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Green chemical synthesis of α-hydroxyphosphonates

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Abstract: A green and efficient method for the preparation of α-hydroxyphosphonates (**3a-n**) in minutes of time with high yields is accomplished by grinding the mixture of various aldehydes (**1a-n**) and diethylphosphite (**2**) at room temperature under solvent free conditions in presence of piperazine as catalyst.

Keywords: α-Hydroxyphosphonates; piperazine; grinding; diethylphosphite; green process.

1. Introduction

The study of organic molecules containing phosphorous offer fascinating possibilities for structural, synthetic and mechanistic approaches and the knowledge of phosphorous compounds has expanded so rapidly as a major branch of chemistry in the form of organophosphorus chemistry.[1-2] The natural phosphorus compounds play important roles as biologically active agents.[3] The cyclic and acyclic phosphate esters are normally considered as important pharmacological compounds.[4-8] In recent the synthesis of α-hydroxy phosphonates, which are acyclic phosphorus esters have received an increasing amount of attention due to significant biological interests.[9-12] Because of their potential bioactivity against wide spectrum of disease manifestations several methods are reported for their synthesis. In such the pudovik reaction involving the addition of dialkylphosphite to carbonyl compounds is a direct method to generate α-hydroxyphosphonates and for the construction of new C-P bonds. Involving the nucleophilic addition of di or trialkylphosphite to aldehydes in the presence of various catalysts, such as, enzymatics,[13] alkaloids,[14] phosphoric acids,[15] Lewis acids,[16] alumina,[17] SALALEN,[18] SALEN,[19] SALAN,[19] BINOL,[20] alumina/potassium fluoride,[21] NH_4VO_3[22] and polymer/ solid supported base[23] were tried for this reaction to improve the yields. But none of these procedures are satisfactory from the points of view of simplicity, efficiency, cost and eco-friendliness. All these disadvantages had diminished by adopting the green chemical synthetic procedures[24-26] involving potassium carbonate, [27] sodium carbonate, [28] triethylamine[29] as catalysts under conventional solvent-free conditions, potassium dihydrogenphosphate[30] catalyst under ultrasound-assisted solvent-free conditions and iodine as catalyst in water as solvent[31] were reported for the synthesis of α-hydroxyphosphonates. In recent, we also had accomplished the potassium bisulphate[32] catalyzed

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synthesis of α-hydroxyphosphonates. In this hierarchy now we are reporting the synthesis of piperazine catalyzed synthesis of α-hydroxyphosphonates by simple grinding method.

2. Results and discussion

As part of our research program directed towards the development of highly expedient methods for the synthesis of diverse bioactive organophosphorus compounds, we had developed a simple and very efficient method for the preparation of α-hydroxyphosphonates under green chemical conditions.

In our initial experiments, nucleophilic addition of diethylphosphite to 4-(2-pyridyl) benzaldehyde (**1m**) in 1:1 molar ratio, in methanol was performed in the presence of different secondary amines as catalysts. These base catalysts even though facilitated the formation of α-hydroxy phosphonates, their yields are poor and reaction times are very long. However when piperazine was used as a catalyst, the reaction occurred fast with better product yield (**Table 1**).

To reduce the reaction time further and to improve the yields, these reactions were carried under solvent free conditions by grinding the substrates. Surprisingly the reaction occurred almost spontaneously within minutes and of course with improved yields. Particularly, the reaction with piperazine as a catalyst completed in just two minutes and the produced yield rose up to 96 % (**Table 1**). The results shows that the catalyst activity of secondary amines particularly piperazine is highest in this reaction under neat conditions.

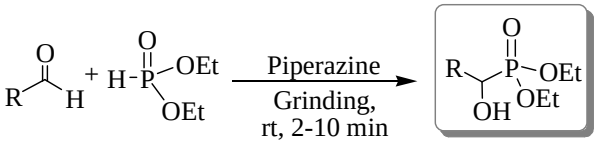
Typical experimental procedure for the synthesis of title compounds:

To 1 mmol of aldehyde (**1a-n**), 1 mmol of diethylphosphite (**2**) and piperazine (1 mmol) were added and grind at room temperature for the appropriate time to complete the reaction (**Scheme 1**). After completion of the reaction, as indicated by thin-layer chromatography the reaction mixture was washed with water (3 × 10 mL) then the compounds (**3a-n**) were extracted with ethylacetate. The organic layer were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to leave the crude product as a white solid which was purified by silica gel column chromatography.

Table 1. Catalytic effect of secondary amines on the synthesis of α-hydroxyphosphonates

		Solvent (Methanol)		Neat (Grinding)	
Entry	**Secondary amines**	**Time (min)**	**Yield (%)[a]**	**Time (min)**	**Yield (%)[a]**
1	Diethylamine	180	65	30	35
2	N-methylaniline	120	58	25	38
3	Pyrrolidine	120	70	25	60
4	Piperidine	100	68	20	55
5	Morpholine	120	76	24	64
6	Thiomorpholine	90	72	27	62
7	N-metylpiperazine	90	84	16	70
8	Piperazine	30	93	2	96

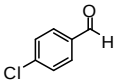
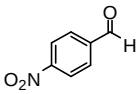
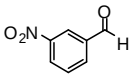
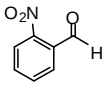
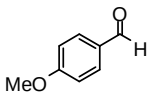
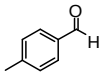
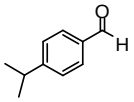
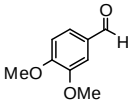
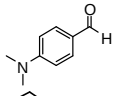
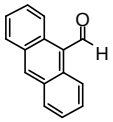
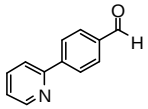
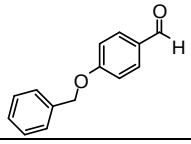
[a]Isolated yield



1a-n **2** **3a-n**

Scheme 1. Synthesis of α-hydroxyphosphonates

Table 2. Synthesis of α-hydroxyphosphonates catalyzed by piperazine in grinding method.

S.No.	Entry	Aldehyde	Time (min)	Yield (%)[a]	Melting point (ºC)	
					Found	Literature
1	**3a**		10	78	74-75	75-76[22,33]
2	**3b**		8	82	67-68	67-68[22,33]
3	**3c**		10	85	75-77	74-75[22,33]
4	**3d**		7	84	86-87	87-88[22,33-34]
5	**3e**		8	85	80-81	81-82[33]
6	**3f**		7	87	114-116	114-116[33]
7	**3g**		6	83	121-122	120-121[22,33]
8	**3h**		7	82	95-96	94-95[22,33]
9	**3i**		5	84	liquid	----
10	**3j**		4	91	96-97	95-97[35]
11	**3k**		5	92	81-82	80-81[33]
12	**3l**		4	95	150-151	149-151[36]
13	**3m**		2	96	132-133	----
14	**3n**		2	96	65-66	----

[a]Isolated yield.

The substrate scope of the reaction was explored in **Table 2**. It was found that electron rich aromatic aldehydes proved to be more reactive and afford high product yields. This effect is more pronounced in case of compounds substituted at para position with more aromatic rings (**Table 2**, entry **3l**, **3m** and **3n**). Even ortho substituted compounds entry **3c** and **3f** with electron withdrawing moieties also experience this effect due to the aldehyde hydrogen bonding. These moieties as in the carbonyl compounds attributed to bearing more electrophilic due to extending delocalization of the electron cloud over the sp^2 carbon cyclic frame with/ without heteroatom. Moreover, these substitutions facilitate the nucleophilic phosphite addition the carbonyl compounds.

3. Conclusion

α-Hydroxyphosphonates were synthesized by the phosphite addition to variety of aryl aldehydes in the presence of piperazine as catalyst under neat condition by simple grinding process is proved to be an excellent method.

4. Experimental

Chemicals were procured from Sigma-Aldrich and Merck, used as such without further purification. All solvents used for the spectroscopic and other physical studies were reagent grade and further purified by literature methods.[37] The melting points (mp) were determined in open capillary tubes on a Mel-Temp apparatus (Tempo Instruments and Equip Pvt. Ltd., Mumbai, India), expressed in degrees centigrade (^{o}C) and are uncorrected. Infrared (IR) Spectra were obtained on a Nicolet (San Diego, CA, USA) 380 Fourier transform infrared (FT-IR) spectrophotometer at the Environmental Engineering Laboratory, Sri Venkateswara University, Tirupati, India and samples were analyzed as potassium bromide (KBr) disks and absorptions (ν_{max}) were reported in wave numbers (cm^{-1}). The ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker (Ettlingen, Germany) AMX 400 MHz nuclear magnetic resonance (NMR) spectrometer operating at 400 MHz for ^{1}H NMR, 100.57 MHz for ^{13}C NMR, and 161.9 MHz for ^{31}P NMR respectively and expressed in parts per million (ppm). All compounds were dissolved in $CDCl_3$ and chemical shifts were referenced to TMS in ^{1}H-NMR and ^{13}C NMR and 85% H_3PO_4 in ^{31}P NMR. Mass spectra were recorded on a Jeol SX 102DA/600 (Tokyo, Japan) mass spectrometer using argon/xenon (6 keV, 10 mA) as the FAB gas. Microanalysis was performed with a Thermo Finnigan (Courtaboeuf, France) Flash EA 1112 I instrument at University of Hyderabad, Hyderabad, India.

The spectral and elemental analysis of some of the representative compounds were given here.

Diethyl (hydroxyl)(phenyl)methylphosphonate (3a): Solid, Yield: 78%, mp 74-75 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.18 (m, 5H), 5.25 (s, 1H), 4.64 (d, $^{2}J_{P\text{-}H}$ = 10.7 Hz, 1H), 4.00-3.90 (m, 4H), 1.26-1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 147.5 (d, $^{2}J_{P\text{-}C}$ = 3.0 Hz), 134.0, 128.8, 127.1, 70.3 (d, $^{1}J_{P\text{-}C}$ = 157.0 Hz), 62.9 (d, $^{2}J_{P\text{-}C}$ = 7.1 Hz), 16.0 (d, $^{3}J_{P\text{-}C}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 22.82; IR (KBr): 3274 (brs, OH), 1240 (P=O), 1043 (P-O-C) cm^{-1}; ESI-MS: *m/z* 244 $(M+H)^{+}$; Anal. calcd. for $C_{11}H_{17}O_4P$: C, 54.10; H, 7.02; Found: C, 53.98; H, 7.00.

Diethyl (4-chlorophenyl)(hydroxy)methylphosphonate (3b): Solid, Yield: 82%, mp 67-68 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.23 (m, 4H), 5.15 (s, 1H), 4.79 (d, $^{2}J_{P\text{-}H}$ = 10.9 Hz, 1H), 4.26-3.99 (m, 4H), 1.35-1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 150.4, 140.3, 129.1, 128.1, 72.4 (d, $^{1}J_{P\text{-}C}$ = 159.0 Hz), 63.79 (d, $^{2}J_{P\text{-}C}$ = 6.8 Hz), 16.9 (d, $^{3}J_{P\text{-}C}$ = 5.8 Hz), 16.4 (d, $^{3}J_{P\text{-}C}$ = 5.8 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 20.8; IR (KBr): 3272 (brs, OH), 1243 (P=O), 1040 (P-O-C) cm^{-1}; ESI-MS: *m/z* 279 $(M+H)^{+}$; Anal. calcd. for $C_{11}H_{16}ClO_4P$: C, 47.41; H, 5.79; Found: C, 47.38; H, 5.64.

Diethyl (2-chlorophenyl)(hydroxy)methylphosphonate (3c): Solid, Yield: 85%, mp 75-77 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.21 (m, 4H), 5.17 (s, 1H), 4.89 (d, $^{2}J_{P\text{-}H}$ = 10.6 Hz, 1H), 4.32-4.10 (m, 4H), 1.38-1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 149.4, 138.3, 128.1, 127.5, 126.3, 126.4, 70.4 (d, $^{1}J_{P\text{-}C}$ = 151.0 Hz), 64.4 (d, $^{2}J_{P\text{-}C}$ = 6.2 Hz), 63.0 (d, $^{2}J_{P\text{-}C}$ = 6.2 Hz), 16.9 (d, $^{3}J_{P\text{-}C}$ = 5.9 Hz), 16.6 (d, $^{3}J_{P\text{-}C}$ = 5.9 Hz). Anal. calcd. for $C_{11}H_{16}ClO_4P$: C, 47.41; H, 5.79; Found: C, 47.24; H, 5.63.

Diethyl (hydroxy)(4-nitrophenyl)methylphosphonate (3d): Solid, Yield: 84%, mp 86-87 ^{o}C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 5.28 (s, 1H), 4.99(d, $^{2}J_{P\text{-}H}$ = 10.6 Hz, 1H), 4.39-4.25 (m, 4H), 1.40-1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 152.4, 148.8, 128.2, 127.9, 70.8 (d, $^{1}J_{P\text{-}C}$ = 153.0 Hz), 64.9 (d, $^{2}J_{P\text{-}C}$ = 6.7 Hz), 63.5 (d, $^{2}J_{P\text{-}C}$ = 6.7 Hz), 16.9 (d, $^{3}J_{P\text{-}C}$ =

6.0 Hz), 16.5 (d, $^{3}J_{P-C}$ = 6.0 Hz). Anal. calcd. for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58; N, 4.84; Found: C, 45.59; H, 5.56; N, 4.82.

Diethyl (hydroxy)(3-nitrophenyl)methylphosphonate (3e): Solid, Yield: 85%, mp 80-81 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (quasi d, J = 8.2 Hz, 2H), 7.49 (quasi d, J = 8.2 Hz, 2H), 5.26 (s, 1H), 4.97 (d, $^{2}J_{P-H}$ = 10.6 Hz, 1H), 4.38-4.26 (m, 4H), 1.41-1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 152.3, 148.9, 129.7, 128.1, 127.7, 126.3, 70.5 (d, $^{1}J_{P-C}$ = 153.0 Hz), 64.7 (d, $^{2}J_{P-C}$ = 6.7 Hz), 63.4 (d, $^{2}J_{P-C}$ = 6.7 Hz), 16.5 (d, $^{3}J_{P-C}$ = 6.0 Hz), 16.2 (d, $^{3}J_{P-C}$ = 6.0 Hz). Anal. calcd. for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58; N, 4.84; Found: C, 45.57; H, 5.54; N, 4.82.

Diethyl (hydroxy)(2-nitrophenyl)methylphosphonate (3f): Solid, Yield: 87%, mp 114-116 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (quasi d, J = 8.2 Hz, 2H), 7.50 (quasi d, J = 8.2 Hz, 2H), 5.29 (s, 1H), 4.99 (d, $^{2}J_{P-H}$ = 10.6 Hz, 1H), 4.38-4.24 (m, 4H), 1.39-1.28 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 151.9, 148.1, 128.0, 127.6, 126.8, 126.1, 70.4 (d, $^{1}J_{P-C}$ = 153.0 Hz), 64.3 (d, $^{2}J_{P-C}$ = 6.7 Hz), 63.2 (d, $^{2}J_{P-C}$ = 6.7 Hz), 16.3 (d, $^{3}J_{P-C}$ = 6.0 Hz), 16.0 (d, $^{3}J_{P-C}$ = 6.0 Hz). Anal. calcd. for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58; N, 4.84; Found: C, 45.56; H, 5.52; N, 4.81.

Diethyl (hydroxy)(4-methoxyphenyl)methylphosphonate (3g): Solid, Yield: 83%, mp 121-122 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.01 (m, 4H), 5.19 (s, 1H), 4.63 (d, $^{2}J_{P-H}$ = 10.4 Hz, 1H), 4.20-4.02 (m, 4H), 3.87 (s, 3H) 1.28-1.19 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 147.4, 137.3, 122.1, 121.3, 69.4 (d, $^{1}J_{P-C}$ = 149.0 Hz), 62.4 (d, $^{2}J_{P-C}$ = 6.1 Hz), 62.1 (d, $^{2}J_{P-C}$ = 6.1 Hz), 57.3, 16.0 (d, $^{3}J_{P-C}$ = 6.1 Hz), 15.7 (d, $^{3}J_{P-C}$ = 5.9 Hz). Anal. calcd. for $C_{12}H_{19}O_5P$: C, 52.55; H, 6.98; Found: C, 52.46; H, 6.93.

Diethyl (hydroxy)(p-tolyl)methylphosphonate (3h): Solid, Yield: 82%, mp 95-96 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.00 (m, 4H), 5.26 (s, 1H), 4.58 (d, $^{2}J_{P-H}$ = 10.1 Hz, 1H), 4.21-4.02 (m, 4H), 2.32 (s, 3H), 1.27-1.19 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 145.4, 137.1, 122.2, 121.4, 69.1 (d, $^{1}J_{P-C}$ = 150.0 Hz), 62.6 (d, $^{2}J_{P-C}$ = 6.0 Hz), 61.3 (d, $^{2}J_{P-C}$ = 6.0 Hz), 21.3, 16.0 (d, $^{3}J_{P-C}$ = 5.8 Hz), 15.4 (d, $^{3}J_{P-C}$ = 5.8 Hz). Anal. calcd. for $C_{12}H_{19}O_4P$: C, 55.81; H, 7.42; Found: C, 55.67; H, 7.39.

Diethyl (hydroxy)(4-isopropylphenyl)methylphosphonate (3i): Liquid, Yield: 84%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 5.14 (s, 1H), 4.94 (d, $^{2}J_{P-H}$ = 10.8 Hz, 1H), 4.08-3.92 (m, 4H), 2.92-2.85 (m, 1H), 1.26-1.17 (m, 12H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 148.7 (d, $^{2}J_{P-C}$ = 3.0 Hz), 134.0, 127.1, 126.2, 70.6 (d, $^{1}J_{P-C}$ = 159.0 Hz), 63.2 (d, $^{2}J_{P-C}$ = 7.0 Hz), 63.0 (d, $^{2}J_{P-C}$ = 7.0 Hz), 33.8, 23.8, 16.3 (d, $^{3}J_{P-C}$ = 6.0 Hz), 16.2 (d, $^{3}J_{P-C}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 22.83; IR (KBr): 3273 (brs, OH), 1240 (P=O), 1042 (P-O-C) cm^{-1}; ESI-MS: *m/z* 287 $(M+H)^+$; Anal. calcd. for $C_{14}H_{23}O_4P$: C, 58.73; H, 8.10. Found: C, 58.78; H, 8.08.

Diethyl (3,4-dimethoxyphenyl)(hydroxy)methylphosphonate (3j): Solid, Yield: 91%, mp 96–97 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (s, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 5.11 (s, 1H), 4.96 (brs, 1H), 4.87 (d, $^{2}J_{P-H}$ = 10.0 Hz, 1H), 4.09–3.90 (m, 4H), 3.86 (s, 6H), 1.28 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 150.2, 148.1, 128.9 (d, $^{2}J_{P-C}$ = 3.0 Hz), 120.1, 116.4, 113.9, 70.3 (d, $^{1}J_{P-C}$ = 161.0 Hz), 62.9 (d, $^{2}J_{P-C}$ = 7.1 Hz), 61.9 (d, $^{2}J_{P-C}$ = 7.1), 56.2, 55.9, 16.1 (d, $^{3}J_{P-C}$ = 7.0 Hz), 15.8 (d, $^{3}J_{P-C}$ = 7.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 23.2; IR (KBr): 3257 (brs, OH), 1212 (P=O), 1011 (P-O-C) cm^{-1}; ESI-MS: *m/z* 304 $(M)^+$; Anal. calcd. for $C_{13}H_{21}O_6P$: C, 51.31; H, 6.96. Found: C, 51.36; H, 6.90.

***Diethyl (4-(dimethylamino)phenyl)(hydroxy)methylphosphonate (3k)*:** Solid, Yield: 92%, mp 81–82 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 5.19 (s, 1H), 4.94 (d, $^{2}J_{P-H}$ = 10.8 Hz, 1H), 4.08-3.92 (m, 4H), 3.10 (m, 1H), 3.12-2.98 (s, 6H), 1.26-1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 148.7 (d, $^{2}J_{P-C}$ = 3.0 Hz), 134.0, 127.1, 126.2, 70.6 (d, $^{1}J_{P-C}$ = 159.0 Hz), 63.2 (d, $^{2}J_{P-C}$ = 7.0 Hz), 63.0 (d, $^{2}J_{P-C}$ = 7.0 Hz), 33.8, 16.3 (d, $^{3}J_{P-C}$ = 6.0 Hz), 16.2 (d, $^{3}J_{P-C}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 22.10; IR (KBr): 3273 (brs, OH), 1240 (P=O), 1042 (P-O-C) cm^{-1}; ESI-MS: *m/z* 287 $(M+H)^+$; Anal. calcd. for $C_{13}H_{22}NO_4P$: C, 54.35; H, 7.72; N, 4.88; Found: C, 54.32; H, 7.64; N, 4.80.

Diethyl anthracen-9-yl(hydroxy)methylphosphonate (3l): Solid, Yield: 95%, mp 150–151 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.51-7.41 (m, 6H), 6.59 (d, $^2J_{P\text{-}H}$ = 16.0 Hz, 1H), 5.27 (s, 1H), 4.02-3.96 (m, 2H), 3.88-3.78 (m, 1H), 3.68-3.58 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 131.6, 130.4, 129.1 (d, $^2J_{P\text{-}C}$ = 4.0 Hz), 129.0, 127.6, 127.5, 125.8, 124.9, 68.2 (d, $^1J_{P\text{-}C}$ = 163.0 Hz), 63.1 (d, $^2J_{P\text{-}C}$ = 7.0 Hz), 62.8 (d, $^2J_{P\text{-}C}$ = 7.0 Hz), 16.3 (d, $^3J_{P\text{-}C}$ = 6.0 Hz), 16.0 (d, $^3J_{P\text{-}C}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 24.20; IR (KBr): 3273 (OH), 1240 (P=O), 1042 (P-O-C) cm^{-1}; ESI-MS: *m/z* 345 $(M+Na)^+$; Anal. calcd. for $C_{19}H_{21}O_8P$: C, 66.27; H, 6.16. Found: C, 66.19; H, 6.12.

Diethyl (hydroxyl)(4-(pyridin-2-yl)phenyl)methylphosphonate (3m): Solid, Yield: 96%, mp 132-133 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, J = 6.8 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 8.0, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.22 (d, J = 4.8 Hz, 1H), 5.24 (brs, 1H), 5.05 (d, $^2J_{P\text{-}H}$ = 12.0 Hz, 1H), 4.07-4.03 (m, 4H), 1.27-1.21 (m, 6H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 157.13, 149.5, 138.8 (d, $^2J_{P\text{-}C}$ = 3.0 Hz), 137.9, 136.8, 127.4, 127.0, 122.1, 120.6, 70.5 (d, $^1J_{P\text{-}C}$ = 159.0 Hz), 63.2 (d, $^2J_{P\text{-}C}$ = 8.0 Hz), 63.0 (d, $^2J_{P\text{-}C}$ = 8.0 Hz), 16.4 (d, $^3J_{P\text{-}C}$ = 6.0 Hz), 16.3 (d, $^3J_{P\text{-}C}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 22.37; IR (KBr): 3280 (brs, OH), 1208 (P=O), 1033 (P-O-C) cm^{-1}; 321 $(M+Na)^+$; Anal. calcd. for $C_{16}H_{20}NO_4P$: C, 59.81; H, 6.26; N, 4.36. Found: C, 59.89; H, 6.22; N, 4.33.

Diethyl (4-(benzyloxy)phenyl)(hydroxy)methylphosphonate (3n): Solid, Yield: 96%, mp 65–66 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.30 (m, 7H), 6.97 (d, J = 8.8 Hz, 2H), 5.20 (s, 1H), 5.06 (s, 2H), 4.94 (d, $^2J_{P\text{-}H}$ = 10.0 Hz, 1H), 4.09-3.92 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H), 1.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.57 MHz): δ 158.8, 136.9, 128.7,128.60, 128.4 (d, $^2J_{P\text{-}C}$ = 6.0 Hz), 128.0, 127.4, 114.9, 70.6 (d, $^1J_{P\text{-}C}$ = 160.0 Hz), 70.13, 63.1 (d, $^2J_{P\text{-}C}$ = 7.0 Hz), 63.0 (d, $^2J_{P\text{-}C}$ = 7.0 Hz), 16.4 (d, $^3J_{P\text{-}C}$ = 6.0 Hz), 16.3 (d, $^3J_{P\text{-}C}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 22.70; IR (KBr): 3257 (brs, OH), 1212 (P=O), 1011 (P-O-C) cm^{-1}; ESI-MS: *m/z* 351 $(M+H)^+$. Anal. calcd. for $C_{18}H_{23}O_5P$: C, 61.71; H, 6.62. Found: C, 61.78; H, 6.58.

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References

[1] Corbridg, D. *Phosphorous*. Elsevier, New York, USA, **1990**.
[2] Hartly, F. R. *The Chemistry of Organophosphorous Compounds*. John Wiley and Sons, New York, USA, **1990**.
[3] Westheimer, F. H. Why nature chose phosphates. *Science* **1987**, *235*, 1173-1178.
[4] Krishna, B. S.; Rao, A. J.; Naidu, K. R. M.; Rao, V. K.; Raju, C. N. Synthesis and antibacterial activity studies of novel 2-substituted-1,3,2-oxazaphosphole-2-oxide derivatives of (S)-(+)-prolinol. *Org. Commun.* **2010**, *3*, 98-105.
[5] Mohan, C.; Rao, A. J.; Raju, C. N.; Nagalakshmi, R. U. Synthesis, spectral and antimicrobial activity of [3-(4-chloro-phenoxy)-2,4-diisopropyl)-2,3,4,5-tetrahydro-1H-3λ^5-benzo[e][1,3,2]diazaphosphepin-3-ylidene]-alkyl-amine (Staudinger reaction). *Org. Commun.*, **2009**, *2*, 120-127.
[6] Reddy, K. R. K. K.; Reddy, C. B.; Kumar, K. S.; Raju, C. N.; Reddy, C. S. Iodine catalyzed and tertiary butyl ammonium bromide promoted preparation of benzoxazaphosphininyl phenylboronates. *Org. Commun.* **2009**, *2*, 28-33.
[7] Reddy, M. V. N.; Annar, S.; Krishna, A. B.; Reddy, G. C. S.; Reddy, C. S. Tetramethyl guanidine (TMG) catalyzed synthesis of novel α-amino phosphonates by one-pot reaction. *Org. Commun.* **2010**, *3*, 39-44.
[8] Babu, Y. H.; Sankar, A. U. R.; Kumar, B. S.; Reddy, C. S. Synthesis, spectral characterization and antimicrobial activity of 2-(substituted)-2,2-[1,3- dihydro-(3,4-1,2,5-oxadiazolediyl) diaza][5', 5'-dimethyl-1', 3' -propanediyl) dioxy] phosphoranes. *Org. Commun.* **2010**, *3*, 15-21.

[9] Kim, D. Y.; Wiemer, D. F. Addition of allylindium reagents to acyl phosphonates: synthesis of tertiary α-hydroxy alkylphosphonates. *Tetrahedron Lett.* **2003**, *44*, 2803-2805.
[10] Neyts, J.; De Clercq, E. Antiviral drug susceptibility of human herpesvirus 8. *Antimicrob. Agents Chemother.* **1997**, *41*, 2754-2756.
[11] Lee, M. V.; Fong, E. M.; Singere, F. R.; Guenette, R. S. Bisphosphonate treatment inhibits the growth of prostate cancer cells. *Cancer Res.* **2001**, *61*, 2602-2608.
[12] Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, J. E. W. α-Hydroxy phosphinyl-based inhibitors of human renin. *J. Med. Chem.* **1995**, *38*, 4557-4569.
[13] Kafarski, P.; Lecjzak, B. Application of bacteria and fungi as biocatalysts for the preparation of optically active hydroxyphosphonates. *J. Mol. Catal. B.* **2004**, *29*, 99-104.
[14] Wynberg, H.; Smaardijk, A. A. Asymmetric catalysis in carbon-phosphorus bond formation. *Tetrahedron Lett.* **1983**, *24*, 5899-5900.
[15] Akiyamam, T.; Morita, H.; Itoh, J.; Fuchibe, K. Chiral brønsted acid catalyzed enantioselective hydrophosphonylation of imines: asymmetric synthesis of α-aminophosphonates. *Org. Lett.* **2005**, *7*, 2583-2585.
[16] Groaning, M. D.; Rowe, B. J.; Spilling, C. D. New homochiral cyclic diol ligands for titanium alkoxide catalyzed phosphonylation of aldehydes. *Tetrahedron Lett.* **1998**, *39*, 5485-5488.
[17] Zhou, X.; Liu, X.; Yang, X.; Shang, D.; Xin, J.; Feng, X. Highly enantioselective hydrophosphonylation of aldehydes catalyzed by tridentate schiff base aluminum (III) complexes. *Angew. Chem., Int. Ed.* **2007**, *120*, 398-400.
[18] Saito, B.; Katsuki, T. Synthesis of an optically active $\boldsymbol{C}_1$-symmetric al (salalen) complex and its application to the catalytic hydrophosphonylation of aldehydes. *Angew. Chem. Int. Ed.* **2005**, *117*, 4676-4678.
[19] Duxbury, J. P.; Cawley, A.; Pett-Thornton, M.; Wantz, L.; Warne, J. N. D.; Greatrex, R.; Brown, D.; Kee, T. P. Chiral aluminium complexes as phospho-transfer catalysts. *Tetrahedron Lett.* **1999**, *40*, 4403-4406.
[20] Arai, T.; Bougauchi, M.; Sasai, H.; Shibaski, M. Catalytic asymmetric synthesis of α-hydroxy phosphonates using the Al−Li−BINOL complex. *J. Org. Chem.* **1996**, *61*, 2926-2927.
[21] Texier-Boullet, F.; Lequitte, M. An unexpected reactivity of simple heterogeneous mixture of γ-alumina and potassium fluoride: 1-hydroxyalkane phosphonic esters synthesis from non-activated ketones in "dry media". *Tetrahedron Lett.* **1986**, *27*, 3515-3516.
[22] Swapnil, S. S.; Amol, H. K.; Madhav, N. W.; Charansingh, H. G. ; Bapurao, B. S. ; Murlidhar, S. S. Ammonium metavanadate: An effective catalyst for synthesis of α-hydroxyphosphonates. *Arkivoc.* **2009**, *ii*, 138-148.
[23] Simoni, D.; Rondanin, R.; Morini, M.; Baruchello, R.; Invidiata, F. P. 1,5,7-Triazabicyclo[4.4.0]dec-1-ene (TBD), 7-methyl-TBD (MTBD) and the polymer-supported TBD (P-TBD): three efficient catalysts for the nitroaldol (Henry) reaction and for the addition of dialkyl phosphites to unsaturated systems. *Tetrahedron Lett.* **2000**, *41*, 1607-1610.
[24] Shinde, P. V.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. An organocatalyzed facile and rapid access to α-hydroxy and α-amino phosphonates under conventional/ultrasound technique. *Tetrahedron Lett.* **2011**, *52*, 2889-2892.
[25] Shen, L.; Liu, R.; Liao, X.; Ye, Y. Green synthesis of α-hydroxyl phosphate under solvent-free condition. *Huaxue Yanjiu*. **2010**, *21*, 40-43.
[26] Sadaphal, S. A.; Sonar, S. S.; Pokalwar, R.; Shitole, N. V.; Shingare, M. Sulphamic acid: an efficient catalyst for the synthesis of α-hydroxyphosphonates using ultrasound irradiation. *J. Korean Chem. Soc.* **2009**, *53*, 536-541
[27] Shen, L.; Liu, R.; Liao, X.; Ye, Y. Green synthesis of α-hydroxyl phosphate under solvent-free condition. *Huaxue Yanjiu Yu Yingyong*. **2010**, *21*, 40-43.
[28] Keglevich, G.; Toth, V. R.; Drahos, L. Microwave-assisted synthesis of α-hydroxy-benzylphosphonates and -benzylphosphine oxides. *Heteroatom Chem.* **2011**, *22(1)*, 15-17.
[29] Sun, J. Y.; Wang, J. X.; Pei, Q.; Jin, C. X.; Zhang, X. N. The synthesis of α-hydroxy phosphonate compounds without solvents. *Xinyang Shifan Xueyuan Xuebao*. **2009**, *22(4)*, 588-589.
[30] Mandhane, P. G.; Joshi, R. S.; Nagargoje, D. R.; Gill, C. H. Ultrasound-promoted greener approach to synthesize α-hydroxy phosphonates catalyzed by potassium dihydrogen phosphate under solvent-free condition. *Tetrahedron Lett.* **2010**, *51(11)*, 1490-1492.
[31] Wang, H. S.; Zeng, J. E. Iodine-catalyzed, efficient synthesis of α-hydroxy phosphonates in water. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010**, *185(7)*, 1425-1428.
[32] Rao, K. U. M.; Sundar, C. S.; Prasad, S. S.; Rani, C. R.; Reddy, C.S. Neat Synthesis and Anti-oxidant Activity of α-Hydroxyphosphonates. *Bull. Korean Chem. Soc.* **2011**, *32(9)*, 3343-3347.

[33] Sardarian, A. R.; Kaboudin, B. Surface-mediated solid phase reactions: preparation of diethyl 1-hydroxyarylmethylphosphonates on the surface of magnesia. *Synth. Commun.* **1997**, *27*, 543-551.
[34] De Noronha, R. G.; Costa, P. J.; Romao, C. C.; Calhorda, M. J.; Fernandes, A. C. MoO_2Cl_2 as a novel catalyst for C-P bond formation and for hydrophosphonylation of aldehydes. *Organometallics.* **2009**, *28*, 6206-6212.
[35] Platonov, A. Y.; Sivakov, A. A.; Chistokletov, V. N.; Maiorova, E. D. Transformations of electrophilic reagents in a diethyl phosphite-potassium carbonate-ethanol system. *Russ. Chem. Bull.* **1999**, *48*, 367-370.
[36] Alexander, C. W.; Albiniak, P. A.; Gibson, L. R. Synthesis of α-hydroxy phosphonates using a solid supported base. *Phosphorus, Sulfur and Silicon and the Related Elements.* **2000**, *167*, 205-209.
[37] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, Fourth Edition, Butterworth-Heinemann, Oxford, **1997**.