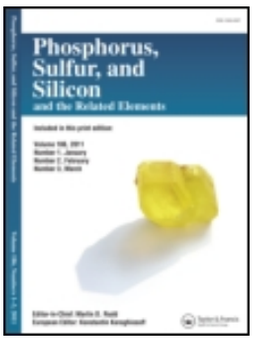

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SILICA-SUPPORTED TUNGSTIC ACID CATALYZED SYNTHESIS AND ANTIOXIDANT ACTIVITY OF α-HYDROXYPHOSPHONATES

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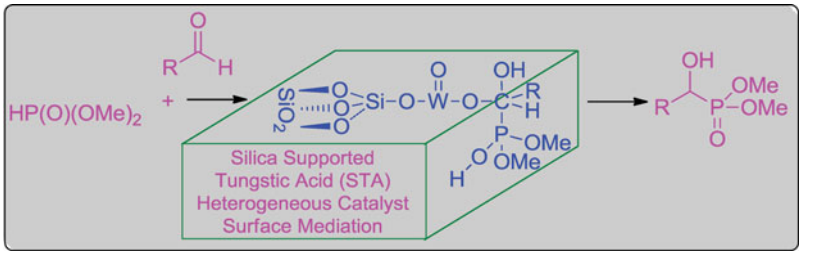
GRAPHICAL ABSTRACT



Abstract *A green and efficient method has been accomplished for the synthesis of α-hydroxyphosphonates using silica-supported tungstic acid (STA) as a heterogeneous catalyst under solvent-free conditions at ambient temperature. The compounds obtained were characterized by spectral and analytical studies and screened in vitro for the antioxidant activity by four methods viz., DPPH free radical scavenging assay, hydrogen peroxide scavenging assay, NO method, FRAP method. The results indicated that the title compounds are potential antioxidants and are comparable to the antioxidant property of the standard ascorbic acid.*

Keywords α-Hydroxyphosphonates; silica-supported tungstic acid (STA); anti-oxidant activity

INTRODUCTION

Phosphonates and phosphoric acids form an important class of organophosphorus compounds. Their importance in various fields is day-by-day increasing. The accelerated

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discovery of a multitude of naturally occurring phosphonates from a number of fungi, bacteria as well as higher order organisms started from the isolation of the first phosphonate, the 2-aminoethane phosphonic acid by Kandatsu and Horiguchi from rumen protozoa in 1959.[1] After this, substantial number of amino and hydroxyphosphonates have been isolated from the natural sources.

α-Hydroxyphosphonates in particular are found to have intriguing biological activities,[2] and are widely used in pharmaceutical and pesticide chemistry and enzyme inhibition. They also serve as biologically important molecules as enzyme, rennin,[3] and HIV protease inhibitors,[4] agonists of calcium transfer, antiviral, [5] and anticancer drugs.[6] In addition to these various applications, the aim of this study is to investigate their antioxidant activity.

Free radicals produced by several different chemical reactions within the body of a living organism include reduction of molecular oxygen during aerobic respiration yielding superoxide and hydroxyl radicals. Overall, free radicals have been implicated in the pathogenesis of at least 50 diseases.[7,8] In disease progression and aging process, the damage to cells by free radicals is predominant. Antioxidants are the first line of defense against free radical damage of living cells and are necessary for maintaining their optimum health.

α-Hydroxylation of alkyl phosphonates,[9] reduction of keto phosphonates[10] and addition of trialkylphosphites to aldehydes[11] methods have been used for the synthesis of α-hydroxyphosphonates. Besides these, the Pudovik reaction[12] is considered as the elegant methodology for the synthesis of α-hydroxyphosphonates. In spite of direct addition of dialkylphosphites to aldehydes, this reaction also requires strong heating conditions and catalytic action. Many research groups have put efforts to develop highly active catalysts for this reaction in the recent years. Among such efforts, developed some Lewis bases such as pyridine,[13] Et_3N[14] and TMG,[15] Bronsted bases such as EtONa [16] and $Ti(OiPr)_4$,[17] metal oxides such as MgO[18] and Al_2O_3,[19] and others like KF [20] and MoO_2Cl_2.[21] But most of these catalysts are successful under high temperature and long reaction times with unsatisfactory yields. The additional drawback of some of these methodologies is possibility of reversible reactions, which reduces the product yields.

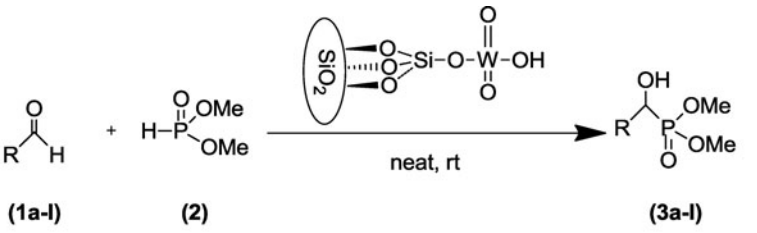
Recently, synthesis of solid-supported catalysts as clean materials has attracted considerable attention.[22–24] The usage of heterogeneous metal Lewis catalyst instead of traditional homogeneous metal lewis and bronsted acid catalyst, provides an environmentally friendly alternative. Solid catalysts could be recovered and recycled from the reaction environment.[25] Although solid supported catalysts are available on different supports such as charcoal, silica and alumina, silica is proved to be more effective over the others due to its good mechanical and thermal stabilities, ease of scalability and absence of swelling property.

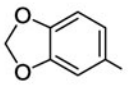
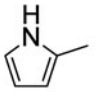
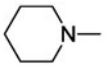
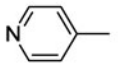
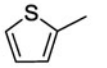
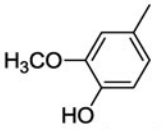
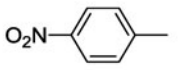
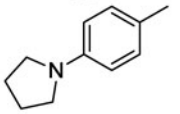
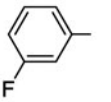
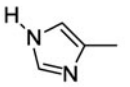
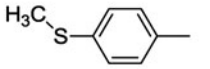
Among various heterogeneous catalysts, the silica-supported tungstic acid (STA),[26] has many advantages as environment friendly, highly efficiency, low cost, ease of preparation and reusability of the catalyst. Thus STA offers enormous potential as a green and a potential acid catalyst to construct carbon–carbon and carbon–heteroatom bonds.[27]

In view of these catalytic potentialities, STA was selected as a catalyst for the synthesis of α-hydroxyphosphonates by direct condensation of aldehydes and dimethylphosphite. The procedure offers several advantages including high yields, operational simplicity, minimal environmental impact, and low costs. All these merits qualify it as an alternative process for the synthesis of α-hydroxyphosphonates.

RESULTS AND DISCUSSION

As part of our research program directed toward the development of one-pot synthesis of α-hydroxyphosphonates with quantitative yields, we used various aldehydes, dimethylphosphite, and STA as a reusable catalyst in quantitative yield (Scheme 1).



Compound	R	Compound	R
1a & 3a		1g & 3g	
1b & 3b		1h & 3h	
1c & 3c		1i & 3i	
1d & 3d		1j & 3j	
1e & 3e		1k & 3k	
1f & 3f		1l & 3l	

Scheme 1 Synthesis of α- hydroxyphosphonates.

To optimize the experimental conditions for the reaction, we investigated various parameters like different metal lewis acid catalysts, temperature, and solvent with the reaction of benzo[d][1,3]dioxole-5-carbaldehyde (**1a**) and dimethylphosphite as standard. A blank reaction was performed without catalyst on the model reaction at room temperature. Only a trace amount of product 3a was formed in the absence of catalyst even after 24 h (Table 1, Entry 1).

The same test reaction when carried out with SiO_2 afforded only 50% of the product yield. The reaction was run with differently supported metal lewis acid catalysts, $ZnCl_2$, SiO_2, BF_3-SiO_2, and TiO_2-SiO_2 under neat conditions at room temperature. Low yield of the desired product (3a) was obtained. Only in the case of STA as catalyst, promising

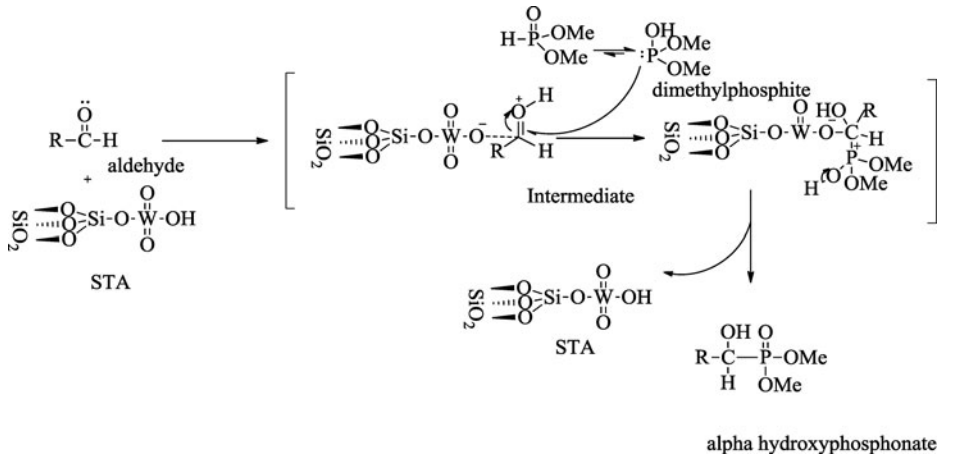
Table 1 Screening of various types of catalysts and solvents for the synthesis of 3a

Entry	Catalyst (20 mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	–	Neat	rt	24	Trace
2	SiO_2	Neat	rt	5	50
3	$ZnCl_2.SiO_2$	Neat	rt	2	52
4	$BF_3.SiO_2$	Neat	rt	2	49
5	$TiO_2.SiO_2$	Neat	rt	2	54
6	STA	Water	rt	1	72
7	STA	THF	rt	1	68
8	STA	Ethanol	rt	1	79
9	STA	Toluene	rt	1	62
10	STA	Neat	rt	0.5	96
11	STA	Neat	50 °C	0.5	64
12	STA	Neat	60 °C	0.5	59
13	STA	Neat	70 °C	0.5	54

results were obtained (96%) at room temperature under neat conditions. The reaction was also carried out in various solvents such as water, THF, ethanol, and toluene. But the yield of the desired product was too low. This reaction at 50°C, 60°C, 70°C under neat conditions also was not encouraging (Table 1, Entries 11, 12, and 13).

The effect of catalyst STA concentration on this reaction was studied using 5 to 25 mol% of STA at room temperature and found that 20 mol% of catalyst was sufficient to drive the reaction forward and to obtain almost quantitative product yield.

Under these optimized conditions, various electron rich and electron deficient aromatic and hetero aromatic aldehydes were used to obtain the corresponding α-hydroxy phosphonates in good yields. The electronic effect of the substituents in the aldehyde played an important role as it was revealed that electron withdrawing groups gave excellent results when compared to electron donating groups. The hetero aromatic aldehydes afforded the desired products in lower yields when compared with the aromatic aldehyes. A possible mechanism of this one pot reaction is explained in Scheme 2.



Scheme 2 Plausible mechanism for STA catalyzed synthesis of α-hydroxyphosphonates.

Table 2 Recyclability of STA in the synthesis of 3a under solvent free conditions

No. of cycles	Yield (%)
1	96
2	95
3	89
4	87
5	86

The reusability of the STA catalyst was examined after the fresh run of the catalyst. The catalyst was removed by filtration and dried under vacuum at 120°C for 12 h for three more times. The product **3a** was obtained in 96, 95, 89, 87% yields after successive reuse of the catalyst in three consequential cycles. There by, the catalyst's reusability was proved in Table 2.

Biology

In Vitro Assays. The in vitro antioxidant activity of the title compounds was evaluated by 2,2-diphenyl-1-picryl hydrazyl (DPPH), H_2O_2, NO, ferric reducing antioxidant power (FRAP) methods. Each in vitro experiment was performed in triplicate and the data were calculated with standard deviation. Ascorbic acid was used as the standard in all the four methods.

DPPH Free Radical Scavenging Assay

Among the title compounds **3a–l** tested for antioxidant activity by DPPH method, the compounds **3d, 3f,** and **3g** showed remarkably high antioxidant activity while the other compounds showed moderate activity when compared with the standard Ascorbic acid (Table S1 Supplemental Materials).

Ferric Reducing-antioxidant Power (FRAP) Assay

FRAP assay was done on the target compounds **3a-l**. Compounds **3d, 3f, 3g,** and **3i** showed the highest antioxidant activity as determined by FRAP assay (Table S2 Supplemental Materials). Their capacity for reducing ferric ion was comparable to that of ascorbic acid.

Hydrogen Peroxide Scavenging Assay

The scavenging ability of hydrogen peroxide by compounds **3d**, **3f**, **3g**, **3i,** and **3c** was found to be comparable with the reference compound ascorbic acid (Table S3 Supplemental Materials). This may be attributed to the phenolics, which can donate electrons to hydrogen peroxide thereby neutralizing it to water. This scavenging activity of hydrogen peroxide is concentration dependent.

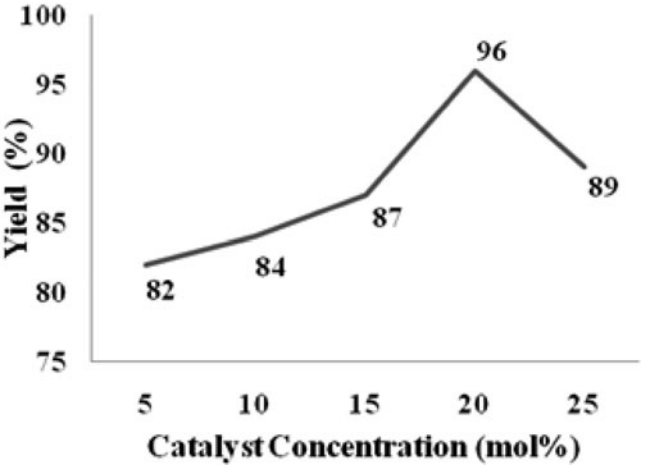


Figure 1 Catalyst concentration optimization.

Nitric Oxide Free Radical Scavenging Activity

The Nitric Oxide free radical scavenging activity of **3a–l** reveals that the compounds **3d**, **3f**, **3g**, **3i,** and **3c** showed the highest NO scavenging activity which is comparable to the reference standard. The remaining compounds exhibited moderate scavenging activity. The results were expressed as a percent of scavenged nitric oxide in Table S4 (Supplemental Materials).

CONCLUSION

A new and neat methodology was developed for the synthesis of α-hydroxyphosphonates using STA as heterogeneous catalyst at room temperature in quantitative yields. The method is operationally simple, economical, and highly efficient. Other main advantages are easy recovery of catalyst, no need for anhydrous condition, and a base and any other additional activator is not required. The synthesized α-hydroxyphosphonates **3d**, **3f**, **3g,** and **3i** were identified as potential antioxidants from the analysis of DPPHfree radical scavenging assay, hydrogen peroxide scavenging assay, Nitric oxide free radical scavenging assay, and FRAP methods. Analysis of the structure-activity relationship of the title compounds **3a–l** show that the –OH- & –NH-substituted compounds exhibited remarkably high activity when compared to substituted heterocyclic and phenolic moieties. The reason for their high antioxidant activity may be due to their ability to form the reactive free radicals to pair up with the free radicals generated in vivo that leads them reduce oxidant properties.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Instrument at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 162.01 MHz for ^{31}P NMR in $CDCl_3$ solution, using TMS as internal and 85% H_3PO_4 as external standard, respectively. Chemical shifts were indicated in ppm and coupling constants (J) in Hz. ESI mass spectra were recorded on a Micromass Quattro LC instrument and the IR spectra of the title compounds were recorded on Bruker

Alpha-EcoATR-FTIR interferometer with single reflection sampling module equipped with Zn Se crystal. Elemental analyses were performed on a Bruker's Instrument. Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Sigma Aldrich and were used without further purification.

Typical Experimental Procedure for the Synthesis of Title Compounds: (3a-l).

To the aldehyde (1a-l, 1.0 mmol), dimethylphosphite (2, 1.5 mmol), 20 mol% of STA was added and stirred at room temperature for 30 min. After completion of the reaction as indicated by the thin layer chromatography, the reaction mixture was diluted with dichloromethane and centrifuged to separate the catalyst for reuse. The organic layer was decanted and added water. It was extracted with dichloromethane (3×10 mL). This extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by column chromatography by silica gel with ethyl acetate/hexane (4:6) as eluent.

All the isolated compounds were characterized by mp, IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and elemental analysis. Spectral data of the representative new products are given.

Dimethyl(benzo[d][1,3]dioxo-5-yl(hydroxy)methyl)phosphonate (3a). White solid, yield 96%, Mp: 117–119°C. IR (KBr) (υ_{max}, cm^{-1}): 3223 (brs, OH), 1226 (P=O), 1018 (P−O−C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.61 (3H, d, J = 12.0 Hz, P−OCH_3), 3.64 (3H, d, J = 12.1 Hz, P−OCH_3), 4.90 (1H, d, J = 8.0 Hz, CH−P), 5.89 (2H, s, −O−CH_2−O); 6.70–7.26 (3H, m, Ar−H). ^{13}C−NMR (100 MHz, $CDCl_3$) δ: 53.5 (d, J = 7.8 Hz, P−OCH_3), 53.8 (d, J = 6.9 Hz, P−OCH_3), 69.3 (d, J = 158.6 Hz, P−CH), 101.0 (C-1^1), 107.7 (C-6), 108.0 (C-3), 120.8 (C-2), 130.6 (C-1), 147.4 (C-4), 147.6 (C-5). ^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 21.6. MS (ESI): *m/z* 261 $[M+H]^+$; anal. calcd. for $C_{10}H_{13}O_6P$: C, 46.16; H, 5.04; O, 36.90. Found: C, 46.06; H, 5.01.

Dimethyl(hydroxyl(piperdin-1-yl)methyl)phosphonate (3b). Pale yellow liquid, yield: 92%. IR (KBr) (υ_{max}, cm^{-1}): 3265 (brs, OH), 1221 (P=O), 1009 (P−O−C). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.56–2.67 (5H, m, -N-piperdine), 3.98 (3H, d, J = 12.1 Hz, $POCH_3$), 4.08 (3H, d, J = 12.6 Hz, $POCH_3$), 4.45 (1H, d, J = 8.7 Hz,−CH−P).^{13}C−NMR (100 MHz, DMSO-d_6) δ: 23.0 (C-4), 24.9 (C-3,5), 51.4 (C-2,C-6), 54.2 (d, J = 7.5 Hz, P-OCH_3), 54.9 (d, J = 7.6 Hz, P−OCH_3), 58.3 (d, J = 161.2 Hz, P−CH). ^{31}P-NMR (162.0 MHz, DMSO-d_6) δ: 21.6. MS (ESI): *m/z* 224 $[M+H]^+$; anal. calcd. for $C_8H_{18}NO_4P$: C,43.08; H, 8.23. Found: C, 43.03; H, 8.01.

Dimethyl(furan-2-yl(hydroxy)methyl)phosphonate (3c). Dark brown semisolid, yield: 91%. IR (KBr) (υ_{max}, cm^{-1}): 3324 (brs, OH), 1215 (P=O), 1012 (P−O−C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.58 (3H, d, J = 12.2 Hz, $POCH_3$), 3.60 (3H, d, J = 12.2 Hz, $POCH_3$), 5.46 (1H, d, J = 7.9 Hz, P−C−H), 6.30–6.54 (3H, m, furan-H).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 53.1 (d, J = 7.8 Hz, P-OCH_3), 53.7 (d, J = 7.2 Hz, P−OCH_3), 58.7 (d, J = 158.8 Hz, P−CH), 108.2 (C-3), 110.7 (C-4), 143.7 (C-5),154.4 (C-2).^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 19.6. MS (ESI): *m/z* 207 $[M+H]^+$; anal. calcd. for $C_7H_{11}O_5P$: C,40.68; H, 5.18. Found: C, 40.65; H, 5.62.

Dimethyl(hydroxy(4-hydroxy-3-methoxy phenyl)methyl)phosphonate (3d). Pale yellow semisolid, yield: 87%. IR (KBr) (υ_{max}, cm^{-1}): 3276 (brs, OH), 1213 (P=O), 1021 (P−O−C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.65 (3H, d, 12.6 Hz, $POCH_3$),

3.71 (3H, d, J = 12.5 Hz, $POCH_3$), 3.86 (3H, s, Ar-OCH_3), 5.21 (1H, d, J = 8.6 Hz, P-C-H), 5.25 (1H, s, Ar-OH), 6.53–6.98 (3H, m, Ar—H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 52.5 (d, J = 7.2 Hz, P—OCH_3), 55.9 (d, J = 7.7 Hz, P-OCH_3), 56.1 (—Ar—OCH_3), 59.2 (d, J = 157.3 Hz, P—CH), 112.7 (C-2), 115.3 (C-5), 120.37 (C-6), 129.8 (C-1), 147.1 (C-4), 147.4 (C-3). ^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 23.4. MS (ESI): *m/z* 263 $[M+H]^+$; anal. calcd. for $C_{10}H_{15}O_6P$: C,45.81; H, 5.78. Found: C, 45.78; H, 5.74.

Dimethyl(hydroxy(4-(pyrrolidin-1-yl)phenyl)methyl)phosphonate (3e). Reddish brown semisolid, yield: 90%. IR (KBr) (υ_{max}, cm^{-1}): 3468 (brs, OH), 1251 (P = O), 1021 (P—O—C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.99 (4H, m, pyrrolidine H C-3,4), 3.31 (4H, m, pyrrolidine H C-2,5), 3.65 (3H, d, J = 12.5 Hz, $POCH_3$), 3.74 (3H, d, J = 12.6 Hz, $POCH_3$), 4.76 (1H, d, J = 7.9 Hz, P—C—H), 6.54–7.29 (4H, m, Ar—H). ^{13}C—NMR (100 MHz, $CDCl_3$) δ: 25.5 (C-3^1, 4^1), 47.6 (C-2^1,5^1), 53.6 (d, J = 8.3 Hz, P—OCH_3), 53.7 (d, J = 7.6 Hz, P—OCH_3), 57.9 (d, J = 159.9 Hz, P—CH), 111.1 (C-3,5), 119.6 (C-1), 129.4 (C-2,6), 148.2 (C-4). ^{31}P—NMR (162.0 MHz, $CDCl_3$) δ: 22.5. MS (ESI): *m/z* 286 $[M+H]^+$; anal. calcd. for $C_{13}H_{20}NO_4P$: C,54.73; H, 7.08. Found: C, 54.56; H, 7.00.

Dimethyl(hydroxy(1H-imidazol-4-yl)methyl)phosphonate (3f). Pink solid, yield: 93%, Mp:120-122°C. IR (KBr) (υ_{max}, cm^{-1}): 3267 (brs, OH), 1214 (P=O), 1021 (P—O—C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.32 (3H, d, J = 12.4 Hz, $POCH_3$), 3.67 (3H, d, J = 12.5 Hz, $POCH_3$), 5.23 (1H, d, J = 8.3 Hz, P—C—H), 7.24–8.70 (2H, m, -imidazole H), 13.00 (1H, s, —NH). ^{13}C—NMR (100 MHz, $CDCl_3$) δ: 51.7 (d, J = 8.3 Hz, P-OCH_3), 58.2 (d, J = 8.2 Hz, P-OCH_3), 60.4 (d, J = 161.3 Hz, P—C), 119.2 (C-5), 122.1 (C-4), 136.4 (C-2). ^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 19.8. MS (ESI): *m/z* 207 $[M+H]^+$; anal. calcd. for $C_6H_{11}N_2O_4P$: C, 34.68; H, 5.38. Found: C, 34.65; H, 5.34.

Dimethyl(hydroxy(1H-pyrrol-2-yl)methyl)phosphonate (3g). Black semisolid, yield: 88%. IR (KBr) (υ_{max}, cm^{-1}): 3165 (brs, OH), 1231 (P=O), 1014 (P—O—C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.59 (3H, d, J = 12.2 Hz, $POCH_3$), 3.67 (3H, d, J = 12.5 Hz, $POCH_3$), 5.11 (1H, s, NH), 5.13 (1H, d, J = 7.8 Hz, P—C—H), 5.02–6.84 (3H, m, pyrrole-H).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 53.5 (d, J = 6.9 Hz, P—OCH_3), 56.5 (d, J = 8.1 Hz, P—OCH_3), 60.0 (d, J = 157.8 Hz, P—CH), 105.3 (C-3), 108.6 (C-4); 117.1 (C-5), 132.2 (C-2). ^{31}P—NMR (162.0 MHz, $CDCl_3$) δ: 21.6. MS (ESI): *m/z* 206 $[M+H]^+$; anal. calcd. for $C_7H_{12}NO_4P$: C,40.58; H, 5.96. Found: C, 40.44; H, 5.64.

Dimethyl(hydroxy(pyridin-4-yl)methyl)phosphonate (3h). Orange semisolid, yield: 91%. IR (KBr) (υ_{max}, cm^{-1}): 3359 (brs, OH), 1227 (P=O), 1037 (P—O—C). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.31 (3H, d, J = 12.8 Hz, $POCH_3$), 3.37 (3H, d, J = 12.7 Hz, $POCH_3$), 4.98 (1H, d, 8.4 Hz, P—C—H), 8.03-8.90 (4H, m, Ar—H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 52.8 (d, J = 7.3 Hz, P-OCH_3), 53.9 (d, J = 7.9 Hz, P—OCH_3), 59.1 (d, J = 160.2 Hz, P—CH), 124.4 (C-2,6), 146.1 (C-1), 149.4 (C-3,5). ^{31}P—NMR (162.0 MHz, DMSO-d_6) δ: 19.1 (P = O). MS (ESI): *m/z* 218 $[M+H]^+$; anal. calcd. for $C_8H_{12}NO_4P$: C,44.68; H, 5.57. Found: C, 44.65; H, 5.54.

Dimethyl(hydroxy(thiophene-2-yl)methyl)phosphonate (3i). Greenish brown semisolid, yield: 85%. IR (KBr) (υ_{max}, cm^{-1}): 3123 (brs, OH), 1227 (P=O), 1019 (P—O—C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.63 (3H, d, J = 12.3 Hz, $POCH_3$), 3.68 (3H, d, J = 12.4 Hz, $POCH_3$), 5.42 (1H, d, J = 7.8 Hz, P—C—H), 6.43–7.58 (3H, m, thiophene-H).^{13}C—NMR (100 MHz, $CDCl_3$) δ: 53.1 (d, J = 6.9 Hz, P—OCH_3), 56.9 (d,

J = 7.2 Hz, P−OCH_3), 57.4 (d, J = 156.8 Hz, P−CH), 126.3 (C-3), 127.0 (C-4), 127.1 (C-5), 146.0 (C-2). ^{31}P−NMR (162.0 MHz, $CDCl_3$) δ: 22.6 (P = O). MS (ESI): *m/z* 223 $[M+H]^+$; anal. calcd. for $C_7H_{11}O_4PS$: C, 37.68; H, 4.98. Found: C, 37.65; H, 5.04.

Dimethyl(hydroxy(4-nitrophenyl)methyl)phosphonate (3j). Reddish brown semisolid, yield: 90%. IR (KBr) (υ_{max}, cm^{-1}): 3364 (brs, OH), 1209 (P=O), 1016 (P−O−C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.53 (3H, d, J = 11.9 Hz, $POCH_3$), 3.55 (3H, d, J = 11.8 Hz, $POCH_3$), 5.23 (1H, d, J = 8.2 Hz, P−C−H), 7.31–8.43 (4H, m, Ar-H).^{13}C-NMR (100 MHz, $CDCl_3$) δ: 52.6 (d, J = 7.5 Hz, P−OCH_3), 53.1 (d, J = 8.1 Hz, P−OCH_3), 58.4 (d, J = 153.8 Hz, P−CH), 124.3 (C-3,5), 128.8 (C-2,4), 142.1 (C-1), 146.8 (C-4). ^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 20.3. MS (ESI): *m/z* 262 $[M+H]^+$; anal. calcd. for $C_9H_{12}NO_6P$: C,41.38; H, 5.38. Found: C, 41.05; H, 5.36.

Dimethyl(fluorophenyl)(hydroxy(methyl)phosphonate (3k). Yellow liquid, yield: 92%. IR (KBr) (υ_{max}, cm^{-1}): 3388 (brs, OH), 1258 (P=O), 1026 (P−O−C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.74 (3H, d, J = 12.1 Hz, $POCH_3$), 3.76 (3H, d, J = 12.2 Hz, $POCH_3$), 5.07 (1H, d, J = 8.0 Hz, P−C−H), 7.01–7.37 (4H, m, Ar-H).^{13}C−NMR (100 MHz, $CDCl_3$) δ: 53.8 (d, J = 7.8 Hz, P-OCH_3), 54.4 (d, J = 7.5 Hz, P−OCH_3), 69.2 (d, J = 154.4 Hz, P−CH), 115.4 (C-2,6), 123.2 (C-4),129.8 (C-5), 138.4 (C-3),164.1 (C-1). ^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 22.3. MS (ESI): *m/z* 235 $[M+H]^+$; anal. calcd. for $C_9H_{12}FO_4P$: C,46.16; H, 5.18. Found: C, 46.07; H, 5.14.

Dimethyl(hydroxy(4-(methylthio)phenyl)methyl)phosphonate (3l). Greenish liquid, yield: 87%. IR (KBr) (υ_{max}, cm^{-1}): 3112 (brs, OH), 1219 (P=O), 1029 (P−O−C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.65 (3H, s, −S−CH_3), 3.65 (3H, d, J = 12.6 Hz, $POCH_3$), 3.69 (3H, d, J = 12.7 Hz, $POCH_3$), 5.27 (1H, d, J = 8.7 Hz, P-C-H), 7.26-7.56 (4H, m, Ar−H).^{13}C−NMR (100 MHz, $CDCl_3$) δ: 14.6 (S−CH_3), 52.5 (d, J = 7.4 Hz, P−OCH_3), 53.9 (d, J = 7.8 Hz, P−OCH_3), 79.8 (d, J = 157.5,P−CH), 127.8 (C-2,6), 128.1 (C-3,5), 133.3 (C-1), 141.1 (C-4). ^{31}P-NMR (162.0 MHz, $CDCl_3$) δ: 22.6. MS (ESI): *m/z* 263 $[M+H]^+$; anal. calcd. for $C_{10}H_{15}NO_4PS$: C, 45.68; H, 5.78. Found: C, 45.65; H, 5.64.

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SUPPLEMENTARY DATA

Tables S1–S4 can be accessed on the publisher's website at http://dx.doi/10.1080/10426507.2014.991825

REFERENCES

1. Horiguchi, M.; Kandatsu, M. *Nature* **1959,** 184, 901-902.
2. Peng, H.; Wang, T.; Xie, P.; Chen, T.; He, H.W. *J. Agric. Food Chem.* **2007,** 55, 1871-1880.
3. Dellaria, J. F.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. *J. Med. Chem.* **1990,** 33, 534-542.
4. Stowasser, B.; Budt, K. H.; Li, J. Q.; Peyman, A.; Ruppert, D. *Tetrahedron Lett*. **1992,** 33, 6625-6628.
5. Snoeck, R.; Holy, A.; Dewolf-Peeters, C.; Van DenOord, J.; DeClercq, E.; Andrei, G. *Antimicrob. Agents Chemother.* **2002,** 46, 3356-3361.
6. Peters, M. L.; Leonard, M.; Licata, A. A. *Clev. Clin. J. Med.* **2001,** 68, 945-951.
7. Langseth, L. *From the Editor: Antioxidant Vitamins Newsletter*. **1993,** 4, 3.
8. Halliwell, B. *Lancet*. **1994,** 344, 721-724.
9. Cristau, H.; Pirat, J.; Drag, M.; Kafarski, P. *Tetrahedron Lett*. **2000,** 41, 9781-9785.
10. Nesterov, V. V.; Kolodyazhnyi, O. I. *Russ. J. Gen. Chem.* **2005,** 75, 1161-1162.
11. Nakanishi, K.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron.* **2008,** 64, 6415-6454.
12. Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979,** 81-96.
13. Li, C.; Yuan, C. *Tetrahedron Lett*. **1993,** 34, 1515-1516.
14. Taylor, W. P.; Zhang, Z.; Widlanski, T. S. *Bioorg. Med. Chem.* **1996,** 4, 1515-1520.
15. Simoni, D.; Rondanin, R.; Morini, M.; Baruchello, R.; Invidiata, F. P. *Tetrahedron Lett*. **2000,** 41, 1607-1610.
16. Keglevich, G.; Sipos, M.; Takacs, D.; Greiner, I. *Heteroatom Chem*. **2007,** 18, 226-229.
17. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. J. *Chem. Soc., Perkin Trans.* **1997,** 1, 1527-1533.
18. Kaboudin, B. *Tetrahedron Lett.* **2003,** 44, 1051-1053. (b) Kaboudin, B. *Tetrahedron Lett.* **2000,** 41, 3169-3171.
19. Texier-Boullet, F.; Foucaud, A. *Synthesis*. **1982,** 916. (b) Jung, M. E.; Cordova, J.; Murakami, M. *Org. Lett*. **2009,** 11, 3882-3885.
20. Texier-Boullet, F.; Foucaud, A. *Synthesis*. **1982,** 2, 165-166. (b) Li, Z.; Sun, H.; Wang, Q.; Huang, R. *Heteroatom Chem.* **2003,** 14, 384-386.
21. de Noronha, R.G.; Costa, P. J.; Romao, C. C.; Calhorda, M. J.; Fernandes, A. C. *Organometallics*. **2009,** 28, 6206-6212.
22. Kantam, M.L.; Roy, M.; Roya, S.; Sreedhara, B.; De, R.L. *Catalysis Communication.* **2008,** 9, 2226-2230.
23. Murkute, A.D.; Jackson J.E.; Miller D. J. *Journal of Catalysis*. **2011,** 278, 189-199.
24. Boudart, M. *Advances in Catalysis.* **1969,** 20, 153-166.
25. Andrews, S.P., Stepan, A.F.; Tanaka, H.; Ley, S.V.; Smith, M.D. *Adv. Synth. Catal.* **2005,** 347, 647-654.
26. Karami, B.; Ghashghaee, V.; Khodabakhshi, S. *Catal. Commun.* **2012,** 20, 71-75.
27. Khodabakhshi, S.; Karami, B. *Catal. Sci. Technol.* **2012,** 2, 1940-1944.