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K_2CO_3/Al_2O_3: An Efficient and Recyclable Catalyst for One-Pot, Three Components Synthesis of α-Aminophosphonates and Bioactivity Evaluation

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A simple and efficient method has been employed for synthesis of a novel series of biologically active α-aminophosphonates (**4a-j**) by reacting 1*H*-benzo[*d*]imidazole-2-carbaldehyde (**1**) and various aromatic amines (**2a-j**) and diethyl/dimethyl phosphite (**3**) by Kabachnik-Field's reaction in the presence of efficient heterogeneous K_2CO_3/Al_2O_3 catalyst under solvent-free conditions at 140 ºC. Structures of all the compounds were confirmed by ^1H, ^{13}C and ^{31}P NMR and LC-MS. In addition to this antioxidant activity were also evaluated.

Keywords: K_2CO_3/Al_2O_3 catalyst, α-Aminophosphonates, Antioxidant activity, Kabachnik-Field's reaction.

INTRODUCTION

α-Aminophosphonates being structural analogues of natural amino acids constitute an important class of compounds are receiving attention in organic and medicinal chemistry due to their broad spectrum in biological activities such as antifungal and antibacterial activities, inhibitors of synthase, HIV protease [1], plant growth regulators [2,3], antithrombotic agents [4], peptide mimetics [5], insecticides [6], herbicides [7] and virucides [8], haptens of catalytic antibodies [9], inhibitors of serine hydrolases [10], inhibitors of UDP-galactopyranose mutase [11], pharmacogenic agents [12] and enzyme inhibitors [13].

α-Aminophosphonates can be synthesized from the three component reaction of carbonyl compound with amine and dialkylphosphite through Kabachnik-Field reaction. It is very important in drug discovery research for generating peptidomimetic compounds. Based on their utility a number of synthetic methods for them have been carried out under neat conditions, such as nano Fe_3O_4 [14], [Yb(PFO)$_3$] [15], $CoCl_2{\cdot}6H_2O$ [16], metal triflate [17] and $Mg(ClO_4)_2$ [18]. α-Aminophosphonates have also been synthesized in organic solvents using $SbCl_3/Al_2O_3$ [19], $Cu(OTf)_2$ [20], $BiCl_3$ [21], $In(OTf)_3/MgSO_4$ [22], GaI_3 [23] and also in the presence of Lewis acid-surfactant-combined catalyst [24-27]. Specific synthetic cases even in solvent free and catalyst-free conditions are also reported [28]. However, these catalysts have few disadvantages, they require long reaction times, moisture sensitive catalysts and stoichiometric amounts of toxic catalysts. They ofen yield poor products and generate large amounts of waste which affects the quality of the reaction. It is a challenging goal to overcome these drawbacks. Due to these problems, development of an efficient and versatile method using heterogeneous and reusable catalysts is still in demand.

In recent years, heterogeneous catalysts have acquired considerable importance in diverse areas of organic synthesis due to their economic and environmental compatibility combined with the good yield and selectivity that can be accomplished [29-34]. In addition, the activity and selectivity of a reagent dispersed on the surface of a support are improved as the effective surface area of the reagent is increased significantly, and hence they are expected to perform more effectively than the individual reagents [35-41]. Among the various supported

catalysts, particu-larly, alumina and silica supported reagents have advantages of low cost, ease of preparation and catalyst recycling [42-46].

Considering the above facts and due to our interest in the solid catalysts for organic reactions [47], we report herein the investigation of K_2CO_3/Al_2O_3 as an efficient, low cost and heterogeneous reusable catalyst for the synthesis of α-aminophosphonates by the reaction of 1*H*-benzo[*d*]imidazole-2-carbaldehyde (**1**) and various aromatic amines (**2a-j**) and diethyl/dimethylphosphite (**3**) under solvent-free conditions (**Scheme-I**).

EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich, Hyderabad, India, and used without further purification. Melting points were determined on Guna Mel-Temp apparatus (Tempo Instruments and Equip., Mumbai, India) and were uncorrected. The IR spectra were recorded on Bruker Alpha ECO-ATR FTIR (Attenuated total reflection-Fourier transform infrared) interferometer with single reflection sampling module equipped with ZnSe crystal. ^{1}H, ^{13}C NMR spectra were taken on Jeol JNM ECP 400 NMR instrument (Tokyo) at room temperature in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as internal standard. EI-Mass spectra were obtained on JEOL GCMATE II GC-MS spectrometer (Tokyo) at SAIF IIT-Madras, Chennai.

General procedure for the synthesis of α-aminophosphonates (4a-j): To a mixture of 1*H*-benzo[*d*]imidazole-2-carbaldehyde (1 mmol) (**1**) and aniline (1 mmol) (**2a**) and diethyl phosphite (1.1 mmol) (**3**) in a round-bottom flask connected to a reflux condenser was added K_2CO_3/Al_2O_3 (0.15 g) and the resulting mixture was stirred in an oil-bath at 140 ºC for an appropriate time (10-15 min). The progress of reaction was monitored by thin-layer chromatography. After completion of reaction, the reaction mixture was cooled to room temperature, hot ethanol (20 mL) was added and filtered to remove the catalyst. Again the catalyst was washed with 10 mL of absolute ethanol (hot). The solvent of combined filtrate was evaporated under reduced pressure, and the crude product was recrystallized from ethyl acetate/*n*-hexane (1:3) or ethanol. The same procedure was adopted for the synthesis of remaining compounds (**4b-j**).

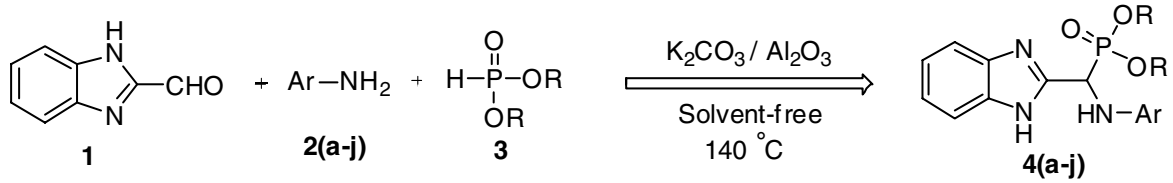
Diethyl (1*H*-benzo[*d*]imidazol-2-yl)(phenylaminomethyl)phosphonate (4a): White solid; Yield 85 %; m.p.: 172-174 ºC; IR (KBr, ν_{max}, cm^{-1}): 3294 (NH), 1242 (P=O), 743 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.20 (s, 1H, imada-zole NH), 7.80-6.75 (m, 9H, Ar-H), 6.40 (s, 1H, NH), 4.71 (d, *J* = 24.4 Hz, 1H, P-C<u>H</u>), 4.24-4.10 (m, 4H, 2 × P-O<u>CH</u>$_2$CH$_3$), 1.32-1.29 (m, 6H, 2 × P-OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 125.4 (C-1 & C-2), 140.2 (C-4 & C-5), 117.4 (C-3 & C-6), 140.5 (C-8), 72.2 (C-10), 114.0 (C-1′ & C-5′), 130.2 (C-2′ & C-4′), 122.0 (C-3′), 148.0 (C-6′), 62.8 (C-11 & C-13), 16.4 (C-12 & C-14). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 22.0; EI-MS (*m/z*, %): 359 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{18}H_{22}N_3O_3P$: C, 60.16 (60.12); H, 6.17 (6.14); N, 11.69 (11.59).

Diethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-fluorophenylaminomethyl)phosphonate (4b): White solid; Yield 89 %; m.p.: 122-124 °C; IR (KBr, ν_{max}, cm^{-1}): 3292 (NH), 1246 (P=O), 752 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.10 (s, 1H, imad-azole NH), 7.65-7.05 (m, 8H, Ar-H), 6.21 (s, 1H, NH), 4.68 (d, *J* = 24.4 Hz, 1H, P-CH), 4.22-4.09 (m, 4H, 2 × P-OCH$_2$CH$_3$), 1.30-1.28 (m, 6H, 2 × P-OCH$_2$CH$_3$); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 124.4 (C-1 & C-2), 140.4 (C-4 & C-5), 117.2 (C-3 & C-6), 140.8 (C-8), 72.4 (C-10), 117.9 (C-1′ & C-5′), 116.2 (C-2′ & C-4′), 156.2 (C-3′), 144.0 (C-6′), 62.6 (C-11 & C-13), 16.2 (C-12 & C-14). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 22.2; EI-MS (*m/z*, %): 377 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{18}H_{21}N_3O_3FP$: C, 57.29 (57.24); H, 5.61 (5.58); N, 11.14 (11.09).

Diethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-chlorophenylaminomethyl)phosphonate (4c): Yellow solid; Yield 91 %; m.p. 194-196 ºC; IR (KBr, ν_{max}, cm^{-1}): 3294 (NH),1252 (P=O), 750 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.98 (s, 1H, imad-azole NH), 7.62-6.50 (m, 8H, Ar-H), 6.18 (s, 1H, NH), 4.64 (d, *J* = 24.2 Hz, 1H, P-CH), 4.21-4.07 (m, 4H, 2 × P-OCH$_2$CH$_3$), 1.31-1.29 (m, 6H, 2 × P-OCH$_2$CH$_3$); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.4 (C-1 & C-2), 140.2 (C-4 & C-5), 116.4 (C-3 & C-6), 140.6 (C-8), 71.5 (C-10), 116.9 (C-1′ & C-5′), 128.8 (C-2′ & C-4′), 126.4 (C-3′), 144.5 (C-6′), 62.2 (C-11 & C-13), 16.4 (C-12 & C-14). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 21.4; EI-MS (*m/z*, %): 393 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{18}H_{21}N_3O_3PCl$: C, 54.90 (54.85); H, 5.38 (5.32); N, 10.67 (10.59).

Diethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-bromophenylaminomethyl)phosphonate (4d): White solid; Yield 90 %; m.p.: 140-142 ºC; IR (KBr, ν_{max}, cm^{-1}): 3290 (NH), 1248 (P=O), 752 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.95 (s, 1H, imadazole NH), 7.64-6.65 (m, 8H, Ar-H), 6.16 (s, 1H, NH), 4.66 (d, *J* = 24.2 Hz, 1H, P-CH), 4.19-4.08 (m, 4H, 2 × P-OCH$_2$CH$_3$), 1.32-1.29 (m, 6H, 2 × P-OCH$_2$CH$_3$); ^{13}C-NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.6 (C-1 & C-2), 139.0 (C-4 & C-5), 116.2 (C-3 & C-6), 140.8 (C-8), 71.2 (C-10), 115.0 (C-1′ & C-5′), 131.8 (C-2′ & C-4′), 116.4 (C-3′), 145.5 (C-6'), 62.3 (C-11 & C-13), 16.2 (C-12 & C-14). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 21.6; EI-MS (*m/z*, %): 438 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{18}H_{21}N_3O_3PBr$: C, 49.33 (49.30); H, 4.83 (4.79); N, 9.59 (9.56).

Diethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-methoxyphenylaminomethyl)phosphonate (4e): White solid; Yield 94 %; m.p.: 126-128 ºC; IR (KBr, ν_{max}, cm^{-1}): 3304 (NH), 1250 (P=O),



Ar = Ph, F-Ph, Cl-Ph, Br-Ph, MeO-Ph
R = Et, Me

Scheme-I: K_2CO_3/Al_2O_3 catalyzed synthesis of α-aminophosphonates

756 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.90 (s, 1H, imadazole NH), 7.60- 6.75 (m, 8H, Ar-H), 6.14 (s, 1H, NH), 4.60 (d, J = 24.2 Hz, 1H, P-CH), 4.18-4.06 (m, 4H, 2 × P-OCH_2CH_3), 3.80 (s, 3H, OCH_3), 1.30-1.28 (m, 6H, 2 × P-OCH_2CH_3); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.2 (C-1 & C-2), 139.4 (C-4 & C-5), 116.6 (C-3 & C-6), 140.6 (C-8), 71.0 (C-10), 115.4 (C-1′ & C-5′), 116.8 (C-2′ & C-4′), 156.4 (C-3′), 140.5 (C-6′), 62.2 (C-11 & C-13), 16.3 (C-12 & C-14). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 22.4; EI-MS (*m/z*, %): 389 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{18}H_{24}N_3O_4P$: C, 58.61 (58.57); H, 6.21 (6.19); N, 10.79 (10.56).

Dimethyl (1*H*-benzo[*d*]imidazol-2-yl)(phenylaminomethyl)phosphonate (4f): Green solid; Yield 84 %; m.p.: 142-146 ºC; IR (KBr, ν_{max}, cm^{-1}): 3312 (NH), 1252 (P=O), 762 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.96 (s, 1H, imad-azole NH), 7.65-6.70 (m, 9H, Ar-H), 6.12 (s, 1H, NH), 4.58 (d, J = 24.2 Hz, 1H, P-CH), 3.60 (s, 6H, 2 × $POCH_3$); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.1 (C-1 & C-2), 138.4 (C-4 & C-5), 116.5 (C-3 & C-6), 140.4 (C-8), 70.2 (C-10), 114.4 (C-1′ & C-5′), 129.8 (C-2′ & C-4′), 120.4 (C-3′), 147.5 (C-6′), 54.2 (C-11 & C-12). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 21.8; EI-MS (*m/z*, %): 331 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{16}H_{18}N_3O_3P$: C, 58.00 (57.96); H, 5.48 (5.40); N, 12.68 (12.58).

Dimethyl (1*H*-benzo[*d*]imidazol-2-yl)((4-fluorophenylaminomethyl)phosphonate (4g): White solid; Yield 86 %; m.p.: 125-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3304 (NH), 1260 (P=O), 764 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.98 (s, 1H, imadazole NH), 7.64-7.06 (m, 8H, Ar-H), 6.10 (s, 1H, NH), 4.56 (d, J = 24.2 Hz, 1H, P-CH), 3.62 (s, 6H, 2 × $POCH_3$); ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.2 (C-1 & C-2), 138.6 (C-4 & C-5), 116.4 (C-3 & C-6), 140.2 (C-8), 70.0 (C-10), 118.4 (C-1′ & C-5′), 117.1 (C-2′ & C-4′), 156.2 (C-3′), 143.5 (C-6′), 53.8 (C-11 & C-12); ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 23.2; EI-MS (*m/z*, %): 349 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{16}H_{17}N_3O_3PF$: C, 55.02 (54.97); H, 4.91 (4.82); N, 12.03 (11.92).

Dimethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-chlorophenylaminomethyl)phosphonate (4h): White solid; Yield 85 %; m.p.: 138-140 ºC; IR (KBr, ν_{max}, cm^{-1}): 3312 (NH), 1258 (P=O), 762 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.92 (s, 1H, imadazole NH), 7.69-6.58 (m, 8H, Ar-H), 6.14 (s, 1H, NH), 4.58 (d, J = 24.2 Hz, 1H, P-CH), 3.64 (s, 6H, 2 × $POCH_3$). ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.4 (C-1 & C-2), 138.8 (C-4 & C-5), 116.6 (C-3 & C-6), 140.0 (C-8), 70.4 (C-10), 114.4 (C-1′ & C-5′), 130.1 (C-2′ & C-4′), 126.4 (C-3′), 144.9 (C-6′), 53.4 (C-11 & C-12). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 22.6; EI-MS (*m/z*, %): 365 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{16}H_{17}N_3O_3PCl$: C, 52.54 (52.42); H, 4.69 (4.54); N, 11.49 (11.39).

Dimethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-bromophenylaminomethyl)phosphonate (4i): White solid; Yield 89 %; m.p.: 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 3310 (NH), 1256 (P=O), 764 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.90 (s, 1H, imad-azole NH), 7.60-6.65 (m, 8H, Ar-H), 6.16 (s, 1H, NH), 4.56 (d, J = 24.2 Hz, 1H, P-CH), 3.68 (s, 6H, 2 × $POCH_3$). ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.2 (C-1 & C-2), 138.6 (C-4 & C-5), 116.4 (C-3 & C-6), 140.1 (C-8), 70.2 (C-10), 114.8 (C-1′ & C-5′), 132.1 (C-2′ & C-4′), 116.4 (C-3′), 144.9 (C-6′), 53.2 (C-11 & C-12). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 21.2; EI-MS (*m/z*, %): 410 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{16}H_{17}N_3O_3PBr$: C, 46.85 (46.70); H, 4.18 (4.08); N, 10.24 (10.04).

Dimethyl (1*H*-benzo[*d*]imidazol-2-yl)(4-methoxyphenylaminomethyl)phosphonate (4j): White solid; Yield 90 %; m.p.: 132-134 ºC; IR IR (KBr, ν_{max}, cm^{-1}): 3306 (NH), 1254 (P=O), 762 (P-$C_{aliphatic}$); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.94 (s, 1H, imadazole NH), 7.62-6.75 (m, 8H, Ar-H), 6.12 (s, 1H, NH), 4.54 (d, J = 24.2 Hz, 1H, P-CH), 3.82 (s, 3H, OCH_3), 3.64 (s, 6H, 2 × $POCH_3$). ^{13}C NMR (100.5 MHz, DMSO-d_6) δ ppm: 123.6 (C-1 & C-2), 138.2 (C-4 & C-5), 116.2 (C-3 & C-6), 140.2 (C-8), 69.8 (C-10), 116.1 (C-1′ & C-5′), 115.6 (C-2′ & C-4′), 152.4 (C-3′), 144.9 (C-6'), 53.3 (C-11 & C-12). ^{31}P NMR (161.7 MHz, DMSO-d_6) δ ppm: 22.3; EI-MS (*m/z*, %): 361 ($M^{+\bullet}$, 100); Elemental anal. calcd. (found) for $C_{17}H_{20}N_3O_4P$: C, 56.51 (56.46); H, 5.58 (5.51); N, 11.63 (11.49).

Biological activity: The compounds 4(a-j) were evaluated for antioxidant property by DPPH [48,49], H_2O_2 [50] and NO [51,52] methods.

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity: The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of purple coloured methanol solution of 1,1-diphenyl-2-picrylhydrazyl radical (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. To 4 mL of 0.004 % w/v methanol solution of DPPH, 1 mL of various concentrations of the test compounds (50, 75 and 100 µg/mL) in methanol were added. After 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. Ascorbic acid was used as the standard. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation:

$$\text{Inhibition } (\%) = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where $A_{control}$ is the absorbance of control reaction (containing all reagents except the test compounds), A_{sample} is the absorbance of the test compound (containing methanolic DPPH and test compound). Tests were carried out in triplicate.

Hydrogen peroxide scavenging activity: The H_2O_2 scavenging ability of the test compound was determined by a solution of H_2O_2 (40 mm) was prepared in phosphate buffer (pH 7.4). 50, 75 and 100 µg/mL concentrations of the test compounds in 3.4 mL phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mm). The absorbance value of reaction mixture was recorded at 230 nm. Ascorbic acid was used as the standard. The percent scavenging of H_2O_2 was calculated by the following equation:

$$\text{Scavenging } (\%) = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where $A_{control}$ is the absorbance of the control reaction (containing all reagents except the test compounds), A_{sample} is the absorbance of the test compound (containing all reagents and test compound). Tests were carried out in triplicate.

Nitric oxide scavenging activity: Sodium nitroprusside (5 µM) in phosphate buffer pH 7.4 was incubated with different concentrations (50, 75 and 100 µg/mL) of test compounds

dissolved in a suitable solvent (methanol) and tubes were incubated at 25 ºC for 2 h. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 mL of incubation solution was taken and diluted with 0.5 mL of Griess reagent (1 % sulfanilamide, 0.1 % N-naphthyl ethylenediamine dihydrochloride and 2 % *o*-phosphoric acid dissolved in distilled water). The absorbance of chromophore formed during diazotization of nitrite with sulfanilamide and subsequent N-naphthylethylenediaminedihydrochloride was read at 546 nm. The experiment was run in triplicate. Nitric oxide scavenging activity was calculated by the following equation:

$$\text{Scavenging (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where $A_{control}$ is the absorbance of the control reaction (containing all reagents except the test compounds), A_{sample} is the absorbance of the test compound (containing all reagents and test compound). Tests were carried out in triplicate.

RESULTS AND DISCUSSION

An efficient and environmentally benign one-pot three components method for the synthesis of α-aminophosphonates (**4a-j**) by reaction of 1*H*-benzo[*d*]imidazole-2-carbaldehyde (**1**), various aromatic amines (**2a-j**) and diethyl/dimethyl phosphite (**3**) in the presence of K_2CO_3/Al_2O_3 as catalyst under neat conditions at 140 ºC (**Scheme-I**) is reported. In order to optimize the reaction conditions, the reaction among 1*H*-benzo[*d*]imidazole-2-carbaldehyde, aniline and diethyl phosphite was taken as a model reaction. Initially, we carried out the model reaction at room temperature, but there is minimal formation of the corresponding α-aminophosphonates in the presence of K_2CO_3/Al_2O_3 catalyst under solvent-free conditions. By Increasing of the reaction temperature from 30 to 140 ºC the formation of α-aminophosphonates took place in 94 % yield. Further by increase in the temperature up to 170 ºC, there is no improvement in product yield. The key step in the one pot synthesis of α-aminophosphonates is the nucleophillic addition of phosphite to the resulting imine. Another important feature of this reaction is survival of different functional groups such as fluoro, chloro, bromo, methoxy groups under these reaction conditions which made possible for the synthesis of α-aminophosphonates (Table-1) with these functional groups and screen them for bioactivity studies in order to establish the relevant structural requirements for more potent bio activity. All the synthesized compounds were characterized by FT-IR, ^1H, ^{13}C and ^{31}P NMR and all the spectral data were in good agreement with the proposed structures.

Antioxidant activity: The compounds **4a-j** were tested for antioxidant activity by 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydrogen peroxide and nitric oxide (Table-2) methods. In all the three methods, compounds **4e** and **4j** showed good radical scavenging activity when compared with the standard drug ascorbic acid. Further, the analysis of data presented in Table-2 indicates that radical scavenging activity in DPPH, hydrogen peroxide and nitric oxide methods increases with increase in concentration. The free radical scavenging activity of compounds **4e** and **4j** was measured at different concentrations and monitored

TABLE-1
K_2CO_3/Al_2O_3 CATALYZED SYNTHESIS OF α-AMINOPHOSPHONATES

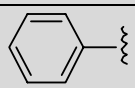
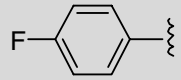
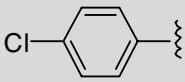
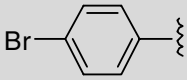
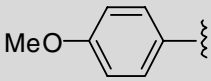
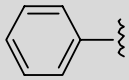
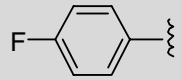
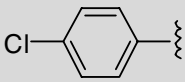
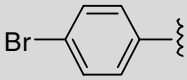
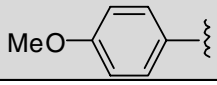
Entry	Ar	R	Product	Time (min)	Yield (%)
2a		Et	**4a**	15	85
2b		Et	**4b**	14	89
2c		Et	**4c**	13	91
2d		Et	**4d**	14	90
2e		Et	**4e**	12	94
2f		Me	**4f**	14	84
2g		Me	**4g**	13	86
2h		Me	**4h**	14	85
2i		Me	**4i**	13	89
2j		Me	**4j**	14	90

TABLE-2
in vitro ANTIOXIDANT ACTIVITY OF **4(a-j)** BY DIFFERENT METHODS

Compd.	DPPH method				H_2O_2 method			NO method		
	50 µg/mL	75 µg/mL	100 µg/mL	IC_{50} (µg/mL)	50 µg/mL	75 µg/mL	100 µg/mL	50 µg/mL	75 µg/mL	100 µg/mL
4a	59.02±0.12	61.59±0.32	63.84±0.38	42.35±0.029	65.42±0.18	66.54±0.22	68.62±0.40	66.20±0.14	68.92±0.24	70.40±0.32
4b	62.32±0.09	65.74±0.14	67.70±0.66	40.11±0.031	66.92±0.24	67.53±0.34	69.84±0.43	67.72±0.26	69.80±0.35	71.80±0.16
4c	64.74±0.14	66.52±0.24	68.38±0.32	38.61±0.029	67.34±0.22	68.20±0.30	70.58±0.37	68.62±0.18	70.10±0.20	72.12±0.34
4d	67.32±0.12	69.24±0.20	71.20±0.30	37.13±0.030	69.98±0.16	70.84±0.22	73.96±0.34	70.96±0.16	72.89±0.22	74.90±0.30
4e	72.04±0.11	74.69±0.34	75.94±0.29	34.70±0.030	74.22±0.32	76.25±0.18	78.34±0.42	76.62±0.22	78.86±0.18	80.92±0.24
4f	50.98±0.10	52.84±0.32	54.92±0.24	49.03±0.028	58.86±0.18	60.90±0.24	62.24±0.36	60.84±0.14	63.76±0.22	66.60±0.28
4g	51.86±0.12	53.80±0.22	55.98±0.20	48.20±0.031	60.92±0.16	62.86±0.22	64.96±0.32	61.86±0.12	63.90±0.24	67.97±0.26
4h	52.35±0.15	54.32±0.32	57.54±0.38	47.75±0.029	62.62±0.19	64.64±0.30	66.52±0.34	62.33±0.20	64.62±0.16	68.75±0.16
4i	58.64±0.14	60.54±0.24	62.90±0.14	42.63±0.030	64.74±0.30	66.32±0.62	68.46±0.42	64.42±0.18	66.86±0.24	69.24±0.20
4j	70.33±0.11	71.34±0.18	73.54±0.20	35.54±0.032	72.85±0.45	74.32±0.64	76.24±0.37	74.92±0.36	76.66±0.12	79.70±0.28
AA	73.23±0.10	75.22±0.13	77.34±0.35	34.04±0.008	75.28±0.19	77.29±0.09	79.20±0.12	77.11±0.31	79.86±0.43	81.36±0.34

AA = Ascorbic acid; Values were the means of three replicates ± SD

the change in absorbance at 10, 20 and 30 min in DPPH method (Table-3). At 10 min intervals, the values are close and the results indicated that the antioxidant activity is independent of time.

TABLE-3
ANTIOXIDANT ACTIVITY OF THE COMPOUNDS **4e** AND **4j** AT 10 min

Compound	10 min	20 min	30 min
4e	72.37	72.42	72.69
4j	71.41	71.50	71.61

Time intervals by DPPH scavenging method.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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