ORIGINAL ARTICLE

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*Org. Commun.*3:3 (2010) 39-44

organic communications

Tetramethyl guanidine (TMG) catalyzed synthesis of novel α-amino phosphonates by one-pot reaction

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(Received October 8, 2009; Revised May 10 2010; Accepted May 16, 2010)

Abstract: An efficient method has been developed for the synthesis of α-amino phosphonates (**4a-j**) by the three component one-pot reaction of equimolar quantities of 2-amino methyl furan (**1**), dimethyl / diethyl phosphite (**2**) and various aldehydes (**3a-j**) in dry toluene at reflux conditions via Kabachnik – Fields reaction in high yields (70-80%) in the presence of tetramethyl guanidine (TMG) as catalyst. The TMG can be easily recovered from the reaction mixture after completion of the reaction and can be reused. Their antimicrobial activity has also been evaluated.

Keywords:α-amino phosphonate; antimicrobial activity; 2-amino methyl furan; dialkyl phosphite.

1. Introduction

α-Amino phosphonates are an important class of compounds since they are considered as structural analogues of the corresponding α-amino acids, and their utilities as enzyme inhibitors, antibiotics and pharmacological agents.[1] Phosphonates are widely used as imaging agents and as antitumor, antihypertensive and antibacterial agents.[2]

The Kabachnik-Fields reaction is one of the most convenient approaches for the preparation of α-amino phosphonates. Previous results demonstrated that TMG catalyzes the Michael addition of nitromethane to α,β-unsaturated ketones. TMG has been used only sporadically and has not yet received full recognition as a strong base in organic synthesis.[3]

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The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/OC/index.htm © Published 07/20/2010 EISSN:1307-6175

2. Results and Discussion

α-Amino phosphonates (**4a-j**) were synthesized by three component one-pot reaction of equimolar quantities of 2-aminomethyl furan (**1**), dimethyl / diethyl phosphite (**2**) and various aldehydes (**3a-j**) in the presence of TMG in dry toluene at reflux conditions for 5-6 h (sheme 1). Progress the reaction was monitored by TLC analysis at different time intervals and the products were purified by column chromatography using ethyl acetate : hexane (2:1) as eluent.

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, ^{1}H, ^{13}C, ^{31}P – NMR and Mass spectra. Compounds **4a-j** exhibited characteristic IR stretching frequencies in the regions 3220-3362, 1212-1240, 746-760 cm^{-1} for N-H, P=O and P-C (aliphatic) respectively[4].

Aromatic protons in title compounds (**4a-j**) resonated as multiplets in the region δ 6.01-7.0. The P-C-H proton signal appeared as a multiplet[5] at δ 3.47- 3.82 due to its coupling with both phosphorus and the N-H proton. The methylene protons of P-O$\underline{CH_2}CH_3$ showed a multiplet and methyl protons of P-O$CH_2\underline{CH_3}$ gave distinct triplets in the region δ 3.72-3.98 and 1.11-1.84 respectively[6]. The methoxy protons of the dimethyl phosphite moiety resonated as two distinct doublets in the range of δ 3.65-4.25 and 4.21-4.33 indicating their non-equivalence[5].

The carbon chemical shifts for P-$\underline{C}H$, P-O$\underline{C}H_3$ and P-O$\underline{C}H_2\underline{C}H_3$ in the title compounds were observed at δ 43.1, 50.1, 62.5, 16.6 respectively[7]. The ^{31}P NMR signals[8] appeared in the region δ 7.73-16.9 for these compounds.

3. Conclusion

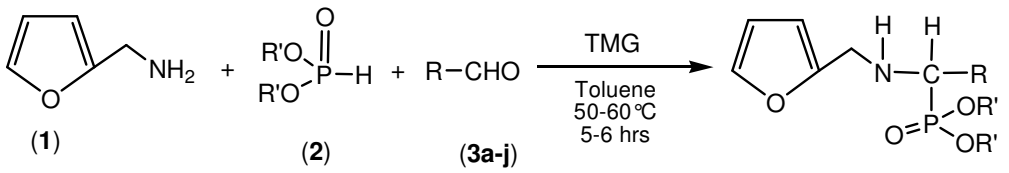
We have reported the one-pot synthesis synthesis of α-aminophosphonates in from aldehydes, amine and dialkyl phosphites using tetramethyl guanidine as a catalyst and good antimicrobial activity.

4. Experimental

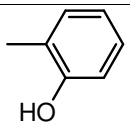
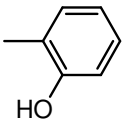
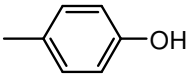
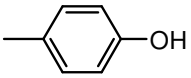
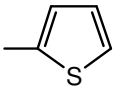
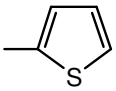
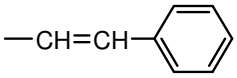
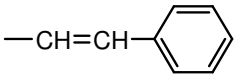
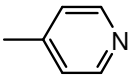
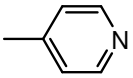
IR spectra were recorded in KBr pellets on a Perkin-Elmer 683 spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ using TMS as internal standard reference. ^{31}P NMR (161.2 MHz) was taken in $CDCl_3$ using 85% H_3PO_4 as external standard with broadband ^{1}H-decoupling. ^{13}C-NMR spectra measurements were performed at 75.4 MHz using TMS as internal standard. ^{1}H, ^{13}C, ^{31}P NMR spectra were taken on varian Gemini 300 MHz spectrometer and mass spectra were recorded at Central Drug Research Institute, Lucknow, India.

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

To a stirred solution of 2-aminomethyl furan (**1**) (0.01 mol), the aldehyde (**3a-j**) (0.01 mol) in anhydrous toluene (20) was added dropwise, and the TMG (10 mol%) was added and stirring continued at RT for 1h. Then dimethyl / diethyl phosphite (0.01 mol) in dry toluene (20ml) was added dropwise. Stirring was continued at RT for another 0.5 h, and then the mixture was heated at gentle reflux for 5-6 h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (80-120 mesh) using ethyl acetate: hexane (2:1) as eluent.



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

Compound	R′	R
4a	CH_3	
4b	C_2H_5	
4c	CH_3	
4d	C_2H_5	
4e	CH_3	
4f	C_2H_5	
4g	CH_3	
4h	C_2H_5	
4i	CH_3	
4j	C_2H_5	

Scheme 1. Synthesized α-amino phosphonates

Dimethyl (furan-2-yl methyl amino) (2-hydroxy phenyl) methyl phosphonate (4a). Yield : 72%; m.p. 200-202°C. Anal. Calcd. for $C_{14}H1_8NO_5P$: C, 54.02; H, 5.83; N, 4.50. Found : C, 53.96; H, 5.77; N, 4.44; IR (KBr, cm^{-1}): 3320 (N-H), 1234 (P=O), 746 (P-C); ^{1}H-NMR (DMSO-d_6): δ 7.61- 6.40 (7H, m, Ar-H), 4.60- 4.30 (3H, m, NH & N-CH_2), 4.17 (3H, d, J = 9.2 Hz, P-OCH_3), 4.12 (3H, d, J = 9.0 Hz, P-OCH_3), 3.82- 3.60 (1H, m, P-CH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.60 (C-2′), 146.84 (C-2), 146.05 (C-5), 131.67 (C-6′), 130.01 (C-4′), 121.59 (C-5′), 117.69 (C-3′), 116.60 (C-1′), 112.50 (C-4), 105.70 (C-3), 55.34 (P-OCH_3, d, J = 6.0 Hz), 50.14 (C-6); ^{31}P NMR (DMSO-d6): δ 8.20; FAB-MS: m/z (%): 312 (M+1, 95), 282 (14), 237 (15), 202 (95), 201 (50), 176 (10), 154 (10), 122 (30).

Diethyl (furan-2-yl methyl amino) (2-hydroxy phenyl) methyl phosphonate (4b). Yield : 74%; m.p. 180-182°C. Anal. Calcd. for $C_{16}H_{22}NO_5P$: C, 56.63; H, 6.53; N, 4.13. Found : C, 56.59; H, 6.49; N, 4.09; IR (KBr, cm^{-1}): 3354 (N-H), 1240 (P=O), 749 (P-C); ^{1}H-NMR (DMSO-d_6): δ 7.57- 6.39 (7H, m, Ar-H), 4.65- 4.32 (3H, m, NH & N-CH_2), 4.10-3.85 (4H, m, P-OCH_2CH_3), 3.72-3.61 (1H, m, P-CH), 1.26 (3H, t, *J* = 7.2 Hz, P-OCH_2CH_3), 1.07 (3H, t, *J* = 6.8 Hz, P-OCH_2CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 156.60 (C-2′), 146.53 (C-2), 145.48 (C-5), 131.67 (C-4′), 129.07 (C-6′), 121.50 (C-5′), 119.69 (C-3′), 117.5 (C-1′), 114.90 (C-4), 107.97 (C-3), 62.77 (P-O<u>C</u>H_2CH_3, d, *J* = 6.8 Hz), 49.63 (C-6), 16.97 (PO-CH_2<u>C</u>H_3, d, *J* = 5.2 Hz); ^{31}P NMR (DMSO-*d*6): 12.5; FAB-MS: *m/z* (%): 340 (M+1, 80), 338 (40), 323 (10), 258 (6), 240 (10), 202 (90), 200 (50), 136 (20).

***Dimethyl (furan-2-yl methyl amino) (4-hydroxy phenyl) methyl phosphonate* (*4c*).** Yield : 71%; m.p. 195-197°C. Anal. Calcd. for $C_{14}H_{18}NO_5P$: C, 54.02; H, 5.83; N, 4.50. Found : C, 53.98; H, 5.79; N, 4.46; .IR (KBr, cm^{-1}): 3350 (N-H), 1239 (P=O), 754 (P-C); ^{1}H-NMR (DMSO-d_6): δ 7.81-6.20 (7H, m, Ar-H), 4.65-4.32 (3H, m, NH & N-CH_2), 4.08 (3H, d, *J* = 10.3 Hz, P-OCH_3), 3.99 (3H, d, *J* = 9.1 Hz, P-OCH_3), 3.82-3.62 (1H, m, P-CH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 150.23 (C-4′), 145.80 (C-2), 145.00 (C-5), 130.67 (C-2′), 130.60 (C-6′), 121.67 (C-1′), 118.59 (C-5′), 116.60 (C-3′), 110.58 (C-4), 107.70 (C-3), 55.34 (OCH_3, d, *J* = 6.0 Hz), 49.10 (C-6); ^{31}P NMR (DMSO-*d*6); δ 14.29.

Diethyl (furan-2-yl methyl amino) (4-hydroxy phenyl) methyl phosphonate (4d). Yield : 70%; m.p. 201-203°C. Anal. Calcd. for $C_{16}H_{22}NO_5P$: C, 56.63; H, 6.53; N, 4.13. Found : C, 56.58; H, 6.47; N, 4.08; IR (KBr, cm^{-1}): 3344 (P-NH), 1228 (P=O), 748 (P-C); ^{1}H-NMR (DMSO-d_6): 7.51-6.21 (7H, m Ar-H), 4.65-4.32 (3H, m, NH & N-CH_2), 3.90-3.84 (4H, m, P-OCH_2CH_3), 3.56- 3.47 (1H, m, P-CH), 1.24 (3H, t, *J* = 7.05 Hz), 1.11 (3H, t, *J* = 7.03 Hz, P-OCH_2CH_3); ^{31}P NMR (DMSO-*d*6): 10.5.

Dimethyl (furan-2-ylmethylamino)(thiophen-2-yl)methylphosphonate (4e). Yield : 75%; m.p. 175-177°C. Anal. Calcd. for $C_{12}H_{16}NO_4PS$: C, 47.84; H, 5.83; N, 4.65. Found : C, 47.80; H, 5.80; N, 4.60; IR (KBr, cm^{-1}): 3328 (P-NH), 1223 (P=O), 259 (P-C); ^{1}H-NMR (DMSO-d_6): 7.68-6.41 (6H, m, Ar-H), 4.45-4.30 (3H, m, NH & N-CH_2), 4.20 (3H, d, *J* = 10.2 Hz, P-OCH_3), 4.10 (3H, d, *J* = 9.8 Hz, P-OCH_3), 3.82-3.71 (1H, m, P-CH); ^{31}P NMR (DMSO-*d*6): 13.5.

***Diethyl furan-2-yl(furan-2-yl methyl amino) methyl phosphonates* (*4f*).** Yield : 72%; m.p. 188-190°C. Anal. Calcd. for $C_{14}H_{20}NO_4PS$: C, 51.05; H, 6.12; N, 4.25. Found : C, 51.00; H, 6.08; N, 4.20; IR (KBr, cm^{-1}): 3344 (P-NH), 1234 (P=O), 748 (P-C); ^{1}H-NMR (DMSO-d_6): δ 7.79-6.42 (6H, m, Ar-H), 4.55-4.30 (3H, m, NH & N-CH_2), 4.10-3.89 (4H, m, P-OCH_2CH_3), 3.80-3.60 (1H, m, P-CH), 1.25 (3H, t, *J* = 6.9 Hz, P-OCH_2CH_3), 1.22 (3H, t, *J* 6.2 Hz, P-OCH_2CH_3); ^{31}P NMR (DMSO-*d*6): 10.9.

Dimethyl 1-(furan-2-yl methyl amino)-3-phenylallyl phosphonates (4g). Yield: 70%; m.p. 186-188°C. Anal. Calcd. for $C_{16}H_{20}NO_4P$: C, 59.81; H, 6.27; N, 4.36. Found : C, 59.77; H, 6.22; N, 4.31; IR (KBr, cm^{-1}): 3362 (P-NH), 1212 (P=O), 754 (P-C); ^{1}H-NMR (DMSO-d_6): δ 7.61-6.60 (8H, m, Ar-H), 6.53 (1H, d, *J* = 15.3 Hz, Ph-CH=CH), 6.18 (1H, d, *J* = 15.2 Hz, Ph-CH=CH), 4.45-4.20 (3H, m, NH & N-CH_2), 4.08 (3H, d, *J* = 9.8 Hz, P-OCH_3), 3.95 (3H, t, *J* = 9.2 Hz, P-OCH_3), 3.69-3.52 (1H, m, P-CH); ^{31}P NMR (DMSO-*d*6): 11.0.

***Diethyl 1-(furan-2-yl methyl amino)-3-phenylallyl phosphonates* (*4h*).** Yield: 78%; m.p. 180-182°C. Anal. Calcd. for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01. Found : C, 61.82; H, 6.88; N, 43.97; IR (KBr, cm^{-1}): 3356 (P-NH), 1221 (P=O), 760 (P-C); ^{1}H-NMR (DMSO-d_6): δ 7.61-6.66 (8H, m, Ar-H), 6.59 (1H, d, *J* = 15.5 Hz, Ph-CH=CH), 6.16 (1H, d, *J* = 15.8 Hz, Ph-CH=CH), 4.55-4.22 (3H, m, NH & N-CH_2), 4.05-3.76 (4H, m, P-OCH_2CH_3), 3.65-3.52 (1H, m, P-CH), 1.25 (6H, t, J = 6.8 Hz, P-OCH_2CH_3); ^{31}P NMR (DMSO-*d*6): 13.2.

Dimethyl (furan-2-yl methyl amino)(pyridine-4-yl) methyl phosphonates (4i). Yield: 78%; m.p. 195-197°C. Anal. Calcd. for $C_{13}H_{17}NO_4P$: C, 52.70; H, 5.78; N, 9.46. Found : C, 52.65; H, 5.72; N, 9.40; IR (KBr, cm^{-1}): 3328 (P-NH), 1229 (P=O), 751 (P-C); ^{1}H-NMR (DMSO-d_6): δ 8.21-6.80 (7H, m, Ar-H), 4.65-4.32 (3H, m, NH & N-CH_2), 4.08 (3H, d, *J* = 9.8 Hz, P-OCH_3), 3.90 (3H, d, *J* = 9.2 Hz, P-OCH_3), 3.72-3.51 (1H, m, P-CH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 151.12 (C-2), 150.10 (C-3′), 150.26 (C-5′), 146.28 (C-1′), 143.30 (C-5), 126.17 (C-2′), 126.16 (C-6′), 112.60 (C-4), 112.32 (C-3), 53.86 (P-OCH_3, d, *J* = 6.7 Hz) 50.33 (C-6), 40.71 (P-CH); ^{31}P NMR (DMSO-*d*6): 11.5.

Diethyl (furan-2-yl methyl amino)(pyridine-4-yl) methyl phosphonates (4j). Yield: 73%; m.p. 186-188°C. Anal. Calcd. for $C_{15}H_{21}N_2O_4P$: C, 55.55; H, 6.53; N, 8.64. Found : C, 55.50; H, 6.49; N, 8.60; IR (KBr, cm^{-1}): 3347 (P-NH), 1236 (P=O), 762 (P-C); ^{1}H-NMR (DMSO-d_6): δ 8.60-6.81 (7H, m, Ar-H), 4.42-4.25 (3H, m, NH & N-CH_2), 4.08-3.72 (4H, m, P-OCH_2CH_3), 3.77-3.58 (1H, m, P-CH), 1.27 (3H, t, *J* = 7.2 Hz, P-OCH_2CH_3), 1.09 (3H, t, *J* = 6.8 Hz, P-OCH_2CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 152.21 (C-5′), 150.91 (C-2), 150.27 (C-3′), 146.22 (C-1′), 143.39 (C-5), 124.65 (C-2′), 124.65 (C-6′), 111.65 (C-4), 108.52 (C-3), 62.31 (P-O-CH_2CH_3, d, *J* = 6.9 Hz), 49.63 (C-6), 48.36 (P-CH), 16.82 (P-OCH_2CH_3, d, *J* = 5.4 Hz); ^{31}P NMR (DMSO-*d*6): 13.5.

Antimicrobial Activity:Compounds (**4a-j**) screened for their antibacterial activity (Table-1) against *Staphylococcus aureus* (Gram + ve) and *Escherichia coli* (Gram –ve) by the disc diffusion method[9] in nutrient agar medium, at various concentrations (100, 50, 25 mg/L) in dimethyl formamide (DMF). The results were compared with the activity of the standard antibiotic penicillin.

Their antifungal activity (Table-2) were evaluated against *Aspergillus niger* and *Curvularsia lunata* at different concentrations (100, 50, 25 mg/L).[10] Griseofulvin was used as the reference compound. Compounds **4a, 4c, 4g, and 4h** exhibited significant antibacterial and antifungal activity.

Table 1. Antibacterial Activity of α-aminophosphonates **(4a-j)***

Compound	Zone of inhibition (%)					
	Staphylococcus aureus			*Escherichia coli*		
	100	**50**	**25**	**100**	**50**	**25**
4a	11	7	4	10	6	5
4b	9	6	4	9	5	4
4c	11	6	5	11	7	5
4d	10	7	6	8	5	4
4e	8	5	4	8	6	4
4f	9	6	6	9	7	5
4g	10	7	5	11	6	5
4h	11	6	4	10	5	4
4i	8	5	4	10	6	5
4j	9	6	5	9	7	4
Penicillin	12	8	--	11	8	--

***mg/L**

Table 2. Antifungal Activity of α-aminophosphonates **(4a-j)***

Compound	Zone of inhibition (%)					
	Aspergillus niger			*Curvularia lunata*		
	100	**50**	**25**	**100**	**50**	**25**
4a	11	6	4	12	7	4
4b	10	7	5	11	8	5
4c	12	8	4	12	8	4
4d	10	7	5	10	7	5
4e	9	6	4	8	6	6
4f	11	8	6	9	8	7
4g	10	7	7	11	9	5
4h	11	6	5	12	6	4
4i	10	8	7	9	5	6
4j	12	6	5	8	7	8
Griseofulvin	13	9	--	14	11	--

***mg/L**

Acknowledgements

The authors thank CSIR, Human Resources Development Group, Govt. of India, New Delhi for providing financial assistance (01/2347/09/EMR-II).

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