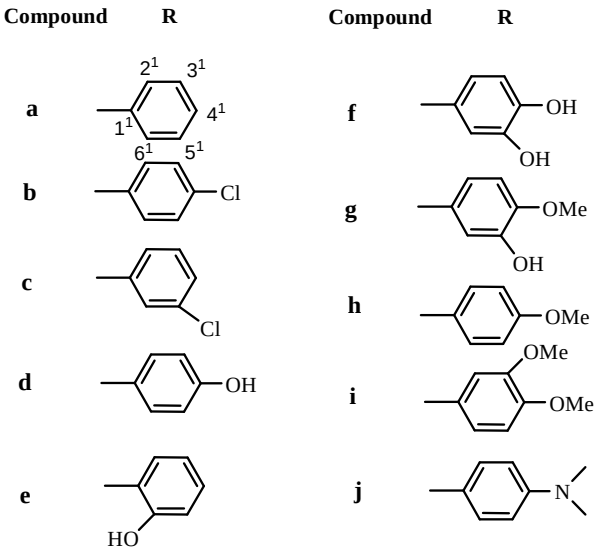
Synthesis of α-aminophosphonates exhibiting high bio-activity has recently attracted a lot of attention.[1-3] Their diverse applications include inhibition of synthase,[4] HIV protease,[5] renin,[6] and PTPases,[7,8]. Some of these derivatives are potential antibiotics[9] and herbicides.[10] α-Aminophosphonates are chief substrates in the synthesis of phosphonopeptides.[11] Due to their structural analogy with α-amino acids, these types of organophosphorus compounds are widely used for the development of new inhibitors of enzymes, neuroactive compounds, and plant growth regulators.[12,13] Among the number of synthetic approaches to α-aminophosphonates, one of the most powerful methods is the Kabachnik-Fields reaction.[14,15] Previous results demonstrated that tetramethylguanidine (TMG) catalyzes the Michael addition of nitromethane to α,β-unsaturated ketones.[16,17] TMG has been used only sporadically and has not yet received full recognition as a strong base in organic synthesis. Its catalytic activity in the Kabachnik-Fields reaction is explored in the present investigation.

MATERIALS AND METHODS

General Procedures

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and were uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer 683 spectrophotometer. ^{1}H-NMR spectra were recorded at 300 MHz in DMSO using TMS as internal standard reference. ^{31}P-NMR (121.4 MHz) was taken in DMSO using 85% H_3PO_4 as external standard with broadband ^{1}H decoupling. ^{13}C-NMR spectra measurements were performed at 75.4 MHz using TMS as internal standard. ^{1}H, ^{13}C, and ^{31}P-NMR spectra were taken on Varian Gemini 300 MHz spectrometer.





Scheme -1

Antimicrobial activity

The antibacterial activity of **4a-j** was assayed[24] against the growth of *Staphylococcus aureus* (gram *+ve*) and *Escherichia coli* (gram *–ve*) at three concentrations (100, 50, 25ppm) using Penicillin as standard reference (**Table I**). Majority of the compounds exhibited moderate to good antibacterial activity against both the bacteria. Similarly compounds **4a-j** were screened for their antifungal activity[25] against *Aspergillus niger* and *Helminthosporium oryzae* species along with the standard fungicide Griseofulvin (**Table II**) by the disc diffusion method[25] at three

different concentrations (100, 50, 25ppm). It is gratifying to observe that the majority of the compounds exhibited moderate to good antifungal activity when compared with the reference.

Table I Antibacterial activity of Compounds 4a-j

Compound	*Zone Of Inhibition (%)*					
	Escherichia coli			***Staphylococcus aureus***		
	100	50	25	100	50	25
4a	08	05	02	09	05	01
4b	07	05	03	09	04	02
4c	09	04	-	08	04	-
4d	05	03	01	07	04	-
4e	09	04	-	06	05	-
4f	08	05	03	10	06	02
4g	08	04	-	09	04	01
4h	08	05	-	08	05	02
4i	08	05	01	06	03	-
4j	05	02	-	07	03	-
Pencillin	12	07	-	11	08	-

Table II Antifungal activity of compounds 4a-j

Compound	*Zone Of Inhibition (%)*					
	Aspergillus Niger			*Helmenthosphorium oryzae*		
	100	50	25	100	50	25
4a	07	05	03	10	06	03
4b	07	05	03	08	05	02
4c	09	06	02	09	05	03
4d	05	03	01	07	04	-
4e	09	04	-	06	05	-
4f	08	05	03	10	06	02
4g	08	04	-	09	04	01
4h	09	04	-	08	04	-
4i	08	05	02	09	05	01
4j	07	03	-	08	04	01
Griseo –fulvin	11	08	06	13	08	06

General procedure for the synthesis of α- aminophosphonates (4a-j)

To a stirred solution of *p*-anisidine (**1)** (0.615 g, 0.005 mole) the aldehyde **(2a-j)** (0.005 mole) in anhydrous toluene (20 mL) was added drop wise, and then TMG (10 mole %) was added and stirring continued at RT for 0.5 h. Then dimethylphosphite(**3**) (1.000 g, 0.005 mole) in anhydrous toluene (20 mL) was added drop wise. Stirring was continued at RT for another 0.5 h, and then the mixture was heated at gentle reflux for 5-6h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction the solvent was removed. The residue was purified by column chromatography on silica gel (80-120 mesh) using hexane–ethyl acetate (3:1) as eluent.

Dimethyl (4-methoxyphenylamino) (phenyl) methylphosphonate (4a).
Yield (70%) mp 115-116°C; IR (KBr) cm^{-1}; 3384 (P-NH), 1223 (P=O), 754 (P-CH); ^{1}H-NMR(DMSO-d_6) δ 6.42-7.28 (m, 9H, Ar-H), 4.90 (s, 1H, NH), 4.53-4.61(m, 1H,P-CH), 3.84 (s, 3H, Ar-OCH_3), 3.53-3.62 (d, $^{3}J_{P-H}$= 10.9 Hz, P-OCH_3), 3.41-3.49 (d, $^{3}J_{P-H}$ = 11.3 Hz, P-OCH_3); ^{13}C-NMR(DMSO-d_6), δ 140.5 (C-1), 113.6 (2C, C-2&6), 115.2 (2C, C-3&5), 149.4 (C-4), 137.6 (C-1'), 126.5 (2C, C-2'&6'), 129.6 (2C, C-3'&5'), 127.1 (C-4') 58.2 (Ar-OCH_3), 53.5(P-CH), 55.9 (P-OCH_3); ^{31}P NMR (DMSO-d_6) δ 27.30; Anal. Calcd. For $C_{16}H_{20}NO_4P$: C, 59.81; H, 6.27; N, 4.36. Found: C, 59.89; H, 6.32; N, 4.41%

Dimethyl (4-methoxyphenylamino) (4-chlorophenyl) methylphosphonate (4b). Yield (64%) mp 147-148°C; IR (KBr) cm^{-1}; 3362 (P-NH), 1224 (P=O), 766 (P-CH). ^{1}H- NMR (DMSO-d_6) δ 6.52-7.54 (m, 8H, Ar-H), 4.80 (s, 1H, NH), 4.56-4.62 (m, 1H, P-CH), 3.75 (s, 3H, Ar-OCH_3), 3.43-3.51 (d, $^{3}J_{P-H}$ = 11.4 Hz, P-OCH_3), 3.21-3.29 (d, $^{3}J_{P-H}$ = 9.80 Hz, P-OCH_3); ^{13}C-NMR(DMSO-d_6), δ 140.5 (C-1), 113.6 (2C, C-2&6), 115.2 (2C, C-3&5), 149.4 (C-4), 132.6 (C-1'), 129.2 (2C, C-2'&6'), 126.2 (2C, C-3'&5'), 133.4 (C-4'), 58.2 (Ar-OCH_3), 53.8(P-CH), 55.4 (P-OCH_3); ^{31}P NMR (DMSO-d_6); δ 30.62; Anal. Calcd. For $C_{16}H_{19}ClNO_4P$: C, 54.02; H, 5.38; N, 3.94. Found: C, 54.09; H, 5.45; N, 3.99%

Dimethyl (4-methoxyphenylamino) (3-chlorophenyl) methylphosphonate (4c). Yield (62%) mp 152-153°C; IR (KBr) cm^{-1}; 3280 (P-NH), 1212 (P=O), 772 (P-CH); ^{1}H NMR(DMSO-d_6) δ : 6.39-7.25 (m, 8H, Ar-H), 4.85 (s, 1H, NH), 4.69-4.74 (m, 1H, P-CH), 3.81 (s, 3H, Ar-OCH_3), 3.57-3.64 (d, $^{3}J_{P-H}$ = 10.4 Hz, P-OCH_3), 3.36-3.43 (d, $^{3}J_{P-H}$ = 10.9 Hz, P-OCH_3); ^{13}C-NMR(DMSO-d_6), δ 141.1 (C-1), 114.2 (2C, C-2&6), 117.9 (2C, C-3&5), 148.6 (C-4), 135.6 (C-1'), 124.7 (C-2'), 137.2 (C-3'), 123.2 (C-4'), 129.1 (C-5'), 127.1 (C-6'), 58.9 (Ar-OCH_3), 53.0 (P-CH), 55.1 (P-OCH_3); ^{31}P NMR(DMSO-d_6) δ 20.18; Anal. Calcd. For $C_{16}H_{19}ClNO_4P$: C, 54.02; H, 5.38; N, 3.94. Found: C, 54.09; H, 5.45; N, 3.99%

Dimethyl (4-methoxyphenylamino) (4-hydroxyphenyl) methylphosphonate (4d). Yield (69%) mp, 118-119°C. IR (KBr) cm^{-1}; 3284 (P-NH), 1233 (P=O), 739 (P-CH); ^{1}H-NMR (DMSO-d_6): δ 6.35-7.19 (m, 8H, Ar-H), 5.42 (bsr, 1H, Ar-OH), 4.94 (s, 1H, NH), 4.59-4.65 (m, 1H, PCH), 3.85 (s, 3H, Ar-OCH_3), 3.52-3.61 (d, $^{3}J_{P-H}$ = 10.2 Hz, P-OCH_3), 3.37-3.42 (d, $^{3}J_{P-H}$ = 10.9 Hz, P-OCH_3), ^{13}C-NMR(DMSO-d_6), δ 138.2 (C-1), 113.3 (2C, C-2&6), 114.5 (2C, C-3&5), 149.8 (C-6), 127.1 (C-1'), 129.2 (2C, C-2'&6'), 115.6 (2C, C-3'&5'), 155.4 (C, C-4'), 58.2 (Ar-OCH_3), 53.5(P-CH), 55.9 (P-OCH_3); ^{31}P-NMR (DMSO-d_6): δ 18.54; Anal. Calcd. For $C_{16}H_{20}NO_5P$: C, 56.97; H, 5.98; N, 4.15. Found: C, 57.02; H, 6.05; N, 4.22%

Dimethyl (4-methoxyphenylamino) (2-hydroxyphenyl) methylphosphonate (4e). Yield (66%)mp 126-127°C; IR (KBr) cm^{-1}; 3384 (P-N-H), 1229 (P=O), 780 (P-CH); ^{1}H-NMR (DMSO-d_6) δ 6.41-7.32 (m, 8H, Ar-H), 5.39 (brs,1H, Ar-OH) 4.82 (s, 1H, NH), 4.58-4.64 (m, 1H, P-CH), 3.89 (s, 3H, Ar-OCH_3), 3.63-3.71 (d, $^{3}J_{P-H}$ = 10.1 Hz, P-OCH_3), 3.42-3.51 (d, $^{3}J_{P-H}$ = 10.5 Hz, P-OCH_3); ^{31}P -NMR (DMSO-d_6): δ 29.37; Anal. Calcd. For $C_{16}H_{20}NO_5P$: C, 56.97; H, 5.98; N, 4.15. Found: C, 57.04; H, 6.04; N, 4.24%

Dimethyl (4-methoxyphenylamino) (3,4-dihydroxyphenyl) methyl phosphonate (4f). Yield 71%mp 105-106°C; IR (KBr) cm^{-1}; 3345 (P-NH), 1213 (P=O), 775 (P-CH); ^{1}H-NMR (DMSO-d_6); δ 6.56-7.51 (m, 7H, Ar-H), 5.71-5.42 (brs, 2H, Ar-OH), 4.82 (s, 1H, NH), 4.61-4.68

(m, 1H, P-CH), 3.81 (s, 3H, Ar-OCH_3), 3.49-3.56 (d, $^3J_{P-H}$ = 9.9 Hz, P-OCH_3), 3.32-3.39 (d, $^3J_{P-H}$ = 10.1 Hz, P-OCH_3); ^{31}P NMR (DMSO-d_6); δ 25.58; Anal. Calcd. For $C_{16}H_{20}NO_6P$: C, 54.39; H, 5.71; N, 3.96 Found: C, 54.45; H, 5.75; N, 3.99%

Dimethyl (4-methoxyphenylamino) (3-hydroxy-4-methoxyphenyl) methyl phosphonate (4g). Yield (68%) mp 102-103°C; IR (KBr) cm^{-1}; 3381 (P-NH), 1236 (P=O), 742 (P-CH); ^{1}H-NMR (DMSO-d_6); δ 6.39-7.42 (m, 7H, Ar-H), 5.52 (brs, 1H, Ar-OH), 4.79 (s, 1H, NH), 4.59-4.68 (m, 1H, P-CH), 3.85 (s, 3H, Ar-OCH_3), 3.59-3.67 (d, $^3J_{P-H}$ = 9.7 Hz, P-OCH_3), 3.31-3.39 (d, $^3J_{P-H}$ = 9.6 Hz, P-OCH_3); ^{31}P NMR (DMSO-d_6); δ 31.50 Anal. Calcd. For $C_{17}H_{22}NO_4P$: C, 55.58; H, 6.04; N, 3.81. Found: C, 55.64; H, 6.09; N, 3.87%

Dimethyl (4-methoxyphenylamino) (4-methoxyphenyl) methyl phosphonate (4h). Yield (67%) mp 115-116°C; IR (KBr) cm^{-1}; 3225 (P-NH), 1234 (P=O), 754 (P-CH); ^{1}H-NMR(DMSO-d_6) δ 6.42-7.28 (m, 8H, Ar-H), 5.10 (s, 1H, NH), 4.53-4.61 (m, 1H, P-CH), 3.84-3.91 (s, 6H, Ar-OCH_3), 3.51-3.60 (d, $^3J_{P-H}$= 11.5 Hz, P-OCH_3), 3.39-3.48 (d, $^3J_{P-H}$ = 11.3 Hz, P-OCH_3); ^{31}P NMR (DMSO-d_6); δ 28.62; Anal. Calcd. For $C_{17}H_{22}NO_5P$: C, 58.12; H, 6.31; N, 3.99. Found: C, 58.18; H, 6.39; N, 4.07%

Dimethyl (4-methoxyphenylamino) (3,4-dimethoxyphenyl) methyl phosphonate (4i). Yield (63%) mp 122-123°C; IR (KBr) cm^{-1}; 3378 (P-NH), 1229 (P=O), 762 (P-CH); ^{1}H-NMR(DMSO-d_6) δ 6.42-7.28 (m, 7H, Ar-H), 4.80 (s, 1H, NH), 4.55-4.65 (m, 1H, P-CH), 3.74-3.93 (s, 9H, Ar-OCH_3), 3.52-3.60 (d, $^3J_{P-H}$= 10.3 Hz, P-OCH_3), 3.30-3.37 (d, $^3J_{P-H}$ = 11.2 Hz, P-OCH_3); ^{31}P NMR (DMSO-d_6); δ 26.22; Anal. Calcd. For $C_{18}H_{24}NO_6P$: C, 56.69; H, 6.34; N, 3.67. Found: C, 56.75; H, 6.39; N, 3.72%

Dimethyl (4-methoxyphenylamino) (4-N,N-dimethylphenyl) methyl phosphonate (4j). Yield (60%) mp 145-146°C; IR (KBr) cm^{-1}; 3365 (P-NH), 1231 (P=O), 758 (P-CH); ^{1}H-NMR(DMSO-d_6); δ 6.22-7.12 (m, 8H, Ar-H), 4.75 (s, 1H, NH), 4.61-4.70 (m, 1H, P-CH), 3.90 (s, 3H, Ar-OCH_3), 3.49-3.57 (d, $^3J_{P-H}$= 10.1 Hz, P-OCH_3), 3.31-3.39 (d, $^3J_{P-H}$ = 10.3, Hz, P-OCH_3); 2.73 (s, 2H, $N(CH_3)_2$); ^{31}P NMR (DMSO-d_6); δ: 31.30; Anal. Calcd. For $C_{18}H_{25}N_2O_4P$: C, 59.33; H, 6.92; N, 7.69. Found: C, 59.39; H, 6.99; N, 7.75%

RESULTS AND DISCUSSION

The *p*-anisidine **(1)** was treated with different aldehydes (**2a-j**) and dimethyl- phosphite (**3**) in the presence of 10 mole % of tetramethylguanidine (TMG) in dry toluene at RT. The mixture was stirred at RT for 1h, and at 70-80°C for another 5h. The progress of the reaction was monitored by thin layer chromatography. The reaction proceeded smoothly, and completed in 5-6 h to afford the corresponding α-aminophosphonates in good yield (59-75%). This showed that TMG acts as an effective catalyst in this reaction. An important feature is that the TMG can be easily recovered from the reaction mixture after completion of the reaction and can be reused. The chemical structures of all the new compounds were confirmed by elemental analysis, IR, ^{1}H-, ^{13}C- and ^{31}P- NMR spectra. Compounds **4a-j** exhibited characteristic IR stretching frequencies in the regions 3215-3384, 1215-1236, 739-780 cm^{-1} for N-H, P=O, and P-C(aliphatic) respectively.[18] The aromatic protons of the benzene rings of the α-aminophosphonates (**4a-j**) showed a complex multiplet at δ 6.35-7.54. The P-C-H proton signal appeared as a multiplet[19] at

δ 4.53-4.74 due to its coupling with both phosphorus and the N-H proton. N-H proton signal appeared at δ 4.75-5.10 as a singlet. The methoxy group protons of the dimethylphosphite moiety resonated as two distinct doublets in the range of δ 3.30-3.62 (d, $^3J_{P-H}$= 9.6 - 11.3 Hz) and δ 3.49-3.71 (d, $^3J_{P-H}$ = 9.7 - 11.5 Hz)[19,20] indicating their non-equivalence. The carbon chemical shifts for P-CH, P-O-CH_3 in the title compounds were observed at δ 53.0-53.8, 55.1-55.9 respectively.[18,21,22] The ^{31}P NMR signals[23] appeared in the region δ 18.54-31.50 for these compounds.

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