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Efficient one pot, three-component synthesis of new α-aminophosphonates and investigation of their antimicrobial activity

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ABSTRACT

A convenient one pot synthesis of new α-aminophosphonates ***(4a-h)*** *containing ethyl acetate moiety was accomplished via Kabachnik-Fields reactions in good yield. All synthesized compounds were characterized by IR,* ^{1}H *NMR,* ^{13}C *NMR,* ^{31}P *NMR and Mass spectroscopy and investigated their antimicrobial activity.*

Key words: α- Aminophosphonates, one pot synthesis, Kabachnik-Fields reactions, Antimicrobial activity.

INTRODUCTION

Organophosphorus compounds have found a wide range of application in industry, agriculture and medicinal chemistry owing to their unique physical and biological properties [1]. Out of them α-aminophosphonates and related α-aminophosphonic acids were studied as the analogous of α-amino acids in which the carboxylic acid moieties are replaced by phosphonates or phosphonic acid groups [2]. α-Aminophosphonates are the key intermediates in the synthesis of naturally occurring α-aminophosphonic acids [3].They are also used in medicinal chemistry as well as in agrochemistry. In medicinal chemistry α-aminophosphonates acts as HIV protease [4], enzyme inhibitors [5], anticancer agents [6], potential antibiotics [7], haptens for catalytic antibodies [8]. In agrochemistry α-aminophosphonates acts as herbicides [9], plant growth regulators [10].

In view of this several methods and modifications in the existing methods have been reported in the literature for the synthesis of α- aminophosphonates such as nucleophilic displacement of α-halo amino derivatives (Michaelis-Arbuzove reaction) [11], Pudovic reaction [12], oximation and reduction of α-oxophosphonates [13], Kabachnik-Fields reaction [14,15]. Recently various synthetic methods of cyclic α-aminophosphonic acids and α-aminophosphonates have been reviewed by Tarik Ali [16]. Zefirov and Matveeva reviewed the synthesis, characterization, stereochemistry and biological activities of acyclic α-aminophosphonates derivatives [17]. The most versatile and widely used approach is the Kabachnik-Fields reaction which is a one-pot, three-component method. In this method the reaction of carbonyl compound, amine and dialkyl or trialkyl phosphite results in the formation of α-aminophosphonates. Therefore we also utilized one pot Kabachnik-Fields reaction for the synthesis of new α-aminophosphonates **(4a-h)**.

MATERIALS AND METHODS

All the chemicals and solvents used were of synthetic grade (Aldrich and s d fine chemicals). The purity of all the synthesized compounds was checked by TLC. Melting points of all the compounds were determined by open

capillary method and are uncorrected. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F254, Merck). IR spectra were recorded on Shimadzu IR Affinity-1 using KBr discs. ^{1}HNMR spectra were scanned in $CDCl_3$ on Varian mercury plus (400MHz) and broker advance (300MHz) spectrometer taking TMS as an internal standard for both the spectrometers and ^{13}C resonant frequency of 75MHz. ^{31}P NMR spectra were recorded in $CDCl_3$ on Varian mercury plus(121MHz)spectrometer in which chemical shifts were referenced to 85% phosphoric acid. LCMS spectra were recorded on a Finnigan LCQ LC-MS system.

Diethyl(2-((ethoxycarbonyl)methyl)-4,5-dimethoxyphenyl) (phenylamino) methyl phosphonates (4a).
IR (KBr, cm^{-1}): 3292 (-NH), 1718 (C=O), 1228 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 7.08-7.13 (m, 3H, Ar*H*), 6.79 (s, 1H, Ar*H*), 6.68-6.72 (t, *J* = 7.15 Hz, 1H, Ar*H*), 6.62 (d, 2H, *J* = 8.2 Hz, Ar*H*), 5.00 (d, 1H, J_{H-P} = 21.9 Hz,, PC*H*), 4.69 (brs, 1H, N*H*), 4.05-4.19 (m, 4H, POCH_2CH$_3$), 3.90-3.97 (m, 2H, OCH_2CH$_3$), 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.61-3.70 (m, 2H, ArCH_2), 1.23-1.31 (m, 6H, POCH$_2$CH_3), 1.12 (t, *J* = 6.9 Hz 3H, OCH$_2$CH_3); ^{31}P NMR (121 MHz, $CDCl_3$, δ ppm): δ 21.72; ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.2, 148.2, 146.2, 146, 128.9, 126.4, 125, 118.3, 113.7, 110.3, 109.8, 63.2, 63.1, 60.8, 55.8, 55.7, 52.3(d, J_{C-P} = 150.9Hz), 38.1, 16.4, 16.1(d, J_{C-P} = 5.7 Hz), 14; LC-MS (*m/z*): 488 (M+Na).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (4-chlorophenyl amino) methyl phosphonates (4b).
IR (KBr, cm^{-1}): 3294 (-NH), 1724 (C=O), 1230 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 7.04 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.02 (s, 1H, Ar*H*), 6.78 (s, 1H, Ar*H*), 6.56 (d, 2H, *J* = 8.5 Hz, Ar*H*), 4.98 (d, 1H, J_{H-P} = 22.9 Hz, PC*H*), 4.73 (brs, 1H, N*H*), 4.07-4.18 (m, 4H, P-O-CH_2-CH$_3$), 3.90-3.98 (m, 2H, OCH_2CH$_3$), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.58-3.70 (m, 2H, ArCH_2), 1.25 & 1.28 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3), 1.12 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{31}P NMR (121 MHz, $CDCl_3$, δ ppm): δ 21.32; ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.27, 148.42, 144.8 (d, J = 13.3Hz), 128.87, 126.14, 125.27 (d, *J* = 7.2Hz), 123.03, 114.96, 113.93, 110.42, 63.30 (d, *J* = 7.2Hz), 63.08 (d, *J* = 6.6Hz), 60.96, 55.84 (d, *J* = 6.1Hz), 52.57 (d, J_{C-P} = 151.5Hz), 38.17, 16.38 (d, *J* = 6.1Hz), 16.17 (d, *J* = 5.5Hz), 14.11; LC-MS (*m/z*): 522 (M+Na).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (4-nitrophenylamino) methyl phosphonate (4c).
IR (KBr, cm^{-1}): 3273 (-NH), 1722 (C=O), 1230 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 8.04 (d, 2H, *J* = 9.1 Hz, Ar*H*), 6.97 (s, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 6.67 (d, 2H, *J* = 9.1 Hz, Ar*H*), 5.50 (brs, 1H, N*H*), 5.13 (d, 1H, J_{H-P} = 21.9Hz, PC*H*), 4.03-4.21 (m, 4H, POCH_2CH$_3$), 3.91-3.98 (m, 2H, OCH_2CH$_3$), 3.88 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.58-3.71 (m, 2H, ArCH_2), 1.26 & 1.30 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3),1.12 (t, 3H, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.1, 151.4, 148.6, 148.4, 138.9, 125.9, 125.3, 125, 113.9,112.3, 110, 63.7, 63, 61.1, 51.93 (d, J_{C-P} = 152 Hz), 38.1, 16.29,16.18, 14; LC-MS (*m/z*): 533(M+Na).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (3-methoxyphenylamino) methyl phosphonate (4d).
IR (KBr, cm^{-1}): 3290 (-NH), 1716 (C=O), 1224 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 7.07(d, 1H, *J* = 1.4 Hz, Ar*H*), 7.0 (t, 2H, *J* = 8.1 Hz, Ar*H*), 6.79 (s,1H, Ar*H*), 6.20-6.27 (m, 2H, Ar*H*), 5.05 (d, 1H, *J* = 21.9Hz, PC*H*), 4.75 (brs, 1H, N*H*), 4.05-4.19 (m, 4H, POCH_2CH$_3$),3.89-3.96 (m, 2H, OCH_2CH$_3$), 3.86 (s, 3H, OCH_3), 3.81(s, 3H,OCH_3), 3.70 (s, 3H, OCH_3), 3.61-3.66 (m, 2H, ArCH_2), 1.25 & 1.28 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3), 1.12 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.28, 160.58, 148.26, 147.65, 147.48, 129.76, 126.54, 125.1 (d, *J* = 6.9Hz), 113.75, 110.3, 106.65, 103.54, 99.87, 63.24 (d, *J* = 6.9 Hz), 63.0, 60.9, 55.84, 55.78, 54.94, 52.29 (d, J_{C-P} = 150.8 Hz), 38.2, 16.39 (d, *J* = 5.8 Hz), 16.19 (d, J_{C-P} = 4.6 Hz), 14; LC-MS (*m/z*): 496 (M+1), 518 (M+Na).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (4-fluro phenylamino) methyl phosphonates (4e).
IR (KBr, cm^{-1}): 3292 (-NH), 1712 (C=O), 1226 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 7.04 (s, 1H, Ar*H*), 6.78-6.80 (m, 3H, Ar*H*), 6.57 (s, 2H, Ar*H*), 4.97 (d, 1H, J_{H-P} = 22.3Hz, PC*H*), 4.60 (brs, 1H, N*H*), 4.09-4.15 (m, 4H, POCH_2CH$_3$), 3.92-3.97 (m, 2H, OCH_2CH$_3$), 3.86 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.58-3.71 (m, 2H, ArCH_2), 1.25 & 1.28 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3), 1.12 (t, *J* = 7.1 Hz 3H, OCH$_2$CH_3); ^{31}P NMR (121 MHz, $CDCl_3$, δ ppm): δ 21.64; ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.41 (d, *J* = 2.3Hz), 156.32 (d, J_{C-F} = *236.6* Hz), 148.41 (d, *J* = 2.7Hz), 142.62 (d, *J* = 13.9Hz), 126.37 (d, *J* = 2.8Hz), 125.34 (d, *J* = 7.2 Hz), 115.56 (d, *J* = 22.7 Hz), 114.92 (d, *J* = 7.8 Hz), 113.92 (d, *J* = 2.8Hz), 110.45 (d, *J* = 4.5), 63.33 (d, *J* = 7.2Hz), 63.17 (d, *J* = 7.2Hz), 61.04,

55.91 (d, *J* = 6.7Hz), 53.11 (d, *Jc-p* = 151.4Hz), 38.24, 16.48 (d, *J* = 6.1Hz), 16.29 (d, *J* = 5.5Hz), 14.19; LC-MS (*m/z*): 506 (M+Na).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (3-chloro-4-fluoro phenylamino) methyl phosphonate (4f).
IR (KBr, cm^{-1}): 3319 (-NH), 1720 (C=O), 1238 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 77.02 (s, 1H, Ar*H*), 6.87 (t, 1H, *J* = 8.9 Hz Ar*H*), 6.80 (s, 1H, Ar*H*), 6.66-6.69 (m, 1H, Ar*H*), 6.48-6.52 (m, 1H, Ar*H*), 4.71 (t, 1H, N*H*), 4.98 (d, 1H, J_{H-P} = 22.15 Hz, PC*H*), 4.01-4.21 (m, 4H, POCH_2CH$_3$), 3.90-3.98 (m, 2H, OCH_2CH$_3$), 3.88 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.57-3.73 (m, 2H, ArCH_2), 1.26 & 1.29 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3),1.13 (t, *J* = 7.1 Hz 3H, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.29, 151.42 (J_{C-F} = 239.6 Hz), 148.44, 143.10 (d, *J* = 11.5 Hz), 125.82, 125.33 (d, *J* = 6.9 Hz), 120.93 (d, *J* = 19.6 Hz), 116.62 (d, *J* = 21.9 Hz), 115.03, 113.96, 113.06 (d, *J* = 3.45 Hz), 110.24, 63.40 (d, *J* = 7.0 Hz), 63.14 (d, *J* = 6.9 Hz), 61.08, 55.80 (d, *J* = 6.9 Hz), 52.80 (d, J_{C-P} = 154.34 Hz), 38.21, 16.40 (d, *J* = 4.6 Hz), 16.23 (d, *J* = 5.7 Hz), 14.14; LC-MS (*m/z*): 540 (M+Na).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (4-bromo phenyl amino) methyl phosphonates (4g).
IR (KBr, cm^{-1}): 3318 (-NH), 1720 (C=O), 1238 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 7.18 (d, 2H, *J* = 7.2 Hz, Ar*H*) 7.04 (s, 1H, Ar*H*), 6.79 (s, 1H, Ar*H*), 6.54 (d, 2H, *J* = 8.2 Hz, Ar*H*), 4.99 (d, 1H, J_{H-P} = 22.15 Hz, PC*H*), 4.80 (d, 1H, N*H*), 4.05-4.16 (m, 4H, POCH_2CH$_3$), 3.87-3.97 (m, 5H, -OCH_3 & -OCH_2CH$_3$), 3.79 (s, 3H, OCH_3), 3.59-3.71 (m, 2H, ArCH_2), 1.26 & 1.28 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3), 1.12 (t, *J* = 6.7 Hz, 3H, OCH$_2$CH_3); ^{31}P NMR (121 MHz, $CDCl_3$, δ ppm): δ 21.41; ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ δ 171.24, 148.37, 145.22 (d, *J* = 13.8Hz), 131.72, 126.01 (d, *J* = 2.8 Hz), 125.23 (d, *J* = 7.1 Hz), 115.41, 113.90, 110.30 (d, *J* = 3.9 Hz), 110.10, 63.29 (d, *J* = 7.2 Hz), 63.06 (d, *J* = 7.2 Hz), 60.95, 55.82 (d, *J* = 6.1 Hz), 52.41 (d, J_{C-P} = 151.5 Hz), 38.13, 16.36 (d, *J* = 6.1 Hz), 16.15 (d, *J* = 5.5 Hz), 14.10; LC-MS (*m/z*): 545, 547 (M+H).

Diethyl (2-((ethoxycarbonyl) methyl)-4, 5- dimethoxyphenyl) (4-iodo phenyl amino) methyl phosphonates (10h).
IR (KBr, cm^{-1}): 3325 (-NH), 1725 (C=O), 1230 (P=O); ^{1}H NMR (300MHz, $CDCl_3$, δ ppm): δ 7.35 (d, 2H, *J* = 8.6 Hz, Ar*H*) 7.03 (s, 1H, Ar*H*), 6.79 (s, 1H, Ar*H*), 6.44 (d, 2H, *J* = 8.5 Hz, Ar*H*), 4.99 (d, 1H, J_{H-P} = 29.1 Hz, PC*H*), 4.79 (t, 1H, N*H*), 4.05-4.19 (m, 4H, POCH_2CH$_3$), 3.90-3.98 (m, 2H, OCH_2CH$_3$), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.58-3.70 (m, 2H, ArCH_2), 1.26 & 1.28 (t, 3H each, *J* = 7.0 Hz, 2 x P-OCH$_2$CH_3), 1.13 (t, *J* = 6.9 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): δ 171.26, 148.38, 145.84 (d, *J* = 13.3Hz), 137.62, 126.01, 125.58 (d, *J* = 7.1 Hz), 116.01, 113.90, 110.25 (d, *J* = 3.8 Hz), 79.41, 63.34 (d, *J* = 7.2 Hz), 63.10 (d, *J* = 7.2 Hz), 61.00, 52.27 (d, J_{C-P} = 151.4 Hz), 38.15, 16.39 (d, *J* = 6.0 Hz), 16.19 (d, *J* = 5.6 Hz), 14.13; LC-MS (*m/z*): 592 (M+H) & 613 (M+Na).

Antimicrobial Activity:
The synthesized compounds **4a-h** was screen for antimicrobial activity by Agar disc-diffusion method [18]. Stock solutions of the synthesized compounds were prepared by dissolving in dimethyl sulfoxide (DMSO) to 100 ppm concentration. These solutions were added to each filter disc and DMSO was used as control. The anti-bacterial activity of **4a-h** was assayed against the growth of gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* by the disc-fusion method in nutrient agar medium and antifungal activities were evaluated against *Aspergillus niger* and *Candida albicans* in Saboround's dextrose agar medium. After incubation for 24 h at 37 °C the zones of inhibition were measured in mm and compared with the activity of the standard drugs. The Ciprofloxacin was used as reference standard during screening of anti-bacterial activity and Amphotericin-B was used as the reference compound for anti-fungal activities.

RESULTS AND DISCUSSION

Chemistry:
Considering the importance of α-aminophosphonates in Medicinal Chemistry as well as in Agrochemistry, we have developed $TiCl_4$ catalyzed [19] (10 mol %) one pot three component Kabachnik-Fields reactions for the synthesis of new α-aminophosphonates **(4a-h)** from ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate **(1)**, simple anilines **(2a-h)** and triethylphosphite **(3)** in acetonitrile. In our previous work we have reported synthesis of **4e** as a useful intermediate for the synthesis of *N*-phenyl isoquinolone-1-phosphonate using TFA as a catalyst [20]. The starting

compound, ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate **(1)** was prepared from commercially available 3,4-dimethoxy phenyl acetic acid by esterification [21] followed by formylation with dichloromethyl methyl ether in presence of aluminium chloride and dichloromethane as a solvent [22]. The synthesis of α-aminophosphonate **4a** involves reactions of ethyl 2-(2-formyl-4, 5-dimethoxyphenyl) acetate **(1)**, simple aniline **(2a)** and triethylphosphite **(3)** in acetonitrile using $TiCl_4$ (10 mol %) as a catalyst at room temperature for 3h **(Scheme)**. The progress of reaction was monitored by TLC and product was purified by column chromatography using hexane: ethyl acetate (70:30) as an eluent, gummy oily product was obtained, scratched it in hexane at 0ºC to obtained a white solid of **4a** in 85% yield, mp.110-112°C.The structure of **4a** was determined on the basis of IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and mass spectroscopy. IR spectrum of **4a** showed presence of -NH, at 3292 cm^{-1}, band at 1718 cm^{-1} indicates presence of C=O of ester, 1228 cm^{-1} indicates presence of P=O and band at 1053 cm^{-1} and 1024 cm^{-1} indicates presence of –C-O stretching of methoxy and phosphate group. ^{1}H NMR spectrum showed doublet at 5.00 δ ($J_{H\text{-}P}$ = 21.9 Hz) which indicates the presence of -P-CH, due to coupling with both phosphorus and the -NH proton. The broad singlet at 4.69 δ indicates presence of –NH proton. The methylene protons of two -P-OCH_2-CH_3 showed a multiplet at 4.05-4.19 δ, and methyl protons of two -P-OCH_2-CH_3 also gave multiplate in the region 1.23-1.31 δ. Due to asymmetric carbon at ortho position, the benzylic protons from –CH_2-$COOC_2H_5$ became non equivalent and exhibited multiplates at δ 3.61-3.70. Two methoxy protons appeared as two singlets at 3.81 and 3.87 δ. The methylene protons of -OCH_2-CH_3 of ester group showed a multiplet at 3.90-3.97 δ. While methyl protons of -OCH_2-CH_3 of ester appeared as a triplet at 1.12 δ (J = 6.9 Hz). Seven aromatic protons appeared in the region of 6.62– 7.13 δ. In ^{31}P NMR (121MHz, $CDCl_3$) one phosphorous of CH–P=O $(OC_2H_5)_2$ appeared at 21.72 δ. In ^{13}C NMR spectrum the carbon chemical shifts for P-CH observed at δ 52.3 ($J_{C\text{-}P}$ = 150.9Hz), methylene carbons of two -P-OCH_2-CH_3 were appeared at δ 63.12 and 63.21. Methyl carbon of two –P-OCH_2-CH_3 in the title compound **4a** was appeared at δ 16.16 and 16.40. The benzylic carbon from –CH_2-$COOC_2H_5$ appeared at δ 38.14, while carbonyl carbon, methylene carbon and methyl carbon of -CO-OCH_2-CH_3 of ester group appeared at δ 171.26, 60.89 and 14.0 respectively. Two methoxy carbon of aromatic ring appeared at 55.73 and 55.81 δ. Aromatic carbons were found in the region 109.89 δ to 148.20 δ. LC-MS spectrum showed base peak of 488 (M + Na).

Scheme:

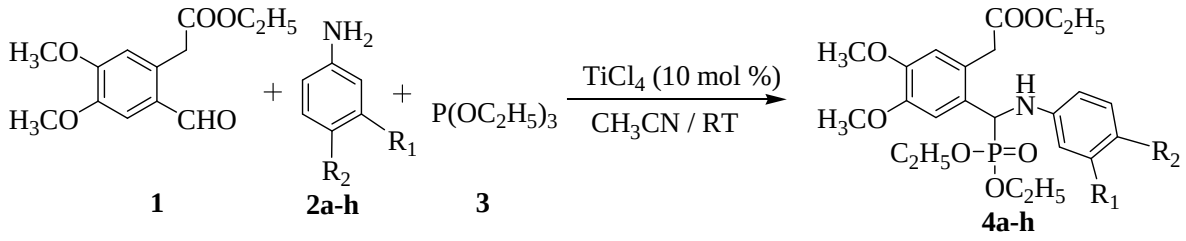

Table-1: Synthesis of new α-aminophosphonates (4a-h) [a].

Compound 2 & 4	R_1	R_2	Time (h)	Yield (%)[b]	MP (°C)
a	H	H	3	85	110-112
b	H	Cl	4	83	98-100
c	H	NO_2	5	72	140-142
d	OCH_3	H	6	82	78-80
e	H	F	3	77	118-120
f	Cl	F	7	75	116-118
g	H	Br	4	80	102-104
h	H	I	5	79	104-106

*[a] Standard reaction condition: **1** (1mmol), anilines **2a-h** (1.1 mmol), **3** (1.2 mmol), $TiCl_4$ (10 mol %) at 25 ºC, Acetonitrile (10 mL), [b] Isolated yield.*

Similarly the compounds **4b-h** was synthesized from ethyl 2-(2-formyl-4,5-dimethoxyphenyl) acetate **(1)** using substituted anilines which have either electron donating or electron withdrawing groups. The time required, yield obtained and melting point of compounds **4a-h** was summarized in **Table 1**.

Antimicrobial Activity:

The synthesized new α-aminophosphonates **(4a-h)** showed moderate to low activity against gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*. The compounds **4a**,

4c, **4e**, and **4g** exhibited appreciable anti-fungal activity against *Aspergillus niger* fungi as compared to *Candida albicans* while compound **4b** and **4h** showed moderate anti-fungal activity.

Table 2. Antimicrobial activity of α-aminophosphonates (4a-h).[a]

Compound	Zone of inhibition in mm				
	Anti-bacterial activity			Anti-fungal activity	
	S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
4a	12.01	12.5	16.7	**12.45**	7.70
4b	11.04	10.97	**14.2**	11.23	9.60
4c	-	-	-	**12.11**	8.55
4d	-	-	-	-	-
4e	9.59	11.34	9.45	**12.11**	7.30
4f	-	-	-	-	-
4g	11.65	12.12	11.15	**12.33**	**10.85**
4h	12.96	13.14	10.34	11.56	11.75
Ciprofloxacin[b]	**22.33**	**21.11**	**22.23**	NA	NA
Amphotericine-B[c]	NA	NA	NA	**15.34**	**14.23**

[a] The concentration of test compounds was 100µg/ml using solvent DMSO, '-' means no zone of inhibition, NA- Not applicable. [b] standard reference as anti-bacterial drug. [c] standard reference as anti-fungal drug.

CONCLUSION

In conclusion, an efficient, one pot synthesis of new α-aminophosphonates **(4a-h)** containing ethyl acetate moiety using $TiCl_4$ as a catalyst has been developed. These are useful intermediates in the synthesis of new *N*-Phenyl isoquinolone-1-phoshonates.[20] These new α-aminophosphonates **(4a-h)** showed low activity against bacteria and moderate to good activity on fungi. Among these, compounds **4a, 4c, 4e,** and **4g** showed significant antifungal activity against *Aspergillus niger* fungi.

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REFERENCES

[1] (a) R. Engel, *Chem. Rev.*, **1977,** 77, 349; (b) H. Kagan, J. Morrison, *Asymmetric Synthesis*, Ed.; Academic press: Orlando, FL, **1985**, 5, 1.
[2] (a) S. C. Fields, *Tetrahedron*, **1999,** 55, 12237; (b) D. Redmore, *J.Org.Chem.*, **1978**, 43, 992; (b) Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity, V. P. Kuhkhar, H. R. Hudson, Eds., fifth ed.; Wiley: Chichester, **2000**.
[3] W. Vander Donk, *J. Org. Chem.,* **2006**, 71, 9561.
[4] S. Bernd, K. Budt, L. Jian, A. Peyman, D. Ruppert, *Tetrahedron Lett.*, **1992**, 33, 6625.
[5] (a) W. Smith, P. Burtlett, *J. Am. Chem. Soc.*, **1998**, 120, 4622; (b) M. Allen, W. Fuhrer, B. Tuck, R. Wade, J. Wood, *J. Med. Chem*., **1989**, 32, 1652; (c) P. Peter, G. Paul, A. Bartlett, *J. Med. Chem.*, **1987**, 30, 1603.
[6] (a) Y. Kiran, D. Reddy, D. Gunasekar, C. Reddy, A. Leon, C. Luiz Barbosa, *Eur. J. Med. Chem.*, **2008**, 43, 885; (b) P. Kafarski, B. Lejczak, *Curr. Med. Chem. Anticancer Agents*, **2001**, 1, 301.
[7] (a) F. Atherton, C. Hassall, R. Lambert, *J. Med. Chem.*, **1986**, 29, 29
[8] R. Hirschmann, A. Smith, C. Taylor, P. Benkovic, S. Taylor, K. Yager, P. Sprengler, S. Benkovic, *Science*, **1994**, 265, 234.
[9] P. Kafarski, B. Lejczak, P. Mastalerz, *Chem. Abstr.*, **1985**, 103, 174532.
[10] D. Miliszkiewicz, P. Wieczorek, B. Lejczak, E. Kowalik, P. Kafarski, *Pestic Sci.*, **1992**, 34, 349.
[11] A. Schmidt, A. Lieberknecht, U. Schanbacher, T. Beuttler and J. Wild, *Angew. Chem.*, **1982**, 94, 797.
[12] A. N. Pudovik, *Dokl. Akad. Nauk SSSR*, **1952**, 83, 865.
[13] W. Xu, S. Zhang, S. Yang, L. Jin, P. Bhadury, D. Hu, and Y. Zhang, *Molecules*, **2010**, 15, 5782.
[14] M. I. Kabachnik, Medved, *Dokl. Akad. Nauk SSSR*, **1952**, 83, 689.
[15] E. K. Fields, *J. Am. Chem. Soc.*, **1952**, 74, 1528.
[16] T. Ali, *Arkivoc*, **2014**, i, 21.
[17] N. Zefirov, E. Matveeva, *Arkivoc*, **2008**, i, 1.

[18] (a) P. Merray, E. Baron, J. Jorgensen, M. Landry, M. Pfaller, Turnidge, Susceptibility test methods: Dilution and disk diffusion methods in manual of clinical microbiology, **2007**, II, 1152; (b) I. Espinel, P. R. Merray, J. Baron, J. H. Jorgensen, M. L. Landry, M. A. Pfaller, Susceptibility test methods: Yeasts and filamentous fungi, in manual of clinical microbiology, **2007,** II, 1972; (c) T. O. S. Popoola, O.D. Yangomodu, A.K. Akintokun, *Res. J. Med. Plant,* **2007**, 1, 60.
[19] Y. Reddy, P. Reddy, B. S. Kumar, P. Rajput, N. Sreenivasulu, B. Rajitha, *Phosphorus, Sulfur, and Silicon and the Related Elements*, **2007**, 182, 161.
[20] A.U. Borse, N. L. Patil, M. N. Patil, R. S. Mali, *Tetrahedron Lett*., **2012**, 53, 6940.
[21] Fulton and R. Robinson, *J. Chem. Soc*., **1933**, 1463.
[22] (a) C. Stearman, M. Wilson, A. Padwa, *J. Org. Chem*., **2009**, 74, 3491; (b) G. A.Kraus, M. E.Krolski, *J. Org. Chem*., **1986**, 51, 3347.