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Chitosan catalyzed synthesis and antioxidant activities of diethyl hydroxy (substituted phenyl) methylphosphonates

N. Bakthavatchala Reddy [1], K. Uma Maheswara Rao [2], Ch. Syama Sundar[1], S. Siva Prasad [1], S. K. Nayak [3] and C. Suresh Reddy [1]*[*]

[1]*Department of Chemistry, Sri Venkateswara University, Tirupati-517 502, India.*

[2]*Department of Chemistry, Yonsei University, Wonju, Gangwon-do 220-710, South Korea.*

[3]*Bio-Organic Division, BARC, Mumbai, India*

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Abstract: Chitosan catalyzed synthetic procedure has been developed for the synthesis of α-hydroxy phosphonates from different aromatic aldehydes and diethyl phosphite at 60 ºC. The title compounds are characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data. All the title compounds **3a-j** were tested for their invitro antioxidant activities by DPPH, Nitric Oxide and H_2O_2 scavenging methods.

Keywords: α-Hydroxy phosphonates; chitosan; heterogeneous catalyst; diethyl phosphite; antioxidant activity.

1. Introduction

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1-4] Particularly Phosphorus-carbon bond formation has attracted growing attention due to the application of P-C compounds in several areas. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[5,6] Among α-functionalized phosphonic acids, α-hydroxy phosphonates emerged as important class of compounds because of their interesting and useful properties. Recently, it was reported that α-hydroxy phosphonates have enzyme inhibitory activity towards rennin,[7] farnesyl protein transferase,[8] human immunodeficiency virus protease and polymerase.[9] They also have anti-virus and anti-cancer activity.[10]

Reported methods for the synthesis of α-hydroxy phosphonates involves the addition of H-Phosphonates to different carbonyl compounds in the presence of various catalysts such as ethyl magnesium bromide,[11] potassium fluoride on alumina,[12] quinine,[13] LDA,[14] TMSCl,[15] guanidine hydrochloride,[16] NH_4VO_3,[17] $KHSO_4$.[18] However, all of them have drawbacks such as long reaction time, requirement of drastic reaction conditions, difficult work ups and low yields. Therefore there is a

* Corresponding author: E-Mail: csrsvu@gmail.com

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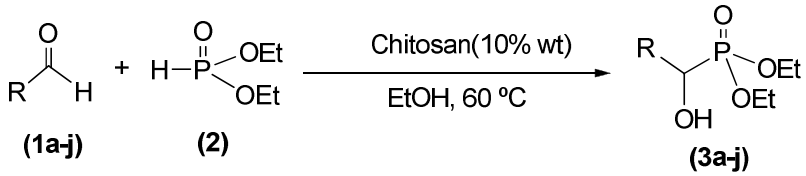
great demand for the development of more convenient and practically efficient methods for the synthesis of such significant scaffolds.

In continuation of our interest to develop efficient synthetic routes for biologically potent organophosphorus compounds using green chemical techniques for organic synthesis,[19,20] we successfully used Chitosan as a catalyst for the synthesis of α-hydroxy phosphonates. Being hydrophilic and possessing basic moieties,[21,22] chitosan has been utilized as heterogeneous eco-friendly basic catalyst for reactions carried out in protic media.[23] This catalyst is inexpensive, easy to handle, non-toxic and does not require the maintenance of anhydrous conditions. There have been no reports on the synthesis of α-hydroxy phosphonates using Chitosan as catalyst.

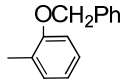
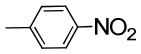
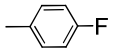
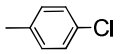
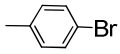
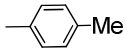
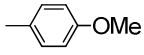
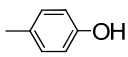
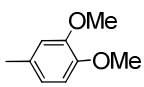


Scheme 1. Chitosan catalyzed synthesis of α-hydroxy phosphonates

2. Results and discussion

In an initial endeavour, we carried out the reaction of o-benzyloxy benzaldehyde and diethyl phosphite in the presence of Chitosan (10% wt) at 60 ºC to give the corresponding α-hydroxy phosphonate in 92% yield (Table 1, entry 2).

Table 1. Synthesis of α-hydroxyphosphonates

Product	R	Time (min)	Yield (%)[a]
3a		30	85
3b		25	92
3c		30	94
3d		25	89
3e		30	86
3f		35	87
3g		40	84
3h		30	82
3i		25	85
3j		60	82

[a]Isolated yield

Excellent results were obtained, when the reaction was performed with 10% wt of Chitosan in EtOH. It was found that the amount of Chitosan affects the yield of the product. Several structurally diverse carbonyl compounds and diethyl phosphite were subjected to this novel procedure to give the corresponding α-hydroxy phosphonates in high to moderate yields. The results are summarized in Table 1. The presence of -NO_2 electron withdrawing group on aldehyde (**3c**) increases the reactivity of

aldehydes to the H-phosphonates and gave the corresponding α-hydroxy phosphonates in higher yields while the -OMe electron donating group in the aldehyde (**3h**) decreases the reactivity of aldehyde and resulted lower yields of the products. The chemical structures of 3a-j were confirmed by elemental analysis, IR, ^{1}H, ^{13}C, ^{31}P- NMR and mass spectral data.

For the products **3a-j** the IR absorptions for hydroxyl group appeared as broad signal in the region 3220-3320 cm^{-1} and for the P=O group absorption appeared in the region 1210-1240 cm^{-1}. In ^{1}H-NMR the P-C-H group exhibited doublet at δ 4.70-5.45 due to its coupling with phosphorus.[24] The carbon chemical shifts in the title compounds were observed in their expected regions.[25] Their ^{31}P NMR chemical shifts were observed at δ 20.24-22.71. ESI-MS spectra gave molecular ions and diagnostic daughter ion peaks at their respective m/z values.

3. Antioxidant activity

The title compounds **3a-j**, α-hydroxy phosphonates exhibited antioxidant activity. This is due to the presence of hetero atoms bearing non bonded electron pairs that serve as binding sites in the bio-matrix. Hence their antioxidant activity was tested by DPPH,[26] nitric oxide[27,28] and H_2O_2[29] methods. The results were interpreted in figure 1 for DPPH, figure 2 for nitric oxide and figure 3 for H_2O_2 methods.

3.1. Determination of 1,1-Diphenyl-2-Picrylhydrazyl (DPPH) free radical Scavenging Activity:

85μM of DPPH was added to a medium containing different α-hydroxy phosphonates. The medium was incubated for 30 min at room temperature. Then the absorbance was taken at 517 nm. A control sample with no added title compounds was also analyzed and the results were expressed as percentage of radical scavenging activity (%RSA). Ascorbic acid was used as standard reference. The DPPH radical scavenging activity was calculated using the following equation.

$$\text{DPPH Scavenged } (\%) = \frac{[(A_{cont} - A_{test}]}{(A_{cont})} \times 100$$

Where, A_{cont} is the absorbance of control without sample. A_{test} is the absorbance in the presence of sample.

In the title compounds **3a-j**, the electron withdrawing, nitro substituted compound diethyl hydroxyl (4-nitrophenyl) methylphosphonate **3c** showed the highest DPPH radical scavenging activity with IC_{50} 29.14 μg/mL when compared with others because the reactive oxygen species (ROS) produced in cells causes the damage cells by starting chemical reactions by oxidizing DNA or Proteins. Since the nitro group ($-NO_2$) is highly electron withdrawing, it scavenges the ROS and prevents the production of ROS. The remaining compounds exhibited radical scavenging activity in the following order in terms of their IC_{50} valves. The IC_{50} valve of ascorbic acid (IC_{50} 32.10 μg/mL) was taken as standard. **3d** (IC_{50} 31.54 μg/mL), **3e** (IC_{50} 32.42 μg/mL), **3f** (IC_{50} 40.14 μg/mL), **3b** (IC_{50} 42.40 μg/mL), **3i** (IC_{50} 45.24 μg/mL), **3h** (IC_{50} 45.73 μg/mL), **3g** (IC_{50} 50.15 μg/mL), **3j** (IC_{50} 51.18 μg/mL), **3a** (IC_{50} 52.14 μg/mL).

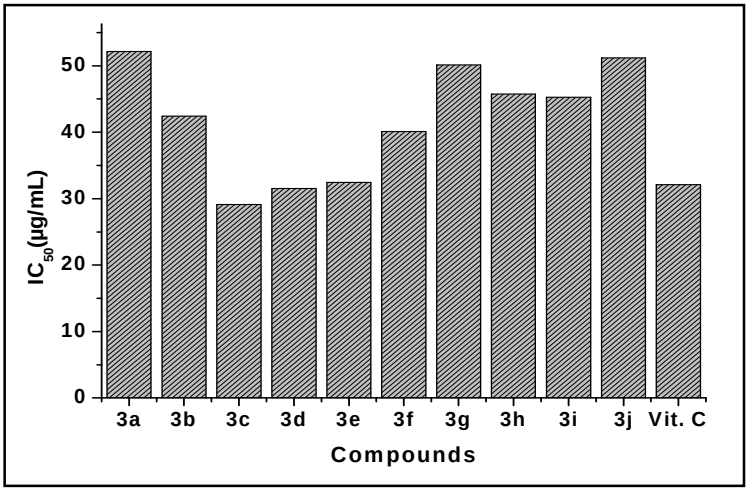


Figure 1. DPPH Radical Scavenging Activity

3.2. Determination of Nitric Oxide (NO) Scavenging Activity:

This method was based on the spontaneous generation of NO from the sodium nitroprusside (SNP) buffered solution. The reaction mixture (3mL) containing 2mL of 10 mM sodium nitroprusside, 0.5mL saline phosphate buffer and 0.5mL of extract (25 -100µg/mL) were incubated at 25°C for 150min. After 150 min of incubation, 0.5mL of the reaction mixture was mixed with 1.5mL Griess reagent [1.0% sulphanilamide, 2.5% H_3PO_4 and 0.1% N- (1 naphtyl) ethylenediamine dihydrochloride]. The absorbance of the nitrite with sulphanilamide and subsequent coupling with N-(1-naphtyl) ethylenediamine dihydrochloride was measured at 546 nm using UV-visible spectrophotometer. The results were expressed as a percent of scavenged nitric oxide with respect to the control without title compounds.

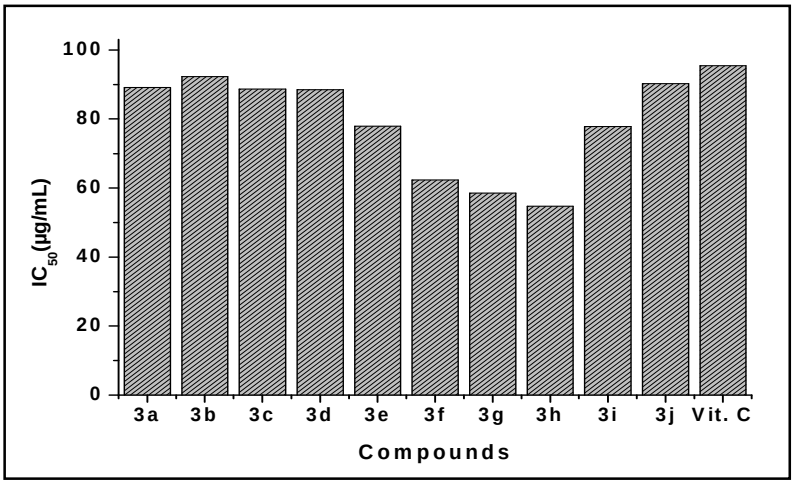


Figure 2. Nitric oxide (NO) Scavenging Activity

In the case of α-hydroxy phosphonates **3a-j** derivatives diethyl hydroxy(4-methoxyphenyl)methyl phosphonate **3h** showed the highest NO scavenging activity with IC_{50} of 54.71 µg/mL when compared with other compounds because the compound **3h** more scavenges the radicals produced during chemical reactions. The remaining compounds exhibited scavenging activity in the following order: **3g** (IC_{50} 58.49 µg/mL), **3f** (IC_{50} 62.29 µg/mL), **3i** (IC_{50} 77.82 µg/mL), **3e** (IC_{50} 77.89 µg/mL), **3d** (IC_{50} 88.51 µg/mL), **3c** (IC_{50} 88.65 µg/mL), **3a** (IC_{50} 89.15 µg/mL), **3j** (IC_{50} 90.22 µg/mL), **3b** (IC_{50} 92.31 µg/mL) and when compared with ascorbic acid (IC_{50} 95.40 µg/mL).

3.3. Determination of Hydrogen Peroxide (H_2O_2) Scavenging Activity:

In this method a solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (pH 7.4) and concentrations were determined spectrophotometrically at 230 nm. Extracts (25 - 100µg/mL) in distilled water was added to a hydrogen peroxide solution (0.6 mL , 40 mM) and the absorbance of hydrogen peroxide at 230 nm was determined after 19 min against a blank solution in phosphate buffer without hydrogen peroxide. The percentages of scavenging of hydrogen peroxide of title compounds were calculated.

In the case of α-hydroxy phosphonates 3a-j derivatives diethyl hydroxy(4nitrophenyl) methylphosphonate 3c showed the highest H_2O_2 scavenging activity with IC_{50} of 32.02 µg/mL when compared with others because it contains $–NO_2$ group. The remaining compounds exhibited reducing power activity in the following order: **3f** (IC_{50} 35.55 µg/mL), **3j** (IC_{50} 35.80 µg/mL), **3g** (IC_{50} 38.02 µg/mL), **3e** (IC_{50} 38.65 µg/mL), **3i** (IC_{50} 45.38 µg/mL), **3b** (IC_{50} 45.78 µg/mL), **3a** (IC_{50} 46.55 µg/mL), **3h** (IC_{50} 46.73 µg/mL), **3d** (IC_{50} 47.88 µg/mL), when compared with ascorbic acid (IC_{50} 52.23 µg/mL).

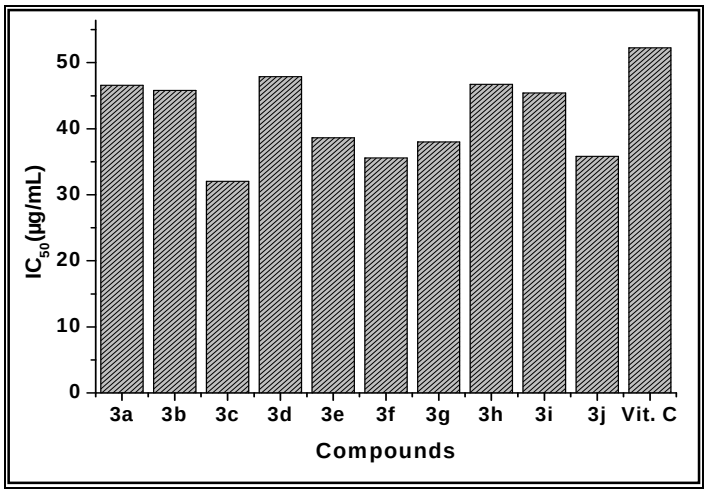


Figure 3. H_2O_2 Scavenging Activity

4. Conclusion

In conclusion, Chitosan was found to be an efficient catalyst for the one-pot reaction of aldehyde and diethyl phosphite to afford the corresponding α-hydroxy phosphonates in good to moderate yields. All the title compounds **3a-j** were tested for their antioxidant activity by three methods namely DPPH, NO and H_2O_2 scavenging methods and they showed the activity in high to moderate. The compound **3c** shows high antioxidant activity in both DPPH and H_2O_2 scavenging methods because **3c** contains high electron withdrawing $–NO_2$ group. The main advantages of the present method are mild reaction conditions, eco-friendly catalyst and easy reaction work-up procedure.

5. Experimental

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. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker avance 500 MHz NMR spectrometer operating at 300 MHz for ^1H NMR, 125 MHz for ^{13}C and 202 MHz for ^{31}P NMR. NMR data recorded in $CDCl_3$ were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectra were recorded on a JEOL GCMATE II GC-MS spectrometer at SAIF, IIT, Chennai. Elemental analyses were performed using Perkin-Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow, India. All chemicals were purchased from Sigma Aldrich and were used without further purification.

General procedure for the preparation of diethyl (2(benzyloxy) phenyl) (hydroxy) methylphosphonate (3b): A mixture of ortho-benzyloxy benzaldehyde (1 mmol) and diethyl phosphite (1.5 mmol) was dissolved in 30 mL absolute ethanol containing a catalytical amount of chitosan (10% wt). The mixture was heated at 60 ºC till completion of the reaction as indicated by thin layer chromatography (TLC). Undissolved chitosan was removed by filtration and the residue obtained by concentration of the filtrate was purified by column chromatography using silica gel (60-120 mesh) and EtOAc/n-hexane (1:3) as eluent to afford the pure product **3b** in 92% yield. This procedure was applied successfully for the preparation of **3a** and **3c-j**. All the compounds were characterized by IR, ^{1}H, ^{13}C, ^{31}P-NMR, mass spectral and elemental analytical data.

Diethyl hydroxy(phenyl)methylphosphonate (3a): Semi solid, yield: 85%. ^{1}H-NMR ($CDCl_3$): δ 1.21 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 1.27 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 3.91-4.06 (4H, m, P-OCH_2CH_3), 5.02 (1H, d, $^{2}J_{P-H}$ = 9.0 Hz, P-C-H), 7.24-7.48 (5Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.4, 63.2, 71.7, 125.4, 126.5, 127.2, 136.7. ^{31}P NMR (DMSO-d_6) δ: 22.25. IR (KBr)(νmax cm^{-1}); 3220 (OH), 1210 (P=O), 1010 (P-O-C). ESI-MS: (*m/z*) 244 (M+•). Anal.Calcd for $C_{11}H_{17}O_4P$: C, 54.10; H, 7.02. Found: C, 54.00; H, 6.99.

Diethyl (2-(benzyloxy)phenyl)(hydroxy)methylphosphonate (3b): Semi solid, yield: 92%. ^{1}H-NMR ($CDCl_3$): δ 1.21 (3H, t, $^{3}J_{H-H}$ = 6.9 Hz, $POCH_2CH_3$), 1.25 (3H, t, $^{3}J_{H-H}$ = 6.9 Hz, $POCH_2CH_3$), 3.69-4.09 (4H, m, P-OCH_2CH_3), 5.05 (2H, s, OCH_2), 5.45 (1H, d, $^{2}J_{P-H}$ = 10.0 Hz, P-C-H), 6.85-7.65 (9Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.5, 63.2, 72.5, 78.5, 112.8, 121.4, 125.5, 127.0, 127.4, 127.5, 128.0, 128.6, 134.5, 155.5. ^{31}P NMR (DMSO-d_6) δ: 22.50. IR (KBr)(νmax cm^{-1}); 3240 (OH), 1220 (P=O), 1015 (P-O-C). ESI-MS: (*m/z*) 350 (M+•). Anal.Calcd for $C_{18}H_{23}O_5P$: C, 61.71; H, 6.62. Found: C, 61.68; H, 6.58.

Diethyl hydroxy(4-nitrophenyl)methylphosphonate (3c): Semi solid, yield: 94%. ^{1}H-NMR ($CDCl_3$): δ 1.22 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 1.26 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 3.81-4.04 (4H, m, P-OCH_2CH_3), 5.12 (1H, d, $^{2}J_{P-H}$ = 9.0 Hz, P-C-H), 6.98-7.48 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.4, 63.4, 79.8, 129.5, 130.2, 144.2, 150.5. ^{31}P NMR (DMSO-d_6) δ: 20.54. IR (KBr)(νmax cm^{-1}); 3230 (OH), 1230 (P=O), 1020 (P-O-C). ESI-MS: (*m/z*) 289 (M+•). Anal.Calcd for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58. Found: C, 45.48; H, 5.48.

Diethyl (4-fluorophenyl)(hydroxy)methylphosphonate (3d): Semi solid, yield: 89%. ^{1}H-NMR ($CDCl_3$): δ 1.23 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 1.26 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 3.85-4.13 (4H, m, P-OCH_2CH_3), 4.99 (1H, d, $^{2}J_{P-H}$ = 9.0 Hz, P-C-H), 6.98-7.37 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.5, 69.4, 71.1, 115.3, 129.8, 132.4, 163.8. ^{31}P NMR (DMSO-d_6) δ: 21.64. IR (KBr)(νmax cm^{-1}); 3255 (OH), 1235 (P=O), 1025 (P-O-C). ESI-MS: (*m/z*) 262 (M+•). Anal.Calcd for $C_{11}H_{16}FO_4P$: C, 50.39; H, 6.15; Found: C, 50.20; H, 6.10.

Diethyl (4-chlorophenyl)(hydroxy)methylphosphonate (3e): Semi solid, yield: 86%. ^{1}H-NMR ($CDCl_3$): δ 1.21 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 1.24 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 3.65-4.20 (4H, m, P-OCH_2CH_3), 4.89 (1H, d, $^{2}J_{P-H}$ = 9.0 Hz, P-C-H), 6.88-7.57 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.5, 62.4, 79.8, 129.5, 130.2, 134.5, 138.2. ^{31}P NMR (DMSO-d_6) δ: 20.54. IR (KBr)(νmax cm^{-1}); 3320 (OH), 1225 (P=O), 1030 (P-O-C). ESI-MS: (*m/z*) 278 (M+•).Anal.calcd for $C_{11}H_{16}ClO_4P$: C, 47.41; H, 5.79; Found: C, 47.20; H, 5.60.

Diethyl (4-bromophenyl)(hydroxy)methylphosphonate (3f): Semi solid, yield: 87%. ^{1}H-NMR ($CDCl_3$): δ 1.22 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 1.25 (3H, t, $^{3}J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 3.55-4.10 (4H, m, P-OCH_2CH_3), 4.84 (1H, d, $^{2}J_{P-H}$ = 9.0 Hz, P-C-H), 6.88-7.47 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.2, 62.3, 79.4, 123.4, 128.5, 130.2, 132.9. ^{31}P NMR (DMSO-d_6) δ: 20.34. IR (KBr)(νmax cm^{-1}); 3250 (OH), 1240 (P=O), 1015 (P-O-C). ESI-MS: (*m/z*) 322 (M+•). Anal.calcd for $C_{11}H_{16}BrO_4P$: C, 40.89; H, 4.99; Found: C, 40.49; H, 4.69.

Diethyl hydroxy(p-tolyl)methylphosphonate (3g): White solid, yield: 84%, mp: 125-127 °C. ^{1}H-NMR ($CDCl_3$): δ 1.09 (3H, t, $^{3}J_{H-H}$ = 8.8 Hz, $POCH_2CH_3$), 1.20 (3H, t, $^{3}J_{H-H}$ = 9.2 Hz, $POCH_2CH_3$),

2.24 (3H, s, CH_3), 3.75-3.99 (4H, m, P-OCH_2CH_3), 4.70 (1H, m, P-C-H), 7.55-8.05 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.3, 22.5, 62.5, 125.5, 130.2, 135.2, 140.2. ^{31}P NMR (DMSO-d_6) δ: 20.40. IR (KBr)(νmax cm^{-1}); 3240 (OH), 1220(P=O), 1025 (P-O-C). ESI-MS: (*m/z*) 258 (M+•). Anal.calcd for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.42. Found: C, 55.61; H, 7.22.

Diethyl hydroxy(4-methoxyphenyl)methylphosphonate (3h): Semi solid, yield: 82%. ^1H-NMR ($CDCl_3$): δ 1.21 (3H, t, $^3J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 1.29 (3H, t, $^3J_{H-H}$ = 6.0 Hz, $POCH_2CH_3$), 3.94 (3H, s, OCH_3), 3.96-4.04 (4H, m, P-OCH_2CH_3), 4.94 (1H, d, $^2J_{P-H}$ = 9.0 Hz, P-C-H), 6.95-7.41 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.2, 62.3, 78.9, 118.5, 130.2, 131.5, 158.5. ^{31}P NMR (DMSO-d_6) δ: 22.35. IR (KBr)(νmax cm^{-1}); 3230 (OH), 1210 (P=O), 1020 (P-O-C). ESI-MS: (*m/z*) 274 (M+•). Anal.Calcd for $C_{12}H_{19}O_5P$: C, 52.25; H, 6.98. Found: C, 52.20; H, 6.68.

Diethyl hydroxy(4-hydroxyphenyl)methylphosphonate (3i): Solid. yield: 85%, mp:110-112. ^1H-NMR ($CDCl_3$): δ 1.13(6H, t, $^3J_{H-H}$ =7.2 Hz, P(O)CH_2CH_3), 3.65-3.84 (4H, m, P(O)CH_2CH_3), 4.80 (1H, d, $^2J_{P-H}$ = 10.4 Hz, P-C-H), 6.56-6.94 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.2, 56.5, 62.5, 79.8, 114.0, 122.2, 126.4, 158.5. ^{31}P NMR (DMSO-d_6) δ: 22.62. IR (KBr)(νmax cm^{-1}); 3240 (OH), 1240 (P=O), 1030 (P-O-C). ESI-MS: (*m/z*) 260 (M+•). Anal.calcd for $C_{11}H_{17}O_5P$: C, 50.77; H, 6.58. Found: C, 50.57; H, 6.38.

Diethyl (3,4-dimethoxyphenyl)(hydroxy)methylphosphonate (3j): Solid. yield: 82%, mp: 101-103. ^1H-NMR ($CDCl_3$): δ 1.28(6H, t, $^3J_{H-H}$ =7.2 Hz, P(O)CH_2CH_3), 3.57 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.90-4.19 (m, 4H, P(O)CH_2CH_3), 4.87 (d, $^2J_{P-H}$ = 10.2 Hz, P-C-H), 6.78-7.07 (4Ar-H, m). ^{13}C NMR ($CDCl_3$) δ: 16.5, 55.3, 71.4, 78.5, 113.9, 114.5, 122.4, 128.6, 147.5, 151.4. ^{31}P-NMR ($CDCl_3$): 22.20. IR (KBr)(νmax cm^{-1}); 3252 (OH), 1235 (P=O), 1040 (P-O-C). ESI-MS: (*m/z*) 304 (M+•). Anal.Calcd for $C_{13}H_{21}O_6P$: C, 51.31; H, 6.96. Found: C, 51.21; H, 6.86.

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