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Synthesis and Bioassay of α-aminophosphonates

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ABSTRACT

An efficient and direct protocol is described for the preparation of α-amino phosphonates derivatives by employing a three component one-pot condensation reaction of aldehyde, amine and dialkyl phosphonates under solvent-free conditions by using microwave irradiation. The green procedure offers advantages such as shorter reaction time, simple work-up and high yields.

Keywords: α-aminophosphonates, bioassay, one-pot condensation, microwave irradiation,

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INTRODUCTION

Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates [1-3]. As a kind of natural amino acid analogues, α-aminophosphonates constitute an important class of compounds that exhibit a variety of interesting and useful properties [4-5]. In recent years, the preparation of α-amino phosphonates has attracted significant attention, due to their wide range of biological properties such as anti-HIV, anti-cancer, anti-biotic, anti-bacterial, anti-tumour and antiviral agents [6-11]. Furthermore, α-aminophosphonates are used in agricultural industry as fungicidal, herbicidal agents and plant growth regulators [12-14]. A number of synthetic methods for α-amino phosphonates have been developed. Of these, the nucleophilic addition of phosphites to imines, catalyzed by a base or an acid, is the most convenient. Lewis acids such as $ZrCl_4$, $ZnCl_2$, $BF_3.OEt_2$ and $SnCl_4$, have been used for this transformation [15-18]. However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, an amine and a dialkyl phosphite because the amine and water present during imine formation can decompose or deactivate the Lewis acid. This drawback has been overcome in some recent methods using lanthanide triflates/$MgSO_4$, $InCl_3$, $TaCl_5$–SiO_2, bismuth nitrate pentahydrate, Amberlite-IR 120, sulfamic acid, lithium perchlorate, and Amberlyst-15 [19-26]. Unfortunately, many of these processes suffer major or minor limitations, such as drastic reaction conditions, expensive reagents, low yields, tedious work-up procedures and the occurrence of several side reactions. The application of microwave irradiation for conducting organic reactions at highly accelerated rates is an emerging technique. In recent years, microwaves have become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and/or improving yields, as well as to promote new reactions [27-28]. Moreover, often when carrying out a reaction in a microwave oven, the use of a solvent can be avoided, which is important in order to make the synthesis more environmentally friendly ('green chemistry') [29-30]. These observations led us to investigate the possibility of improving the methods used for the synthesis of the α-amino phosphonate scaffold.

This paper describes a facile synthesis of α-amino phosphonates by condensation of aldehyde, amine and dialkyl phosphonates under solvent-free conditions by using microwave irradiation (Scheme 1).

MATERIALS AND METHODS

General

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 683 spectrophotometer using KBr optics. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker avance 400 MHz NMR spectrometer in $CDCl_3$ using TMS as internal standard. ^{31}P NMR (202.44 MHz) was taken in $CDCl_3$ using 85% H_3PO_4 as external standard with broadband ^{1}H decoupling. Mass spectra were recorded on a JEOL GCMATE II GC–MS spectrometer at SAIF, IIT, Chennai. Elemental analyses were performed using a Perkin–Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow, India. All chemicals were purchased from Sigma-Aldrich and used without further purification.

Chemistry

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

General procedure for preparation of α-amino phosphonates under microwave irradiation: aldehyde, aniline and dialkyl phosphite were added into a closed vessel. Then mixture was irradiated with microwave at 80 ºC for 4-6 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (3 X 10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and the crude product was purified by silica gel flash column chromatography eluted with 2:1 petroleum ether/acetone to give pure α-amino phosphonate.

Spectral data for compounds 4(a-l):

Dimethyl (2-amino-3,5-dibromophenyl)(4-cyanophenylamino)methylphosphonate 4(a):

Yield: 85 %. mp 156-158 ºC. IR (KBr) (ν_{max} cm^{-1}): 3333 (NH), 1262 (P=O), 752 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 (3H, s, P-OCH_3), 3.96 (3H, s, P-OCH_3), 4.80 (1H, d, *J* = 24.0 Hz, P-CH), 5.44 (2H, s, Ar-NH), 6.55 (1H, s, NH), 6.63-8.52 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 52.0 (d, *J* = 154.8 Hz, P-CH), 53.0.9 (d, *J* = 6.2 Hz, P-OCH_3), 53.8 (d, *J* = 5.9 Hz, P-OCH_3), 100.8 (C-4^1), 112.7 (C-2^1 & C-6^1), 115.1 (C-5), 118.0 (CN), 119.8 (C-3), 129.8 (C-4), 133.1 (C-6), 133.4 (C-1), 133.8 (C-3^1 & C-5^1), 140.9 (C-2), 150.8 (C-1^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 22.80. EI-MS (m/z, %): 488 (M+2, 60), 486 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{16}H_{16}Br_2N_3O_3P$: C, 39.29; H, 3.30; N, 8.59. Found: C, 39.22; H, 3.24; N, 8.48.

Diethyl (2-amino-3,5-dibromophenyl)(4-cyanophenylamino)methylphosphonate 4(b):

Yield: 81 %. mp 181-183 ºC. IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1268 (P=O), 753 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, t, *J* = 8.0 Hz, P-$OCH_2C\underline{H}_3$), 1.22 (3H, t, *J* = 8.0 Hz, P-$OCH_2C\underline{H}_3$), 3.62-3.72 (2H, m, P-$OC\underline{H}_2CH_3$), 3.81-3.90 (2H, m, P-$OC\underline{H}_2CH_3$), 4.95 (1H, d, *J* = 24.0 Hz, P-CH), 5.35 (2H, s, Ar-NH), 6.50 (1H, s, NH), 6.33-8.12 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.2(d, *J* = 6.2 Hz, P-$OCH_2\underline{C}H_3$), 16.8 (d, *J* = 5.8 Hz, P-$OCH_2\underline{C}H_3$), 52.8 (d, *J* = 152.0 Hz, P-CH), 54.2 (d, *J* = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 62.9 (d, *J* = 7.0 Hz, P-$O\underline{C}H_2CH_3$), 102.6 (C-4^1), 113.8 (C-2^1 & C-6^1), 115.8 (C-5), 118.7 (CN), 120.8 (C-3), 128.7 (C-4), 132.2 (C-6), 133.2 (C-1), 133.8 (C-3^1 & C-5^1), 141.2 (C-2), 151.8 (C-1^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 20.08. EI-MS (m/z, %): 518 (M+2, 60), 516 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{18}H_{20}Br_2N_3O_3P$: C, 41.80; H, 3.90; N, 8.13. Found: C, 41.74; H, 3.87; N, 8.09.

Dibutyl (2-amino-3,5-dibromophenyl)(4-cyanophenylamino)methylphosphonate 4(c)

Yield: 79 %. mp 174-176 ºC. IR (KBr) (ν_{max} cm^{-1}): 3325 (NH), 1260 (P=O), 750 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, t, *J* = 8.0 Hz, P-$OCH_2CH_2CH_2C\underline{H}_3$), 1.28-1.32 (2H, m, P-$OCH_2CH_2C\underline{H}_2CH_3$), 1.62-1.72 (2H, m, P- $OCH_2C\underline{H}_2CH_2CH_3$), 3.85-4.10 (2H, m, P-O $C\underline{H}_2CH_2CH_2CH_3$), 4.94 (1H, d, *J* = 24.0 Hz, P-CH), 5.32 (2H, s, Ar-NH), 6.55 (1H, s, NH), 6.63-8.52 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 13.3(d, *J* = 6.2 Hz, P-O $CH_2CH_2CH_2\underline{C}H_3$), 18.8 (d, *J* = 5.8 Hz, P-O $CH_2CH_2\underline{C}H_2CH_3$), 31.2(d, *J* = 6.2 Hz, P-O $CH_2\underline{C}H_2CH_2CH_3$), 66.2(d, *J* = 6.2 Hz, P-O $\underline{C}H_2CH_2CH_2CH_3$), 53.4 (d, *J* = 152.0 Hz, P-CH), 101.2 (C-4^1), 114.1 (C-2^1 & C-6^1), 116.1 (C-5), 119.2 (CN), 121.1 (C-3), 129.1 (C-4), 133.0 (C-6), 133.2 (C-1), 132.1 (C-3^1 & C-5^1), 140.1 (C-2), 152.1 (C-1^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 20.18. EI-MS (m/z, %): 575 (M+2, 60), 573 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{22}H_{28}Br_2N_3O_3P$: C, 46.50; H, 4.91; N, 7.34. Found: C, 46.2; H, 4.92; N, 7.33.

Dimethyl (2-amino-3,5-dibromophenyl)(2,4-dibromo-6- (hydroxymethyl)phenylamino)methylphosphonate 4(d):

Yield: 84 %. mp 169-171 ºC. IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1261 (P=O), 748 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48 (3H, s, P-OCH_3), 3.68 (3H, s, P-OCH_3), 4.34 (2H, s, OH-$C\underline{H}_2$), 4.52 (1H, d, *J* = 24.8 Hz, P-CH), 5.28 (1H, s, CH_2-O$\underline{H}$), 5.34 (2H, s, Ar-NH), 6.38 (1H, s, NH), 6.96-8.38 (4H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 52.4 (d, *J* = 152.7 Hz, P-CH), 52.9 (d, *J* = 6.2 Hz, P-OCH_3), 54.4 (d, *J* = 6.0 Hz, P-OCH_3), 60.4 (O-CH_2), 107.4 (C-5^1), 112.4 (C-5), 111.8 (C-4^1), 118.7 (C-3), 127.8 (C-4), 128.8 (C-6^1), 131.2 (C-6), 131.9 (C-3^1), 132.4 (C-1), 138.4 (C-1^1), 139.8 (C-2), 142.5 (C-2^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 22.40. EI-MS (m/z, %): 653 (M+2, 60), 651 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{16}H_{16}Br_2N_3O_3P$: C, 39.29; H, 3.30; N, 8.59. Found: C, 39.22; H, 3.24; N, 8.48. Anal. Calcd for $C_{16}H_{17}Br_4N_2O_4P$: C, 29.48; H, 2.63; N, 4.30. Found: C, 29.40; H, 2.59; N, 4.25.

Diethyl (2-amino-3,5-dibromophenyl)(2,4-dibromo-6-(hydroxymethyl)phenylamino)methylphosphonate (4e):
Yield: 91 %. mp 188-190 ºC. IR (KBr) (ν_{max} cm^{-1}): 3348 (NH), 1269 (P=O), 750 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (3H, t, *J* = 8.2 Hz, P-$OCH_2C\underline{H}_3$), 1.24 (3H, t, *J* = 8.0 Hz, P-$OCH_2C\underline{H}_3$), 3.48-3.62 (2H, m, P-$OC\underline{H}_2CH_3$), 3.80-3.94 (2H, m, P-$OC\underline{H}_2CH_3$), 4.40 (2H, s, OH-$C\underline{H}_2$), 4.69 (1H, d, *J* = 24.0 Hz, P-CH), 5.20 (1H, s, CH_2-O$\underline{H}$), 5.38 (2H, s, Ar-NH), 6.42 (1H, s, NH), 6.90-8.44 (4H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.8 (d, *J* = 6.0 Hz, P-$OCH_2\underline{C}H_3$), 17.1 (d, *J* = 5.7 Hz, P-$OCH_2\underline{C}H_3$), 49.4 (d, *J* = 150.8 Hz, P-CH), 56.8 (d, *J* = 7.4 Hz, P-$O\underline{C}H_2CH_3$), 58.4 (d, *J* = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 60.2 (O-CH_2), 108.5 (C-5[1]), 111.4 (C-4[1]), 112.8 (C-5), 118.7 (C-3), 125.6 (C-4), 127.4 (C-6[1]), 130.4 (C-6), 132.2 (C-3[1]), 133.5 (C-1), 137.4 (C-1[1]), 138.7 (C-2), 142.9 (C-2[1]). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 20.08. EI-MS (m/z, %): 653 (M+2, 60), 651 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{18}H_{21}Br_4N_2O_4P$: C, 31.79; H, 3.11; N, 4.12. Found: C, 31.70; H, 3.08; N, 4.08.

Dibutyl (2-amino-3,5-dibromophenyl)(2,4-dibromo-6- (hydroxymethyl)phenylamino)methylphosphonate (4f):
Yield: 90 %. mp 211-213 ºC. IR (KBr) (ν_{max} cm^{-1}): 3330 (NH), 1267 (P=O), 741 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 8.0 Hz, P-$OCH_2CH_2CH_2C\underline{H}_3$), 1.38-1.45 (2H, m, P-$OCH_2CH_2C\underline{H}_2CH_3$), 1.82-1.70 (2H, m, P- $OCH_2C\underline{H}_2CH_2CH_3$), 4.05-4. 18 (2H, m, P-O $C\underline{H}_2CH_2CH_2CH_3$), 4.95 (1H, d, *J* = 24.0 Hz, P-CH), 5.33 (2H, s, Ar-NH), 6.56 (1H, s, NH), 6.13-8.12 (5H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 13.5(d, *J* = 6.2 Hz, P-O $CH_2CH_2CH_2\underline{C}H_3$), 18.9 (d, *J* = 5.8 Hz, P-O $CH_2CH_2\underline{C}H_2CH_3$), 31.5(d, *J* = 6.2 Hz, P-O $CH_2\underline{C}H_2CH_2CH_3$), 66.5(d, *J* = 6.2 Hz, P-O $\underline{C}H_2CH_2CH_2CH_3$), 53.5 (d, *J* = 152.0 Hz, P-CH), 60.5 (d, *J* = 152.0 Hz, Ar-CH_2-), 101.3 (C-4[1]), 113.9 (C-2[1] & C-6[1]), 115.8 (C-5), 119.4 (CN), 121.0 (C-3), 129.3 (C-4), 132.8 (C-6), 133.3 (C-1), 133.3 (C-3[1] & C-5[1]), 141.2 (C-2), 153.0 (C-1[1]). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 22.28. EI-MS (m/z, %): 536 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{22}H_{29}Br_4N_2O_4P$: C, 35.88; H, 3.99; N, 3.83. Found: C, 35.90; H, 3.97; N, 3.81.

Dimethyl (2-amino-3,5-dibromophenyl)(4-bromophenylamino)methylphosphonate (4g):
Yield: 88 %. mp 199-201 ºC IR (KBr) (ν_{max} cm^{-1}): 3220 (NH), 1256 (P=O), 742 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48 (3H, s, P-OCH_3), 3.67 (3H, s, P-OCH_3), 4.84 (1H, d, *J* = 24.4 Hz, P-CH), 5.28 (2H, s, Ar-NH), 6.48 (1H, s, NH), 6.62-8.24 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 52.8 (d, *J* = 152.4 Hz, P-CH), 53.0 (d, *J* = 6.0 Hz, P-OCH_3), 53.7 (d, *J* = 5.8 Hz, P-OCH_3), 115.8 (C-4[1]), 112.7 (C-2[1] & C-6[1]), 113.1 (C-5), 115.4 (C-4[1]), 119.4 (C-3), 127.4 (C-4), 131.2 (C-6), 133.4 (C-1), 132.6 (C-3[1] & C-5[1]), 139.4 (C-2), 148.8 (C-1[1]). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 21.21. EI-MS (m/z, %): 544 (M+2, 20), 542 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{15}H_{16}Br_3N_2O_3P$: C, 33.18; H, 2.97; N, 5.16. Found: C, 33.12; H, 2.86; N, 5.08.

Diethyl (2-amino-3,5-dibromophenyl)(4-bromophenylamino)methylphosphonate (4h):
Yield: 82 %. mp 156-158 ºC IR (KBr) (ν_{max} cm^{-1}): 3338 (NH), 1262 (P=O), 759 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (3H, t, *J* = 7.8 Hz, P-$OCH_2C\underline{H}_3$), 1.19 (3H, t, *J* = 7.6 Hz, P-$OCH_2C\underline{H}_3$), 3.44-3.58 (2H, m, P-$OC\underline{H}_2CH_3$), 3.66-3.84 (2H, m, P-$OC\underline{H}_2CH_3$), 4.92 (1H, d, *J* = 22.8 Hz, P-CH), 5.12 (2H, s, Ar-NH), 6.32 (1H, s, NH), 6.78-8.20 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.2 (d, *J* = 6.8 Hz, P-$OCH_2\underline{C}H_3$), 16.8 (d, *J* = 6.4 Hz, P-$OCH_2\underline{C}H_3$), 52.2 (d, *J* = 150.8 Hz, P-CH), 52.8 (d, *J* = 7.4 Hz, P-$O\underline{C}H_2CH_3$), 54.4 (d, *J* = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 114.8 (C-4[1]), 112.4 (C-2[1] & C-6[1]), 113.8 (C-5), 116.2 (C-4[1]), 120.4 (C-3), 126.4 (C-4), 130.2 (C-6), 132.8 (C-1), 133.3 (C-3[1] & C-5[1]), 140.4 (C-2), 146.6 (C-1[1]). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 22.20. EI-MS (m/z, %): 544 (M+2, 20), 542 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{17}H_{20}Br_3N_2O_3P$: C, 35.76; H, 3.53; N, 4.91. Found: C, 35.68; H, 3.49; N, 4.85.

Dibutyl (2-amino-3,5-dibromophenyl)(4-bromophenylamino)methylphosphonate (4i):
Yield: 80 %. mp 171-173 ºC. IR (KBr) (ν_{max} cm^{-1}): 3340 (NH), 1265 (P=O), 755 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.11 (3H, t, *J* = 8.0 Hz, P-$OCH_2CH_2CH_2C\underline{H}_3$), 1.29-1.33 (2H, m, P-$OCH_2CH_2C\underline{H}_2CH_3$), 1.61-1.70 (2H, m, P- $OCH_2C\underline{H}_2CH_2CH_3$), 3.89-4.15 (2H, m, P-O $C\underline{H}_2CH_2CH_2CH_3$), 4.98 (1H, d, *J* = 24.0 Hz, P-CH), 5.36 (2H, s, Ar-NH), 6.57 (1H, s, NH), 6.11-8.12 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 13.4(d, *J* = 6.2 Hz, P-O $CH_2CH_2CH_2\underline{C}H_3$), 18.7 (d, *J* = 5.8 Hz, P-O $CH_2CH_2\underline{C}H_2CH_3$), 31.3(d, *J* = 6.2 Hz, P-O $CH_2\underline{C}H_2CH_2CH_3$), 66.1(d, *J* = 6.2 Hz, P-O $\underline{C}H_2CH_2CH_2CH_3$), 53.5 (d, *J* = 152.0 Hz, P-CH), 101.2 (C-4[1]), 114.4 (C-2[1] & C-6[1]), 116.6 (C-5), 119.4 (CN), 121.3 (C-3), 129.5 (C-4), 133.1 (C-6), 133.3 (C-1), 132.2 (C-3[1] & C-5[1]), 140.3 (C-2), 152.2 (C-1[1]). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 22.50. EI-MS (m/z, %): 627 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{21}H_{28}Br_3N_2O_3P$: C, 40.15; H, 4.51; N, 4.49. Found: C, 40.22; H, 4.50; N, 4.47.

Dimethyl (2-amino-3,5-dibromophenyl)(4-methoxyphenylamino)methylphosphonate (4j):
Yield: 79 %. mp 224-226 ºC. IR (KBr) (ν_{max} cm^{-1}): 3328 (NH), 1248 (P=O), 759 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.41 (3H, s, P-OCH_3), 3.58 (3H, s, P-OCH_3), 3.84 (3H, s, Ar-OCH_3), 4.80 (1H, d, *J* = 24.2 Hz, P-CH), 5.22 (2H, s, Ar-NH), 6.30 (1H, s, NH), 6.84-8.34 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 50.4 (d, *J* = 150.8 Hz, P-CH), 53.4 (d, *J* = 6.4 Hz, P-OCH_3), 53.9 (d, *J* = 6.2 Hz, P-OCH_3), 138.4 (C-4[1]), 109.8 (C-2[1] & C-6[1]), 112.8 (C-5), 113.6 (C-3[1] & C-5[1]), 118.8 (C-3), 127.4 (C-4), 130.5 (C-6), 133.8 (C-1), 138.4 (C-4[1]), 139.5 (C-2), 145.5 (C-1[1]). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 20.18. EI-MS (m/z, %): 496 (M+2, 20), 494 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{16}H_{19}Br_2N_2O_4P$: C, 38.89; H, 3.88; N, 5.67. Found: C, 38.81; H, 3.79; N, 5.61.

Diethyl (2-amino-3,5-dibromophenyl)(4-methoxyphenylamino)methylphosphonate (4k):
Yield: 81 %. mp 184-186 ºC. IR (KBr) (ν_{max} cm^{-1}): 3330 (NH), 1242 (P=O), 748 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t, *J* = 7.2 Hz, P-$OCH_2C\underline{H}_3$), 1.19 (3H, t, *J* = 7.4 Hz, P-$OCH_2C\underline{H}_3$), 3.40-3.52 (2H, m, P-$OC\underline{H}_2CH_3$), 3.59-3.74 (2H, m, P-$OC\underline{H}_2CH_3$), 3.80 (3H, s, Ar-OCH_3), 4.88 (1H, d, *J* = 24.8 Hz, P-CH), 5.14 (2H, s, Ar-NH), 6.28 (1H, s, NH), 6.80-8.42 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.4 (d, *J* = 7.0 Hz, P-$OCH_2\underline{C}H_3$), 16.9 (d, *J* = 6.8 Hz, P-$OCH_2\underline{C}H_3$), 50.8 (d, *J* = 150.2 Hz, P-CH), 53.8 (d, *J* = 7.0 Hz, P-$O\underline{C}H_2CH_3$), 54.4(d, *J* = 6.8 Hz, P-$O\underline{C}H_2CH_3$), 138.0 (C-4^1), 108.4 (C-2^1 & C-6^1), 111.4 (C-5), 114.7 (C-3^1 & C-5^1), 119.7 (C-3), 129.8 (C-4), 134.4 (C-6), 135.4 (C-1), 138.9 (C-4^1), 139.9 (C-2), 144.4 (C-1^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 21.19. EI-MS (m/z, %): 524 (M+2, 20), 522 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{18}H_{23}Br_2N_2O_4P$: C, 41.40; H, 4.44; N, 5.36. Found: C, 41.32; H, 4.37; N, 5.28.

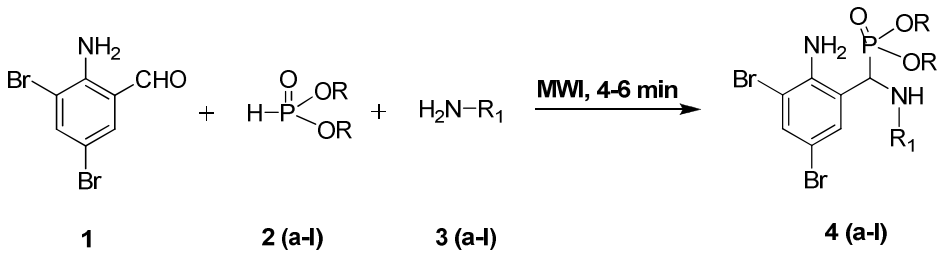
Dibutyl (2-amino-3,5-dibromophenyl)(4-methoxyphenylamino)methylphosphonate (4l):
Yield: 85 %. mp 210-212 ºC. IR (KBr) (ν_{max} cm^{-1}): 3350 (NH), 1266 (P=O), 755 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1. 60 (3H, t, *J* = 8.0 Hz, P-$OCH_2CH_2CH_2C\underline{H}_3$), 1.26-1.34 (2H, m, P-$OCH_2CH_2C\underline{H}_2CH_3$), 1.61-1.72 (2H, m, P- $OCH_2C\underline{H}_2CH_2CH_3$), 3.88-4.01 (2H, m, P-O $C\underline{H}_2CH_2CH_2CH_3$), 3.85 (3H, s, Ar-O-$CH_3$), 4.99 (1H, d, *J* = 24.0 Hz, P-CH), 5.35 (2H, s, Ar-NH), 6.65 (1H, s, NH), 6.60-8.50 (6H, m, Ar-H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 13.1(d, *J* = 6.2 Hz, P-O $CH_2CH_2CH_2\underline{C}H_3$), 18.3 (d, *J* = 5.8 Hz, P-O $CH_2CH_2\underline{C}H_2CH_3$), 31.3(d, *J* = 6.2 Hz, P-O $CH_2\underline{C}H_2CH_2CH_3$), 66.3(d, *J* = 6.2 Hz, P-O $\underline{C}H_2CH_2CH_2CH_3$), 55.3 (O-$CH_3$) 53.3 (d, *J* = 152.0 Hz, P-CH), 101.3 (C-4^1), 114.3 (C-2^1 & C-6^1), 116.5 (C-5), 119.6 (CN), 121.5 (C-3), 129.6 (C-4), 133.5 (C-6), 133.3 (C-1), 132.3 (C-3^1 & C-5^1), 141.3 (C-2), 152.3 (C-1^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 21.80. EI-MS (m/z, %): 579 (M+1, 60), 578 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{22}H_{31}Br_2N_2O_4P$: C, 45.70; H, 5.42; N, 4.86. Found: C, 45.69; H, 5.40; N, 4.84.

Antimicrobial Activity
Antimicrobial activity [31-36] of **4a-l** was tested against the growth of *Staphylococcus aureus* (ATCC 25923) (gram +ve) and *Escherichia coli* (ATCC 25922) (gram –ve) by disc diffusion method at various concentrations (100, 50 ppm) **Table 2**. Penicillin was used as the reference compound. All the compounds showed moderate to good activity against both the bacteria.

Table 2: Antibacterial activity of compounds 4a-l (µg/mL)

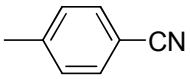
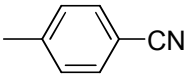
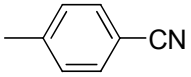
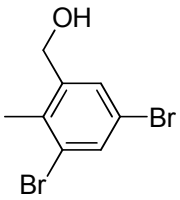
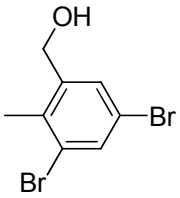
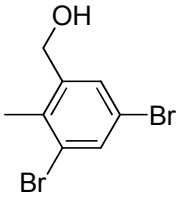
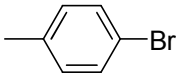
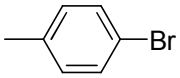
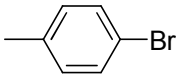
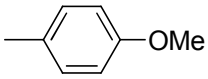
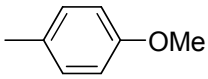
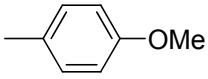
Compound	Zone of inhibition (mm)			
	Escherichia coli		*Staphylococcus aureus*	
	100	50	100	50
4a	8	6	8	5
4b	8	6	7	5
4c	9	6	8	6
4d	8	5	7	6
4e	7	5	7	5
4f	9	7	8	5
4g	9	7	8	6
4h	8	6	6	6
4i	7	6	9	6
4j	9	7	8	5
4k	8	5	9	6
4l	8	6	9	6
Penicillin[a]	12	8	10	7

[a]*Reference Compound*



Scheme 1

Table 1: Synthesis of α-aminophosphonates by microwave irradiation

Entry	R	R_1	Product	Time (min)	Yield (%)[a]
1	CH_3		4a	4	85
2	C_2H_5		4b	5	81
3	C_4H_7		4c	5	79
4	CH_3		4d	6	84
5	C_2H_5		4e	4	91
6	C_4H_7		4f	5	90
7	CH_3		4g	6	88
8	C_2H_5		4h	4	82
9	C_4H_7		4i	4	80
10	CH_3		4j	6	79
11	C_2H_5		4k	5	81
12	C_4H_7		4l	5	85

[a]*Isolated Yield*

Table 3: Antifungal activity of compounds 4a-l (µg/mL)

Compound	Zone of inhibition (%)			
	Aspergillus niger		*Helminthosporium oryzae*	
	100	50	100	50
4a	8	6	8	7
4b	9	5	9	7
4c	9	6	8	7
4d	9	6	9	8
4e	10	6	10	7
4f	10	5	9	8
4g	9	6	9	5
4h	9	6	12	8
4i	9	6	10	8
4j	8	5	12	8
4k	8	6	10	7
4l	10	6	10	8
Griseofulvin[a]	12	7	12	9

[a]*Reference Compound*

They were also screened for antifungal activity against *Aspergillus niger* (ATCC 16404) and *Helminthosporium oryzae* (ATCC 11000) species along with the standard fungicide Griseofulvin by the disc diffusion method at two different concentrations (100, 50 ppm) **Table 3**. All the compounds **4a-l** showed good activity against both the fungi.

Thus new group of compounds with good antimicrobial/fungicidal activity than the presently used commercial bactericides/fungicides have been discovered.

RESULTS AND DISCUSSION

The synthesis of α-aminophosphonates derivatives (**4a-l**) is accomplished in a single step process. The synthetic route involves the reaction of 2-amino-3,5-dibromobenzaldehyde, various amines and various dialkyl phosphonates under solvent-free conditions by using microwave irradiation to afford the title compounds (**4a-l**) in good yields (**Scheme 1**) in 4-6 Minutes. The progress of the reaction was monitored by TLC analysis and the crude products obtained after removing the solvent were purified by flash column chromatography on silica gel using 2:1 petrolium ether/acetone as eluents. The synthetic and analytical data of title compounds (**4a-l**) are given in the experimental part. All the compounds (**4a-l**) exhibited absorption bands for NH, P=O and P-C $_{\text{aliphatic}}$ in the regions 3320-3348, 1242-1269 and 741-759 cm^{-1} respectively. The ^{1}H NMR spectra (400 MHz) of **4a-l** exhibited as doublets in the range of δ 4.80-4.99 accounting for P-CH protons. The aromatic protons of **4a-l** resonated as multiplets at δ 6.13-8.52. The Ar–NH proton signal was observed at δ 5.32-5.44 as a singlet. The remaining protons gave signals in the expected regions. The ^{13}C NMR spectral data of all the compounds were recorded and the data are given in the experimental part. The remaining carbon signals are observed in the expected regions. Compounds **4a-l** exhibited phosphorus-31 resonance signals in the range of 20.08-22.80 ppm. The EI-MS of all the compounds were recorded and the presence of M^{+}, (M+2), (M+1) ions in their mass spectra indicate that they undergo a similar fragmentation pattern and the data are presented in the experimental section.

CONCLUSION

A new class of α-amino phosphonates under microwave irradiation with moderate antimicrobial activity were conveniently synthesized in good yields.

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