Research Article

Synthesis and Antimicrobial Activity of Novel mono- and bis-α-Aminophosphonate Derivatives

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ABSTRACT

Synthesis of new series of mono and bis α-aminophosphonates in good to excellent yields by one pot three component reaction. The synthesis involved the reaction of carbonyl compounds with amines, triphenyl phosphite at room temperature in dry acetonitrile in presence of lithium perchlorate as Lewis acid catalyst. The chemical structures of the products were characterized by IR, ^{1}HNMR, ^{13}CNMR and mass spectral data. All the synthesized compounds were screened for their *in vitro* antifungal and antibacterial activity against both Gram positive and Gram negative bacterial strains. Compounds **4b**, **4d**, **5d**, **9a** showed the highest antibacterial activity against Bacillus subtilis strain with minium inhibition zone 23 mm.

Keywords: Carbonyl compounds, amines, triphenylphosphite, Lewis Acid, α-aminophosphonates, Antibacterial Activity.

INTRODUCTION

α-Aminophosphonic acids I and their corresponding ester II are a phosphorus analogues of naturally occurring α-amino acids III (*cf.* Fig. 1). These classes of organophosphorus compounds have received much interest due to their biological activity and insignificant toxicity towards mammalian cells. The versatile biological activities of α–aminophosphonates have rendered the α-aminophosphonate moiety the status of a novel pharmacophore in the context of drug design.[1-3]

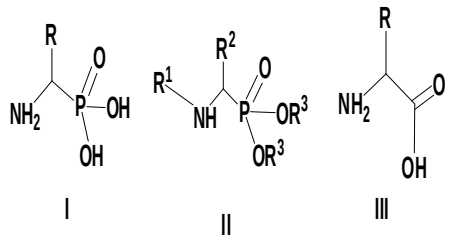


Figure 1: Structures of α- Aminophosphonic acid I , α -Aminophosphonates II and α -Amino acids III

α-Aminophosphonic acid esters II received much attention in recent years due to their wide range of biological applications as anti-HIV,[4] anti-cancer,[5] antibacterial[6] and antiviral agents.[7] Moreover, α-aminophosphonates are used in agricultural industry as antifungal agents,[8-9] and herbicides[10-11]. Recently, various methodologies have been developed for the synthesis of aminophosphonates. However, still there remains a need to develop a more efficient method, particularly keeping in view the disadvantages associated with some of the reported procedures.[12-16] In this context, our interest in finding a cheapest catalyst as well as convenient synthetic protocol to synthesized a biologically active α-aminophosphonates received much of our attention. In this study we focused on efficient synthesis and antimicrobial screening of some new mono- and bis α-aminophosphonates.

MATERIALS AND METHODS

All ^{1}HNMR and ^{13}CNMR experiments (solvent DMSO-d6) were carried out with a 300 MHz varian & 400MHz varian and Bruker Avance at the University of Ulm, Germany and Okayama University, Japan. Chemical shifts are reported in part per million (ppm) relative to the respective solvent. The mass spectroscopy experiments were recorded on shimadzu QL 800 15-70 V at central lab, faculty of science, Al-Azhar University and IR spectroscopy were performed at Cairo University, Egypt. Melting points (m.p) were recorded on Stuart scientific melting point apparatus and are uncorrected. The biological activity analysis was carried out at, Division of Pharmaceutical Industries, National Research Center, Cairo, Egypt. All reactions were followed by thin layer chromatography (TLC) on kiesel gel F254 precoated plates (Merck). Starting materials and solvents such as acetonitrile and diethyl ether were purchased and used without further purification.

Synthesis of mono α-aminophosphonate using 1,2 phenylene diamine and 1,4 phenylene diamine as amine (general procedure)

To the carbonyl compound **1** (2.35 mmol), bisamine **2** (2.35 mmol) and triphenylphosphite **3** (2.35 mmol, 0.62 mL) in acetonitrile (10 mL), lithium perchlorate (10 mol %) was added. The reaction mixture was stirred at room temperature until the starting materials were consumed as monitored by TLC (3 days). After the completion of the reaction the precipitated product was filtered off and crystallized by using diethyl ether and cooling.

Diphenyl(2-aminophenylamino)(phenyl)methylphosphonate (4a)

Yield (50%), (m.p): 170-172°C, IR (KBr) cm^{-1}:- 3453, 3370 (-NH_2), 3205 (-NH), 1607 (C=C, Ar), 1272 (P=O), 752 (P-C). ^{1}HNMR (DMSO-d_6 400 MHz): 5.33 - 5.40 (m, 1H,CH), 6.05 (br, s, 2H, NH_2), 6.40 – 7.64 (m, 19H, CH_{Ar}), 9.33 (br,s,1H,NH). ^{13}CNMR (DMSO-d_6 100 MHz):- 56.1, 114.1, 115.0, 116.5, 118.7, 120.2, 121.9, 122.4, 128.1, 129.3, 135.9, 136.0, 137.2, 138.1, 139.3, 149.0, 150.0, 154.0, 157.0. ESIMS, m/z ($C_{25}H_{23}N_2O_3P$) calcd, 430.14 $[M]^+$; found, 430.0.

Diphenyl(4-aminophenylamino)(phenyl)methyl phosphonate (4b)

Yield (98.5 %), (m.p): 140-142 °C, IR (KBr) cm^{-1}:- 3381 (-NH_2+NH overlap), 1621 (C=C, Ar), 1265 (P=O), 758 (P-C). ^{1}HNMR (DMSO-d_6 400 MHz) :- 5.35 - 5.44 (m, 1H, CH), 6.08 (br, s, 2H, NH_2), 6.56 (s, 1H, NH), 6.68 – 7.65 (m, 19H, CH_{Ar}). ESIMS, m/z ($C_{25}H_{23}N_2O_3P$) calcd, 430.14 $[M]^+$; found, 430.0.

Diphenyl(2-aminophenylamino)(4-(dimethylamino)phenyl)methylphosphonate (4C)

Yield: 50%, melting point: 160 - 162 °C, IR (KBr) cm^{-1}: 3453, 3375 (-NH_2), 3232 (NH), 1607 (C=C, Ar), 1289 (P=O), 751 (P-C). ^{1}HNMR (DMSO-d_6, 400MHz): 2.85 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 4.71 – 4.78 (m, 1H, CH), 6.25 (s, 2H, NH_2), 6.57-8.06 (m, 19H, CH_{Ar}+ NH). ESIMS, m/z ($C_{27}H_{29}N_3O_3P$) calcd, 473.19 $[M+1]^+$; found, 474.0.

Diphenyl (4-aminophenylamino)(4-(dimethylamino)phenyl)methylphosphonate (4d)

Yield (75%), (m.p): 115-116 °C, IR (KBr) cm-^{1}: 3434 ,3380 (-NH_2), 3303(-NH), 1604 (C=C, Ar), 1257 (P=O), 765 (P-C). ^{1}HNMR (DMSO-d_6, 400 MHz): 2.84 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 5.14 – 5.21 (m, 1H, CH), 5.88 (br.s, 2H, NH_2), 6.60 - 7.81 (m, 18H, CH_{Ar}), 9.40 (br, s, 1H, NH). ESIMS, m/z ($C_{27}H_{28}N_3O_3P$) calcd, 473.19 $[M]^+$; found, 473.0.

Synthesis of bis α-aminophosphonate using 1,2 phenylene diamine and 1,4 phenylene diamine as amine (general procedure)

To the carbonyl compound **1** (4.7 mmol), bisamine **2** (2.35 mmol) and triphenylphosphite **3** (4.7 mmol, 1.25 mL) in acetonitrile (10 mL), lithium perchlorate (10 mol%) was added. The reaction mixture was stirred at room temperature until the starting materials were consumed as monitored by TLC (3 days). After the completion of the reaction the precipitated product was filtered off and crystallized by using diethyl ether and cooling.

Tetraphenyl(1,2-phenylenebis(azanediyl))bis(phenylmethylene)bisphosphonate (5a)

Yield (50%), (m.p): > 300 °C, IR(KBR)cm^{-1}: 3440 (-NH), 1594 (C=C, Ar), 1290(P=O), 772 (P-C). ^{1}HNMR (DMSO-d_6, 400 MHz): 5.33 - 5.41 (m, 2H, 2 CH), 6.01(br, s, 2H, 2 NH), 6.68 -7.87 (m, 34H, CH_{Ar}). ^{13}CNMR (DMSO-d_6 400 MHz): 56.12, 114.07, 115.0, 188.7, 119.8, 120.0, 125.0, 128.0, 129.3, 130.2, 135.9, 138.0, 141.1, 145.88, 149.0, 150.0. ESIMS, m/z ($C_{44}H_{38}N_2O_6P_2$) calcd, 752.22 $[M]^+$; found, 752.0.

Tetraphenyl (1,4phenylenebis(azanediyl)bis(phenylmethylene)bis phosphonate (5b)

Yield (78%),(m.p): 170 -172 °C, IR (KBr) cm^{-1}:- 3381 (-NH), 1589 (C=C, Ar), 1265 (P=O), 758 (P-C). ^{1}HNMR (DMSO-d_6 400 MHz):- 5.36 - 5.44 (m, 2H, 2CH), 6.10 (br, s, 2H, 2NH), 6.70 – 7.66 (m, 34H, CH_{Ar}), ESIMS, m/z ($C_{44}H_{38}N_2O_6P_2$) calcd, 752.22 $[M]^+$; found, 752.0.

Tetraphenyl (1,2-phenylenebis(azanediyl))bis((4-(dimethylamino)phenyl)methylene)bisphosphonate (5c)

Yield (50%), (m.p): **>** 300 °C, IR (KBr) cm^{-1}: 3394 (-NH), 1607 (C=C, Ar), 1289 (P=O), 769 (P-C). ^{1}HNMR (DMSO-d_6 400 MHz): 2.75- 2.87 (m, 6 H, 2 CH_3), 3.00 (s, 6H, 2 CH_3), 3.52-3.57 (m, 2H, 2CH), 6.69 – 7.66 (m, 32H, CH_{Ar}). EIMS, m/z ($C_{48}H_{48}N_4O_6P_2$) calcd, 838.30 $[M]^+$; found, 838.0.

Tetraphenyl (1,4-phenylenebis(azanediyl))bis((4-(dimethylamino)phenyl)methylene)bisphosphonate (5d)

Yield (70%), (m.p): 120 -122 °C, IR (KBr)cm^{-1}: 3430, 3379 (-NH), 1595 (C=C, Ar), 1261 (P=O), 767 (P-C). ^{1}HNMR (DMSO-d_6 400 MHz): 2.84 (s, 6H, 2 CH_3), 3.06 (s, 6H, 2 CH_3), 5.15 – 5.21 (m, 2H, 2 CH), 5.88 (br, s, 1H, NH), 6.66 – 7.51 (m, 32H, CH_{Ar}), 9.37 (br, s, 1H, NH). ESIMS, m/z ($C_{48}H_{48}N_4O_6P_2$) calcd, 838.30 $[M]^+$; found, 838.0.

Synthesis of mono α-aminophosphonate using aniline as amine (general procedure)

To the carbonyl compound **6** (2.4 mmol), aniline **7** (2.4 mmol, 0.215 mL) and triphenylphosphite **3** (2.4 mmol, 0.625 mL) in acetonitrile (10 mL), lithium perchlorate (10 mol%) was added. The reaction mixture was stirred at room temperature until the starting materials were consumed as monitored by TLC (3 days). After the completion of the reaction the precipitated product was filtered off and crystallized by using diethyl ether and cooling.

Diphenyl2-oxo-1,2-diphenyl-1-(phenylamino)ethylphosphonate (8a)

Yield (65%), (m.p): 100 - 102 °C, IR (KBR) cm^{-1}:- 3424 (NH), 1665 (C=O), 1617 (C=C, Ar), 1287 (P=O), 767(P-C). ^{1}HNMR (DMSO-d_6 400 MHz):- 6.83 (d, 3H, J =8 Hz, CH_{Ar}), 6.94 - 6.96 (m, 2H, CH_{Ar}), 7.15 - 7.18 (t, 3H, J =8 Hz, CH_{Ar}), 7.43-7.62 (m, 10H, CH_{Ar}), 7.72 -7.80 (m, 6H, CH_{Ar}), 7.91 (d, 1H, J =8 Hz, CH_{Ar}). ^{13}C NMR (DMSO-d_6 100 MHz):- 113.9, 115.7, 120.0, 124.5, 127.7, 128.7, 129.0, 129.1, 129.5, 129.6, 132.2, 135.5, 148.9, 165.8, 194.8, 196.8. ESIMS, m/z ($C_{32}H_{26}NO_4P$) calcd, 519.16 $[M]^+$; found, 519.0.

Diphenyl3-oxo-1-phenyl-1-(phenylamino)butylphosphonate (8b)

Yield (50%), (m.p): >300 °C, IR (KBr) cm^{-1}:- 3429 (-NH), 1682 (C=O), 1616 (C=C, Ar), 1299 (P=O), 748 (P-C). ^{1}HNMR

(DMSO-d_6 400 MHz):- 2.18 (s, 3H, CH_3), 4.96 (br, s, 1H, NH), 5.87 (s, 1H, CH_2), 6.08 (s, 1H, CH olefin ,CH_2), 6.44 - 6.54 (m, 7H, CH_{Ar}), 6.96 - 7.00 (t, 3H, J = 8 Hz, CH_{Ar}), 7.24 - 7.30 (m, 2H, CH_{Ar}), 7.40 -7.51 (m, 6H, CH_{Ar}), 7.91 (d, 2H, J = 8 Hz, CH_{Ar}), 13.14 (s, 1H, OH tautomer). ESIMS, m/z ($C_{28}H_{26}NO_4P$) calcd, 471.16 $[M]^+$; found, 471.0.

Synthesis of bis α-aminophosphonate using aniline as amine (general procedure)

To the carbonyl compound **6** (2.4 mmol), aniline **7** (4.8 mmol, 0.43 mL) and triphenylphosphite **3** (4.8 mmol, 1.25 mL) in acetonitrile (10 mL), lithium perchlorate (10 mol%) was added. The reaction mixture was stirred at room temperature until the starting materials were consumed as monitored by TLC (3 days). After the completion of the reaction the precipitated product was filtered off and crystallized by using diethyl ether and cooling.

Tetraphenyl1,2-diphenyl-1,2-bis(phenylamino)ethane-1,2-diylbisphosphonate (9a)

Yield (60%), (m.p): 105 -107 °C, IR (KBr) cm^{-1} :- 3317 (-NH), 1587 (C=C, Ar), 1211 (P=O), 792 (P-C). ^{1}HNMR(DMSO-d_6 400 MHz) :- 6.47 - 6.55 (m, 2H, CH_{Ar}), 6.97 -7.01 (t, 1H, J = 8 Hz, CH_{Ar}), 7.33-7.35 (m, 1H, CH_{Ar}), 7.45 -7.51 (m, 1H, CH_{Ar}), 7.59 -7.64 (m, 14H, CH_{Ar}), 7.77 - 7.81 (m, 7H, CH_{Ar}), 7.92 (d, 13H, J = 8.4 Hz, CH_{Ar}), 7.98 (d, 1H, J = 8 Hz, CH_{Ar}). ESIMS, m/z ($C_{50}H_{42}N_2O_6P_2$) calcd, 828.25 $[M]^+$; found, 828.0.

Tetraphenyl1-phenyl-1,3bis(phenylamino)butane1,3diylbis(phosphonate) (9b)

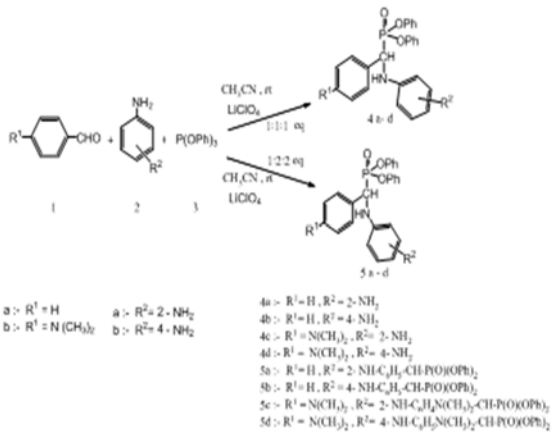
Yield (50%), (m.p): > 300 °C, ^{1}HNMR (DMSO-d_6 300 MHz):- 2.17 (s, 3H, CH_3), 5.63 (s, 1H, CH_2), 5.86 (br, s, 2H, 2 NH), 6.07 (s, 1H, CH olefin, CH_2), 6.45 - 6.56 (m, 10H, CH_{Ar}), 6.74 (d, 4H, J = 8.1 Hz, CH_{Ar}), 6.96 - 7.01 (t, 7H, J = 6 Hz, CH_{Ar}), 7.11 - 7.30 (m, 6H, CH_{Ar}), 7.38 - 7.50 (m, 5H, CH_{Ar}), 7.70 (s, 1H, CH_{Ar}), 7.92 (d, 2H, J=6Hz, CH_{Ar}), 13.14(s, 1H, OH tautomer). ESIMS, m/z ($C_{46}H_{42}N_2O_6P_2$) calcd, 780.25 $[M]^+$; found, 780.0.

RESULTS AND DISCUSSION

1. Chemistry: In order to synthesize of mono α-aminophosphonates 4, the three components, carbonyl compounds (aldehyde. 1eq.), aromatic diamines 2 (1eq), and triphenylphosphite 3 (1 eq) in acetonitrile were reacted in the presence of catalytic amount (10 mol.%) of $LiClO_4$ (Scheme 1).

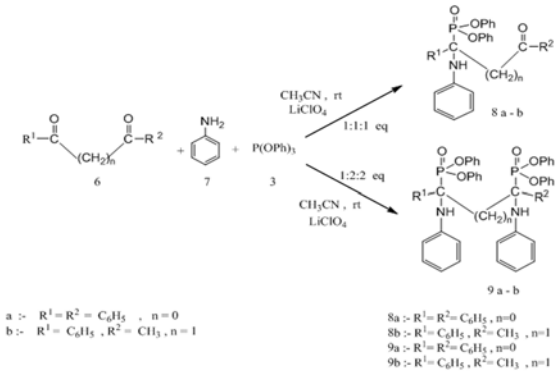
The reaction completely proceeded after 3 days with good isolated yields. On the other hand, bis- α-aminophosphonates **5** were synthesized in good yields by reacting the aldehyde (2eq.) with diamines (1eq.) and triphenylphosphite (2eq) in acetonitrile with presence of catalytic amount of $LiClO_4$ (Scheme 1).

The chemical structures of mono- and bis- α-aminophosphonates **4** and **5** respectively were confirmed by IR, ^{1}H NMR and mass spectral data and agreed very well with the proposed structures (*cf*. experimental section).



Scheme 1: Synthesis of mono- and bis-α aminophosphonates using from aldehydes.

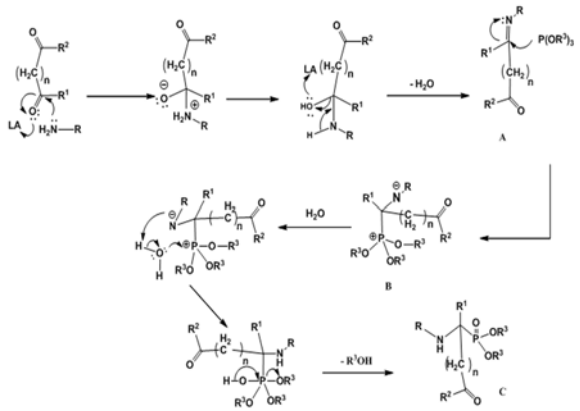
In order to extend the scope and limitation of the reaction. In an attempt to extend the scope of this catalytic reaction, we tried to perform the one-pot three component synthesis using $LiClO_4$ as a catalyst reaction with 1,2 and 1,3- diketones such as benzil and benzoylacetone respectively. In a typical experiment, the one-pot three component reaction of diketones **6**, aniline **7** and triphenylphosphite **3** in presence of catalytic amount of $LiClO_4$ in acetonitrile afforded mono- and bis-α-aminophosphonates 8 and 9 respectively in good yields after stirring 5 days at room temperature (*cf*. Scheme 2).



Scheme 2: Synthesis of mono- and bis-α aminophosphonates using diketone

The formation of mono- and bis- α-aminophosphonates **8** and **9** were based on the molar ratio of carbonyl compounds, aniline and phosphite. Finally, the synthesized compounds 8 and 9 were structurally characterized on the basis of IR, ^{1}H-NMR and MS spectral data and the structures were consistent with the data (cf. experimental section). The recommended mechanism for preparation of α-aminophosphonates using $LiClO_4$ as a catalyst is shown in Scheme 3. As shown in scheme 3, the reaction starts with activation of carbonyl group by Lewis acid catalyst ($LiClO_4$) followed by condensation of the carbonyl group of the starting aldehydes or diketones with amines to afford the Schiff base. Then the nitrogen of Schiff base that is formed in the first step of α-aminophosphonates formation donates a pair of electron to make a coordinante bond with $LiClO_4$. This makes

nitrogen positively charged which induces partial positive charge on sp^2 carbon. The free pair of electrons of phosphorus attacks to the partially positively charged carbon followed by protonation of nitrogen and elimination of phenol to afford α-aminophosphonates as depicted in Scheme 3.



Scheme 3: Suggested mechanism for synthesis of α aminophosphonates

Antimicrobial Screening

The antibacterial activities of the synthesized compounds were tested against *Escherichia coli* NRRL B-210 and *Pseudomonas* NRRL B-23 (Gram ve bacteria), *Bacillus subtilis* NRRL B-543 and *Staphylococcus aureus* NRRL B-313 (Gram +ve bacteria) using nutrient agar medium. The antifungal activity of these compounds was also tested against *Candida albicans* NRRL Y-477 using Sabouraud dextrose agar medium.

Agar Diffusion Medium

The synthesized compounds were screened *in vitro* for their antimicrobial activity against, by agar diffusion method (Cruickshank). 0.5 ml suspension of each of the aforementioned microorganisms was added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 0.9cm in diameter were made using a cork borer. Amounts of 0.1ml of the synthesized compounds were poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 hour at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The diameters of the inhibition zone of were measured and compared with that of the standard and the values were tabulated. The same method was carried out using Sabouraud dextrose agar medium on using *Candida albicans* NRRL Y-477. The plates were then incubated at 30°C for 24 hours and observed for antibacterial activity. The diameters of inhibition zone were measured and compared with that of the standard, the values were tabulated. Ciprofloxacin (50 µg/ml) and Fusidic acid (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively[17-19]. The observed zone of inhibition is presented in Table 1.

Table 1: *In vitro* antimicrobial activity by agar diffusion method of tested Compounds

Compds.	Microorganism inhibition zone diameter (mm)				
	Gram +ve bacteria		Gram –ve bacteria		Fungi
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*
4a	11	16	20	20	20
4b	23	18	20	18	20
4c	12	-ve	11	-ve	-ve
4d	23	-ve	20	-ve	20
5a	22	18	20	20	20
5b	11	-ve	-ve	-ve	ve
5c	15	11	20	11	20
5d	23	-ve	18	20	20
8a	18	11	20	12	18
8b	12	-ve	13	11	12
9a	23	18	20	18	20
9b	20	1	18	11	20
Ciprofloxacin	24	24	24	24	-
Fusidic acid	-	-	-	-	25

Highly active (+++)= (inhibition zone > 20 mm)
Moderately active (++)=(inhibition zone 15 - 19 mm)
Slightly active (+)= (inhibition zone 10 - 14 mm)
Inactive (-ve) = (inhibition zone < 10 mm)

CONCLUSION

We have reported one-pot three-component synthesis of mono – and bis- α-aminophosphonates as a valuable bioactive compounds to be investigated starting from aldehydes or diketones, amines, and triphenylphosphite using $LiClO_4$ as a catalyst. The biological assays show that most of the compounds containing mono- and bis-α-aminophosphonates had potent antibacterial and antifungal activity

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