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A METHODOLOGY STUDY OF HYDROPHOSPHONYLATION OF ALDEHYDES DERIVATIVES WITH $H_6P_2W_{18}O_{62}•14H_2O$ AS A CATALYST

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Abstract. A catalytic process for hydrophosphonylation of aldehydes with $H_6P_2W_{18}O_{62}·14H_2O$ has been developed in this paper. Various aldehydes were reacted with diethylphosphite in the presence of 1 % of heteropolyacids (HPAs) as a catalyst to generate the α-hydroxyphosphonates. All the synthesized compounds were sys tematically characterized by IR, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR. Simple and mild method, short reaction time, solvent-free conditions, availability and reusability of the catalyst are the main advantages of this procedure.

Keywords: aldehyde, diethylphosphite, Pudovik reaction, α-hydroxyphosphonate.

1. Introduction

In the recent years, the chemistry of organophosphorus compounds has attracted considerable attention, owing to their biological activities [1]. Phosphorus-carbon bond formation reactions are one of the most important reactions in organic transformations as they give rise to many naturally occurring biological and pharmaceutical active organophosphorus compound.

In particular, α-hydroxyphosphonates are an important type that was applied widely in a wide range of pharmaceutical, medicinal and biomedical fields [2]. They possess many properties such as antiviral [3], anticancer [4], antibacterial [5], anti-oxidant [6], pesticide [7], as potent inhibitor for renin enzyme [8], and anti-HIV [9].

In addition, α-hydroxyphosphonates are suitable precursors for a variety of α-substituted phosphonate such as α-acetoxy, α-amino, α-keto and α-halogenophosphonates with potent biological activities [10-13].

The Pudovik and Abramov phosphonylation reaction of aldehydes with dialkylphosphite or trialkylphosphite is the most authoritative method used for the synthes of α-hydroxyphosphonates [14, 15].

The preparation of α-hydroxyphosphonates has been investigated with various techniques such as: EtMgBr [16], piperazine [17], quaternary ammonium hydroxide [18], quinine [19], amberlyst-15 [20], LDA [21], Al(salalen) complex [22], KF/Al_2O_3[23], KF on natural phosphates [24], trimethylamine [25], Na_2CO_3 [26] or CaO [27], K_2CO_3 [28], MgO [29], 1,4-dimethylpiperazine under ultrasonic irradiation [30], and using MW system [31]. In addition, several examples of the reaction under thermal noncatalyzed conditions were reported [32].

However, some of these approaches suffer from various drawbacks such as low yields, use of expensive and commercially unavailable catalysts, high heating, long reaction time, moisture sensitive catalysts, and high catalyst loading (more than 10 mol %). In addition, it has been reported that some of the α-hydroxyphosphonates decomposed to the corresponding starting materials or rearranged to phosphate esters when drastic conditions are employed [33]. Consequently, the development of an inexpensive environmentally friendly process for α-hydroxyphosphonate (HPPs) synthesis under neat conditions is highly preferred.

In the last two decades, HPA have attracted much attention as environmentally benign catalysts for organic synthetic transformations. They possess unique physicochemical properties, such as super-acidity, chemical stability, ability to accept and release electrons, high proton mobility, and ease of recyclability [34]. In continuation of our interest towards the development of a new method for the synthesis of organophosphorus compounds [35, 36, 37], we report in this paper a facile process for the synthesis of various α-hydroxyphosphonates *via* the reaction of diethylphosphite with aldehydes in the presence of HPA as a catalyst under solvent-free conditions.

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2. Experimental

2.1. Instruments and Materials

The chemicals were used without purification. All reactions were monitored by thin layer chromatography (TLC) on silica Merck 60F 254 percolated aluminum plates. Melting points were determined in open capillary tubes on an electro-thermal apparatus and were uncorrected. Mass spectra were recorded on a SHIMADZU QP 1100 Ex mass spectrometer. IR spectra were recorded on a Perkin-Elmer FT-600 spectrometer. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with a Brüker spectrometer at 400, 100, 161 MHz, respectively, using $CDCl_3$ as solvent. Chemical shifts are reported in δ units (ppm) with tetramethylsilane (TMS) as a reference. All coupling constants (J) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

2.2. Catalyst Preparation

The saturated heteropolyanion $K_6P_2W_{18}O_{62}\cdot 12H_2O$ was obtained by polycondensation of tungstate ions under acidic conditions medium. The acid form ($H_6P_2W_{18}O_{62}\cdot 14H_2O$) was prepared by extraction with ether in hydrochloric acid medium [38].

The IR spectrum was recorded on KBr pellets using a Shimadzu FTIR-8400 spectrophotometer. The ^{31}P NMR shifts were measured for 10^{-3}M solution of polyanion in D_2O solution and were referenced to H_3PO_4 85%.

The IR spectrum of acid Wells-Dawson compound $H_6P_2W_{18}O_{62}\cdot 14H_2O$ is characterized by the elongation bands of P–O at 1090 cm^{-1} and W–O terminal band, inter and intra W–O–W at 962, 914 and 769 cm^{-1}, respectively.

It is well known that phosphorus NMR is an appropriate and powerful way to check the purity of the product. Phosphorous NMR spectra of $H_6P_2W_{18}O_{62}\cdot 14H_2O$ reveal a virtually pure products with a single resonance peak at δ = -12.44 ppm.

2.3. Representative Procedure for Hydrophosphonylation of Aromatic Aldehydes

A mixture of diethylphosphite (106.13 mg, 1 mmol) and various aromatic aldehydes (138.11 mg, 1 mmol) was stirred at room temperature in the presence of $H_6P_2W_{18}O_{62}\cdot 14H_2O$ (46.21 mg, 1 mol %) as catalyst under solvent-free conditions for the appropriate time (see Table 2). The progress of reaction was monitored by thin-layer chromatography using DCM-MeOH (9.5–0.5) as a mobile phase. After 10 min, the mixture was diluted with DCM, and HPA catalyst was precipitated and filtered for the next cycle of reaction. Then, the organic phase was removed by evaporation in a vacuum and the crude product was purified by column chromatography (eluted with diethyl acetate: petroleum ether 9.5/0.5) or recrystallization in (diethyl ether/*n*-hexane) to afford the pure α-hydroxyphosphonates in excellent yields.

This reported process is a good contribution to the synthetic organic transformations; it allows the access to therapeutic compounds in a single synthesis step.

The further applications of this reaction asymmetric synthesis of α-hydroxyphosphonates are in progress.

Diethyl [hydroxy(phenyl)methyl]phosphonate (**1**, $C_{11}H_{17}O_4P$). White solid. Yield 97 %, mp 351–353 K. FTIR (KBr): 3261, 1225, 1057 cm^{-1}. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 21.37 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J_{H-H} = 7.2 Hz, 3H,C**H**$_3$), 1.25 (t, J_{H-H} = 6.8 Hz, 3H, C**H**$_3$), 3.93-4.07 (m, 4H, C**H**$_2$), 4.99 (d, $^1J_{H-P}$ = 10.8 Hz, 1H, C**H***), 7.29-7.37 (m, 3H, **H**-Ar), 7.46-7.49 (m, 2H, **H**-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (t, $^3J_{C-P}$ = 6.0 Hz, 2**C**H$_3$), 63.0 (d, $^2J_{C-P}$ = 7.0 Hz, **C**H$_2$), 63.2 (d, $^2J_{C-P}$ = 7.0 Hz, **C**H$_2$), 70.1 (d, $^1J_{C-P}$ = 157.0 Hz, **C***), 127.0 (d, J_{C-P} = 6.0 Hz, **C**H-Ar), 128.1 (d, J_{C-P} = 3.0 Hz, **C**H-Ar), 128.2 (d, J_{C-P} = 2.0 Hz, **C**H-Ar), 136.5 (d, J_{C-P} = 2.0 Hz, **C**H-Ar) ppm. ESI-MS: (m/z) $[M+Na]^+$ 267.

Diethyl [hydroxy(naphthalen-2-yl)methyl] phosphonate (**2**, $C_{15}H_{19}O_4P$). White solid. Yield 95 %, mp 391–393 K. FTIR (KBr): 3270, 1235, 1045. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 21.25 ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, J_{H-H} = 7.2 Hz, 3H,C**H**$_3$), 1.25 (t, J_{H-H} = 7.2 Hz, 3H, C**H**$_3$), 3.94-4.09 (m, 4H, C**H**$_2$), 5.17 (d, $^1J_{H-P}$ = 10.8 Hz, 1H, C**H***), 7.46-7.48 (m, 2H, **H**-Ar), 7.56-7.61 (m, 1H, **H**-Ar), 7.81-7.84 (m, 3H, **H**-Ar), 7.95 (brs, 1H, **H**-Ar) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 (t, $^3J_{C-P}$ = 5.0 Hz, 2**C**H$_3$), 63.1 (d, $^2J_{C-P}$ = 7.0 Hz, **C**H$_2$), 63.3 (d, $^2J_{C-P}$ = 7.0 Hz, **C**H$_2$), 70.3 (d, $^1J_{C-P}$ = 157.0 Hz, **C***), 124.8 (d, J_{C-P} = 4.0 Hz, **C**H-Ar), 126.0 (d, J_{C-P} = 7.0 Hz, **C**H-Ar), 126.2, 127.7, 128.0 (d, J_{C-P} = 10.0 Hz, **C**H-Ar), 133.1, 133.8 ppm. ESI-MS: (m/z) $[M+Na]^+$ 317.

Diethyl [(2-fluorophenyl)(hydroxyl)methyl] phosphonate (**3**, $C_{11}H_{16}FO_4P$). White solid. Yield 90 %, mp 330–332 K. FTIR (KBr): 3320, 1250, 1040. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 20.83 (d, J_{F-P}=6.5 Hz) ppm. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J_{H-H} = 6.8 Hz, 3H,C**H**$_3$), 1.31 (t, J_{H-H} = 7.2 Hz, 3H, C**H**$_3$), 4.0-4.18 (m, 4H, C**H**$_2$), 5.37 (d, $^1J_{H-P}$ = 11.2 Hz, 1H, C**H***), 7.02-7.07 (m, 1H, **H**-Ar), 7.17-7.21 (t, J_{H-H} =7.6 Hz 1H, **H**-Ar), 7.27-7.30 (m, 1H, **H**-Ar), 7.61-7.68 (tt, $J_{H-H,}$ = 4.0 Hz, J_{H-P} = 8.0 Hz,1H, **H**-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (t, $^3J_{C-P}$ = 7.0 Hz, 2**C**H$_3$), 63.1 (d, $^2J_{C-P}$ = 7.0 Hz, **C**H$_2$), 63.4 (d, $^2J_{C-P}$ = 7.0 Hz, **C**H$_2$), 63.5 (d, $^1J_{C-P}$ = 130.0 Hz, **C***), 114.9, 115.1, 124.2, 124.4, 128.8, 129.6 (t, $J_{C\text{-}P}$ = 3.0 Hz, $\underline{\mathbf{C}}$H-Ar) ppm. ESI-MS: (m/z) $[\mathrm{M{+}Na}]^{+}$ 285.

Diethyl [(2-bromophenyl)(hydroxy)methyl] phosphonate (**4**, $C_{11}H_{16}BrO_4P$). White solid. Yield 91 %, mp 345–347 K. FTIR (KBr): 3315, 1230, 1022 cm^{-1}. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 21.10 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.17 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H,C$\underline{\mathbf{H}}_3$), 1.31 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, C$\underline{\mathbf{H}}_3$), 3.75 (brs, 1H, OH), 3.86-3.98 (m, 1H, C$\underline{\mathbf{H}}_2$), 4.00-4.05 (m, 1H, C$\underline{\mathbf{H}}_2$), 4.12-4.17 (m, 2H, C$\underline{\mathbf{H}}_2$), 5.48 (d, $^{1}J_{H\text{-}P}$ = 12.0 Hz, 1H, C$\underline{\mathbf{H}}$*), 7.13-7.15 (tt, $J_{H\text{-}H}$ = 1.2 Hz, $J_{H\text{-}p}$ = 6.0 Hz, 1H, $\underline{\mathbf{H}}$-Ar), 7.30-7.36 (t, $J_{H\text{-}H}$ = 7.2 Hz, 1H, $\underline{\mathbf{H}}$-Ar), 7.52-7.54 (dt, $J_{H\text{-}H}$ = 1.2 Hz, $J_{H\text{-}p}$ = 8.0 Hz,1H, $\underline{\mathbf{H}}$-Ar), 7.69-7.72 (dt, $J_{H\text{-}H}$ = 2.0 Hz, $J_{H\text{-}p}$ = 8.0 Hz, 1H, $\underline{\mathbf{H}}$-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.2 (t, $^{3}J_{C\text{-}P}$ = 6.0 Hz, $\underline{\mathbf{C}}$H$_3$), 16.3 (t, $^{3}J_{C\text{-}P}$ = 5.0 Hz, $\underline{\mathbf{C}}$H$_3$), 63.1 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.5 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 68.8 (d, $^{1}J_{C\text{-}P}$ = 159.0 Hz, $\underline{\mathbf{C}}$*), 123.2 (d, $J_{C\text{-}P}$ = 8.0 Hz, $\underline{\mathbf{C}}$H-Ar), 129.4, 129.5 (d, $J_{C\text{-}P}$ = 3.0 Hz, $\underline{\mathbf{C}}$H-Ar), 132.5 (d, $J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$H-Ar), 136.6 ppm. ESI-MS: (m/z) $[\mathrm{M{+}Na}]^{+}$ 345.

Diethyl [(4-chlorophenyl)(hydroxy)methyl] phosphonate (**5**, $C_{11}H_{16}ClO_4P$). White solid. Yield 93 %, mp 338–340 K. FTIR (KBr): 3393, 1224, 1038 cm^{-1}. ^{31}P NMR (161.9MHz, CDCl$_3$): δ = 21.37 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.21-1.28 (m, 6H, C$\underline{\mathbf{H}}_3$), 3.98-4.09 (m, 4H, C$\underline{\mathbf{H}}_2$), 4.97 (d, $^{1}J_{H\text{-}P}$ = 10.8 Hz, 1H, C$\underline{\mathbf{H}}$*), 7.30-7.33 (m, 2H, $\underline{\mathbf{H}}$-Ar), 7.40-7.42 (m, 2H, $\underline{\mathbf{H}}$-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.3 (t, $^{3}J_{C\text{-}P}$ = 6.0 Hz, 2$\underline{\mathbf{C}}$H$_3$), 63.1 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.4 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 69.4 (d, $^{1}J_{C\text{-}P}$ = 159.0 Hz, $\underline{\mathbf{C}}$*), 128.3, 128.4, 133.8 (d, $J_{C\text{-}P}$ = 3.0 Hz, $\underline{\mathbf{C}}$H-Ar), 135.2 (d, $J_{C\text{-}P}$ = 3.0 Hz, $\underline{\mathbf{C}}$H-Ar) ppm. ESI-MS: (m/z) $[\mathrm{M{+}Na}]^{+}$ 301.

Diethyl [hydroxy(4-methoxyphenyl)methyl] phosphonate (**6**, $C_{12}H_{19}O_5P$). White solid. Yield 93 %, mp 392–394 K. FTIR (KBr): 3258, 1228, 1068 cm^{-1}. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 21.59 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): 1.21 (t, $J_{H\text{-}H}$ = 6.8 Hz, 3H,C$\underline{\mathbf{H}}_3$), 1.27 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, C$\underline{\mathbf{H}}_3$), 3.92 (s, 3H, OC$\underline{\mathbf{H}}_3$), 3.92-4.09 (m, 4H, C$\underline{\mathbf{H}}_2$), 4.92 (d, $^{1}J_{H\text{-}P}$ = 10.0 Hz, 1H, C$\underline{\mathbf{H}}$*), 6.87 (d, J = 8.4 Hz, 2H, $\underline{\mathbf{H}}$-Ar), 7.38-7.40 (m, 2H, $\underline{\mathbf{H}}$-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.4 (t, $^{3}J_{C\text{-}P}$ = 5.0 Hz, 2$\underline{\mathbf{C}}$H$_3$), 55.2, 63.0 (d, $^{2}J_{C\text{-}P}$ = 8.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.1 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 69.7 (d, $^{1}J_{C\text{-}P}$ = 200.0 Hz, $\underline{\mathbf{C}}$*), 113.8 (d, $J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$H-Ar), 128.4 (d, $J_{C\text{-}P}$ = 6.0 Hz, $\underline{\mathbf{C}}$H-Ar) ppm. ESI-MS: (m/z) $[\mathrm{M{+}Na}]^{+}$ 297.

Diethyl [hydroxy(4-nitrophenyl)methyl] phosphonate (**7**, $C_{11}H_{16}NO_6P$). Orange solid. Yield 94 %, mp 360–362 K. FTIR (KBr): 3351, 1232, 1047 cm^{-1}. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 19.68 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): 1.27-1.30 (m, 6H, C$\underline{\mathbf{H}}_3$), 4.04-4.16 (m, 4H, C$\underline{\mathbf{H}}_2$), 5.14 (d, $^{1}J_{H\text{-}P}$ = 12.0 Hz, 1H, C$\underline{\mathbf{H}}$*), 6.65-6.68 (m, 2H, $\underline{\mathbf{H}}$-Ar), 8.21 (d, $J_{H\text{-}H}$ = 8.0 Hz, 2H, $\underline{\mathbf{H}}$-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.4 (d, $^{3}J_{C\text{-}P}$ = 3.0 Hz, $\underline{\mathbf{C}}$H$_3$), 16.5 (d, $^{3}J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$H$_3$), 63.5 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.9 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 69.6 (d, $^{1}J_{C\text{-}P}$ = 157.0 Hz, $\underline{\mathbf{C}}$*), 123.5 (d, $J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$H-Ar), 127.7 (d, $J_{C\text{-}P}$ = 5.0 Hz, $\underline{\mathbf{C}}$H-Ar) ppm. ESI-MS: (m/z) $(\mathrm{M{+}1}]^{+}$ 290.

Diethyl [(4-cyanophenyl)(hydroxy)methyl] phosphonate (**8**, $C_{12}H_{15}O_5P$). Colorless oil. Yield 92 %. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 19.90 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): 1.24-1.28 (m, 6H, C$\underline{\mathbf{H}}_3$), 4.02-4.13 (m, 4H, C$\underline{\mathbf{H}}_2$), 5.07 (d, $^{1}J_{H\text{-}P}$ = 12.0 Hz, 1H, C$\underline{\mathbf{H}}$*), 7.58-7.65 (m, 4H, $\underline{\mathbf{H}}$-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.3 (d, $^{3}J_{C\text{-}P}$ = 4.0 Hz, 2$\underline{\mathbf{C}}$H$_3$), 63.3 (d, $^{2}J_{C\text{-}P}$ = 8.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.7 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 69.5 (d, $^{1}J_{C\text{-}P}$ = 157.0 Hz, $\underline{\mathbf{C}}$*), 111.7 (d, $J_{C\text{-}P}$ = 3.0 Hz, $\underline{\mathbf{C}}$H-Ar), 118.6, 127.4 (d, $J_{C\text{-}P}$ =5.0 Hz, $\underline{\mathbf{C}}$H-Ar), 131.9 (d, $J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$H-Ar), 142.0 ppm. ESI-MS: (m/z) $[\mathrm{M{+}H}]^{+}$ 270.

Diethyl [hydroxy(3,4-dimethoxyphenyl)methyl] phosphonate (**10**, $C_{13}H_{21}O_6P$). White solid. Yield 90 %, mp 369–371 K. FTIR (KBr): 3268, 1234, 1065 cm^{-1}. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 21.45 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): 1.20 (t, $J_{H\text{-}H}$ = 6.8 Hz, 3H,C$\underline{\mathbf{H}}_3$-CH$_2$), 1.25 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, C$\underline{\mathbf{H}}_3$-CH$_2$), 3.90 (s, 3H, C$\underline{\mathbf{H}}_3$), 3.87 (s, 3H, C$\underline{\mathbf{H}}_3$), 3.92-4.09 (m, 4H, C$\underline{\mathbf{H}}_2$), 4.92 (d, $^{1}J_{H\text{-}P}$ = 10.0 Hz, 1H, C$\underline{\mathbf{H}}$*), 6.87 (s, 1H, $\underline{\mathbf{H}}$-Ar), 7.38-7.40 (m, 2H, $\underline{\mathbf{H}}$-Ar) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.4 (t, $^{3}J_{C\text{-}P}$ = 5.0 Hz, $\underline{\mathbf{C}}$H$_3$), 55.2 (OC$\mathbf{H}_3$), 53.4 (OC$\mathbf{H}_3$) 63.0 (d, $^{2}J_{C\text{-}P}$ = 8.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.1 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 69.7 (d, $^{1}J_{C\text{-}P}$ = 200.0 Hz, $\underline{\mathbf{C}}$*), 113.8 (d, $J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$H-Ar), 128.4 (d, $J_{C\text{-}P}$ = 6.0 Hz, $\underline{\mathbf{C}}$H-Ar) ppm. ESI-MS: (m/z) $[\mathrm{M{+}Na}]^{+}$327.

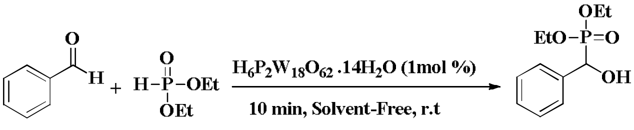
Diethyl [furan-2-yl(hydroxy)methyl]phosphonate (**12**, $C_{10}H_{15}O_5P$). Yellow oil. Yield 88 %. FTIR (KBr): 3275, 1250, 1046 cm^{-1}. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 19.19 ppm. ^{1}H NMR (300 MHz, CDCl$_3$): 1.25 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, C$\underline{\mathbf{H}}_3$), 1.33 (t, $J_{H\text{-}H}$ = 7.2 Hz, 3H, C$\underline{\mathbf{H}}_3$), 4.02-4.20 (m, 4H, 2C$\underline{\mathbf{H}}_2$), 4.96 (d, $^{1}J_{H\text{-}P}$ = 13.5 Hz, 1H, C$\underline{\mathbf{H}}$*), 6.38 (t, $J_{H\text{-}H}$ = 2.4 Hz, 1H,$\underline{\mathbf{H}}$-vinyl), 6.51 (t, $J_{H\text{-}H}$ = 2.7 Hz, 1H, $\underline{\mathbf{H}}$-vinyl), 7.42-7.43 (m, 1H, $\underline{\mathbf{H}}$-vinyl) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.3 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, $\underline{\mathbf{C}}$H$_3$), 16.4 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.4 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.4 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, $\underline{\mathbf{C}}$H$_2$), 63.9 (d, $^{1}J_{C\text{-}P}$ = 165.0 Hz, $\underline{\mathbf{C}}$*), 109.3 (d, $J_{C\text{-}P}$ = 6.0 Hz, $\underline{\mathbf{C}}$-vinyl), 110.7, 142.9 (d, $J_{C\text{-}P}$ = 2.0 Hz, $\underline{\mathbf{C}}$-vinyl), 149.8 ppm. ESI-MS: (m/z) $[\mathrm{M{+}Na}]^{+}$ 257.

Diethyl [hydroxy(thiophen-2-yl)methyl] phosphonate (**13**, $C_9H_{15}O_4PS$). Yellow oil. Yield 89 %. FTIR (KBr): 3276, 1225, 1036 cm^{-1}. ^{31}P NMR (161.9 MHz, CDCl$_3$): δ = 19.61 ppm. ^{1}H NMR (400 MHz, CDCl$_3$): 1.26 (t, $J_{H\text{-}H}$ = 6.8 Hz,C$\underline{\mathbf{H}}_3$), 1.31 (t, $J_{H\text{-}H}$ = 7.2 Hz,C$\underline{\mathbf{H}}_3$), 4.05-4.17 (m, 4H, 2C$\underline{\mathbf{H}}_2$), 5.21 (d, $^{1}J_{H\text{-}P}$ = 10.4 Hz, 1H, C$\underline{\mathbf{H}}$*), 6.99-7.01 (m, 1H, $\underline{\mathbf{H}}$-vinyl), 7.18-7.20 (m, 1H, $\underline{\mathbf{H}}$-vinyl), 7.29-7.31 (dt, $J_{H\text{-}H}$ = 1.2 Hz, $J_{H\text{-}P}$ = 5.2 Hz,1H, $\underline{\mathbf{H}}$-vinyl) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 16.3 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, 2$\underline{\mathbf{C}}$H$_3$), 63.3

(d, $^2J_{C\text{-}P}$ = 7.0 Hz, $\underline{C}H_2$), 63.6 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, $\underline{C}H_2$), 66.2 (d, $^1J_{C\text{-}P}$ = 166.0 Hz, $\underline{C}$*), 125.7 (d, $J_{C\text{-}P}$ = 3.0 Hz, $\underline{C}$-vinyl), 126.1 (d, $J_{C\text{-}P}$ = 8.0 Hz, $\underline{C}$-vinyl), 126.8 (d, $J_{C\text{-}P}$ = = 3.0 Hz, $\underline{C}$-vinyl), 139.4 ppm. ESI-MS: (m/z) $[M+Na]^+$ 273.

3. Results and Discussion

The reaction between benzaldehyde and diethyl phosphite (Scheme1) was selected as a model to optimize the reaction conditions.



Scheme 1. HPA-catalyzed phospho-aldol reaction of diethylphosphite with benzaldehyde

Initially, an equimolar of benzaldehyde and diethylphosphite was stirred at room temperature under solvent free conditions without catalyst; no product was formed after 12 h (Table 1, entry 1).

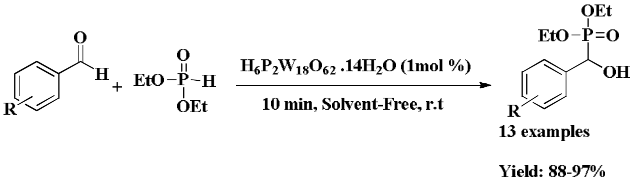
Secondly, to improve the necessity and to determine the exact requirement of catalyst for the reaction, we investigated the model reaction using different concentrations of HPA such as 0.1, 0.5, 1, 3, 5, and 10 mol %. During this, the formation of α-hydroxyphosphonate was observed in 25, 30, 97, 96, 96 and 97 % yield, respectively. This results indicates that 1 mol % of HPA is sufficient to carry out the reaction smoothly.

In order to examine the effect of solvent, we decided to repeat the model reaction with 1 % of catalyst in several solvents such as THF, CH_2Cl_2, CH_3CN, and H_2O. No significant improvement of yield was observed even after half an hour of reaction time.

In addition, we tested the effect of temperature elevation by using different temperatures in this synthesis; the results show that the reaction occurred efficiently at room temperature and no modification of yield was remarked after the increase of temperature.

Finally, there is no change on yield when we use 1.1 eq of diethylphosphite and a partial consumption of starting material with 1.2 eq.

After optimizing reaction conditions established above, a series of α-hydroxyphosphonates (1-13) were prepared involving different aromatic aldehydes (Table 2). All reactions were completed within 10 min in excellent yields at room temperature, under solvent-free conditions and in the presence of $H_6P_2W_{18}O_{62}\cdot 14H_2O$ (1 mol %) as a catalyst. To show the essential role of $H_6P_2W_{18}O_{62}\cdot 14H_2O$ as the catalyst, this excellent result encourages us to extend this study toward various structurally aldehydes. The reaction on ketones does not show any conversion even after prolonged reaction time and increasing catalyst concentration. These results confirmed that the reaction proceeds only on the aldehydes and not on ketones.



Scheme 2. Catalysts synthesis of α-hydroxyphosphonates with various aldehydes

Table 1

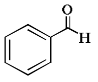
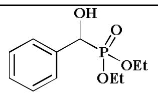
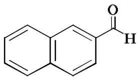
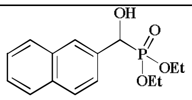
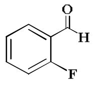
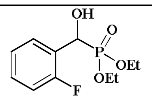
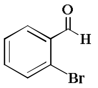
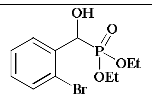
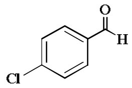
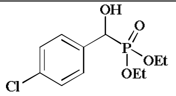
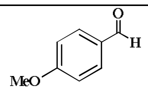
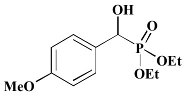
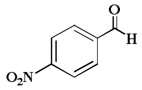
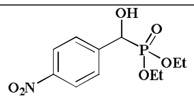
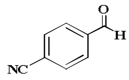
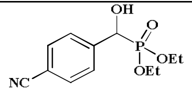
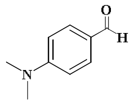
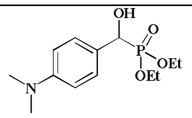
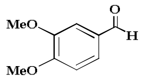
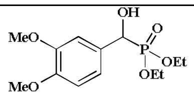
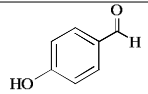
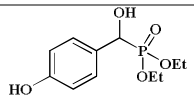
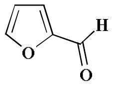
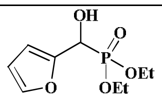
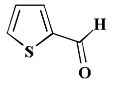
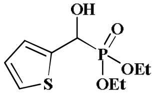
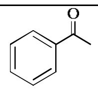
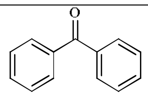
Optimization of reaction conditions

Entry	Catalyst	Solvent	Temperature, K	Equivalent number	Time	Yield, %
1	Catalyst free	Neat	r.t	Equimolar	12 h	No reaction
2	HPA, (0.1 mol %)	Neat	r.t	Equimolar	5 h	25
3	HPA (0.5 mol %)	Neat	r.t	Equimolar	5 h	30
4	HPA (1 mol %)	Neat	r.t	Equimolar	10 min	97
5	HPA (3 mol %)	Neat	r.t	Equimolar	10 min	96
6	HPA (5 mol %)	Neat	r.t	Equimolar	10 min	96
7	HPA (10 mol %)	Neat	r.t	Equimolar	10 min	97
8	HPA (1 mol %)	THF	r.t	Equimolar	10 min	90
9	HPA (1 mol %)	CH_2Cl_2	r.t	Equimolar	10 min	75
10	HPA (1 mol %)	CH_3CN	r.t	Equimolar	10 min	70
11	HPA (1 mol %)	H_20	r.t	Equimolar	10 min	85
12	HPA (1 mol %)	Neat	313	Equimolar	10 min	90
13	HPA (1 mol %)	Neat	333	Equimolar	10 min	92
14	HPA (1 mol %)	Neat	r.t	a	10 min	95
15	HPA (1 mol %)	Neat	r.t	b	10 min	Partial consumption

Notes: [a] 1 eq of benzaldehyde and 1.1 eq of diethylphosphite; [b] 1 eq of benzaldehyde and 1.2 eq of diethylphosphite

Table 2

Hydrophosphorylation of aldehydes with $H_6P_2W_{18}O_{62}\cdot14H_2O$ as a recyclable catalyst

Entry	Aldehyde	Compound	Yield, %	mp, K	
				Found	Ref.
1			97[a]	351–353	[6]
2			95[a]	391–393	[40-41]
3			90[a]	330–332	[40-41]
4			91[b]	345–347	[40-41]
5			93[a]	338–340	[6]
6			93[b]	392–394	[6]
7			94[a]	360–362	[6]
8			92[b]	Oil	[39]
9			90[b]	353–355	[6]
10			90[a]	369–371	[6]
11			91[a]	452–454	[42]
12			88[b]	Oil	[39]
13			89[b]	Oil	[39]
14		No reaction	–	–	–
15		No reaction	–	–	–

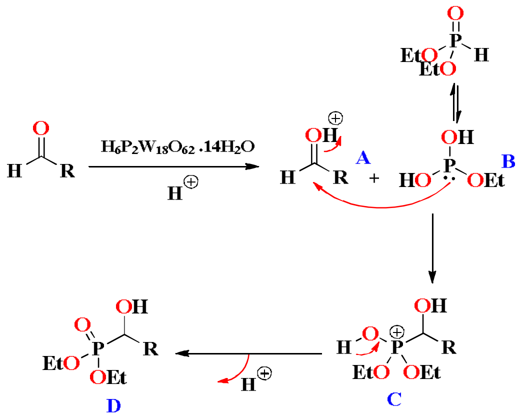
Notes: [a] isolated yields with recrystallization in diethyl ether/*n*-hexane; [b] isolated yields with purification in column chromatography eluted with diethyl acetate:petroleum ether

The structures of all the compounds were verified by usual spectroscopic methods, infrared (IR) spectroscopy, ^{1}H, ^{13}C, ^{31}P NMR, and MS.

The IR spectra of compounds (1-13) showed absorption bands in the region of 3330–3240 cm^{-1} and 1250-1200 cm^{-1}, which are attributed to O–H and P=O stretching vibrations, respectively. In the ^{1}H NMR spectrum, CH* proton signal appeared as a doublet in the region of 4.80–5.20 ppm confirming the formation of α-hydroxyphosphonates. In the ^{13}C NMR spectra, the doublet at 71.0–68.0 ppm confirms the presence of asymmetric carbon. In the ^{31}P NMR spectrum, the presence of a signal at 19.1 21.4 ppm approves all hydroxyphosphonates structures [39]. In mass spectra; $(M^{+\cdot})$ ions were observed in the expected m/z values.

Aromatic aldehydes containing electron-withdrawing and electron-donating groups generate the desired products in high yield and short reaction times. The quality of the substituent has no significant influence on the yield and on the reaction time (Table 2).

A probable mechanism for this reaction was proposed and depicted by Scheme 3. The reaction occurred stepwise. First, the HPA catalyst reacts with the aldehyde by giving its acidic proton, which leads to the formation of an oxonium cation (A) and makes the carbonyl group of the aldehyde more susceptible for nucleophilic attack by the phosphite B, and an intermediate hydroxyphosphonium cation (C) is formed. Next, the HPA catalyst recuperates its proton, leading to the formation of the final hydroxyphosphonate product (D).



Scheme 3. Proposed mechanism for the synthesis of α-hydroxyphosphonates

4. Conclusions

An efficient, mild, greener, and expeditious synthetic protocol for the synthesis of α-hydroxyphosphonates has been developed in this paper. The main advantages of our process include classical performance, reduced reaction times, non-toxic and economically viable catalyst, omission of solvents, ambient reaction temperature, simplified work-up procedure, gives the final products in very good yields, and enables reusability of catalyst without significant loss of its activity.

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References

[1] Corbridge D.: Phosphorus: An Outline of its Chemistry, Biochemistry and Technology, 5th edn. Elsevier, Amesterdam 1995.

[2] Francis M., Martodam R.: Chemical, Biochemical and Medicinal Properties of the Diphosphonates [in:] Hilderbrand R. (Ed), The Role of Phosphonates in Living Systems. CRC Press, Boca Raton 1983, 55.

[3] Neyts J., De Clercq E.: Antimicrob. Agents Chemother., 1997, **41**, 2754.

[4] Lee M., Fong E., Singer F., Guenette R.: Cancer. Res., 2001, **61**, 2602.

[5] Fleisch H.: Endocr. Rev., 1998, **19**, 80. https://doi.org/10.1210/edrv.19.1.0325

[6] Naidu K., Kumar K., Arulselvan P. *et al.*: Arch. Pharm., 2012, **345**, 957. https://doi.org/10.1002/ardp.201200192

[7] Kafarski P., Lejczak B.: J. Mol. Catal. B, 2004, **29**, 99. https://doi.org/10.1016/j.molcatb.2003.12.013

[8] Tao M., Bihovsky R., Wells G., Mallamo J.: J. Med. Chem., 1998, **41**, 3912. https://doi.org/10.1021/jm980325e

[9] Zheng X., Nair V.: Tetrahedron, 1999, **55**, 11803. https://doi.org/10.1016/S0040-4020(99)00681-X

[10] Kaboudin B.: Tetrahedron Lett., 2003, **44**, 1051. https://doi.org/10.1016/S0040-4039(02)02727-2

[11] Firouzabadi H., Iranpoor N., Sobhani S., Amoozgar Z.: Synthesis, 2004, **11**, 1771. https://doi.org/10.1055/s-2004-829124

[12] Firouzabadi H., Iranpoor N., Sobhani S.: Synth. Commun., 2004, **34**, 1463. https://doi.org/10.1081/SCC-120030697

[13] Lorga B., Eymery F., Savignac P.: Tetrahedron, 1999, **55**, 2671. https://doi.org/10.1016/S0040-4020(99)00037-X

[14] Abramov V.: Dokl. Akad. Nauk SSSR, 1950, **73**, 487.

[15] Pudovik A., Arbuzov B.: Dokl. Akad. Nauk SSSR, 1950, **73**, 327.

[16] Gawron O., Grelecki C., Reilly W., Sands J.: J. Am. Chem. Soc., 1953, **75**, 3591. https://doi.org/10.1021/ja01110a508

[17] Kumar K., Reddy C., Reddy M. *et al.*: Org. Commun., 2012, **5**, 50.

[18] Alexander C., Albiniak P., Gibson L.: Phosphorus Sulfur, 2000, **167**, 205. https://doi.org/10.1080/10426500008082399.

[19] Smaardijk A., Noorda S., Bolhuis F.,Wynberg H.: Tetrahedron Lett., 1985, **26**, 493. https://doi.org/10.1016/S0040-4039(00)61920-2

[20] Tajbakhsh M., Heydari A., Khalizadeh M. *et al.*: Synlett., 2007, **15**, 2347. https://doi.org/10.1055/s-2007-985595

[21] Blazis V., Koeller K., Spilling C.: J. Org. Chem., 1995, **60**, 931. https://doi.org/10.1021/jo00109a025

[22] Saito B., Egami H., Katsuki T.: J. Am. Chem.Soc., 2007, **129**, 1978. https://doi.org/10.1021/ja0651005

[23] Textier-Boullet F., Lequitte M.: Tetrahedron. Lett., 1986, **27**, 3515. https://doi.org/10.1016/S0040-4039(00)84837-6

[24] Smahi A., Solhy A., Tahir R. *et al.*: Catal. Commun., 2008, **9**, 2503.https://doi.org/10.1016/j.catcom.2008.07.005

[25] Baraldi P., Guarnieri M., Moroder F. *et al.*: Synthesis, 1982, **8**, 653. https://doi.org/10.1055/s-1982-29888

[26] Keglevich G.,Toth V., Drahos L.: Heteroatom. Chem., 2011, **22**, 15. https://doi.org/10.1002/hc.20649

[27] Martinez-Castro E., Lopez O., Maya I. *et al.*: Green Chem., 2010, **12**, 1171. https://doi.org/10.1039/C0GC00026D

[28] Jeanmaire T., Hervaud Y., Boutevin B.: Phosphorus Sulfur, 2002, **177**, 1137. https://doi.org/10.1080/10426500211718

[29] Sardarian A., Kaboudin B.: Synth. Commun., 1997, **27**, 543. https://doi.org/10.1080/00397919708003324

[30] Rasheed S., Venkata Ramana K., Madhava G. *et al.*: Phosphorus Sulfur, 2014, **189**, 606. https://doi.org/10.1080/10426507.2013.843002

[31] Feng D.,Chen R.,Huang Y., Song H.: Heteroatom. Chem., 2007, **18**, 347. https://doi.org/10.1002/hc.20304

[32] Kharasch M., Mosher R., Bengelsdorf I.: J. Org. Chem., 1960, **25**, 1000. https://doi.org/10.1021/jo01076a035

[33] Samanta S.,Zhao C.: J. Am. Chem. Soc., 2006, **128**, 7442. https://doi.org/10.1021/ja062091r

[34] Pope M.: Heteropoly and IsopolyOxometalates. Springer Verlag, NewYork 1983.

[35] Bouzina A., Aouf N., Berredjem M.: Res. Chem. Intermed., 2016, **42**, 5993. https://doi.org/10.1007/s1116

[36] Belhani B., Berredjem M., Le Borgne M. *et al.*: RSC Adv., 2015, **5**, 39324. https://doi.org/10.1039/C5RA03473F

[37] Boughaba S., Bouacida S., Aouf Z. *et al.*: Curr. Org. Chem, 2018, **22**, 1335. https://doi.org/10.2174/1385272822666180404145804

[38] Rao U., Sundar S., Prasad S. *et al.*: Bull. Korean Chem. Soc., 2011, **32**, 3343. https://doi.org/10.5012/bkcs.2011.32.9.3343

[39] Ciabrini J.,Contant R., Fruchart J.: Polyhedron,1983, **2**, 1229. https://doi.org/10.1016/S02775387(00)84366-1

[40] Angelini T., Bonollo S., Lanari D. *et al.*: Org. Biomol. Chem., 2013, **11**, 5042. https://doi.org/10.1039/C3OB40767E

[41] Ramesh K., Madhav B., Murthy S., NageswarY.: Synth. Commun., 2012, **42**, 258. https://doi.org/10.1080/00397911.2010.523492

[42] Zhou X., Liu X., Yang X. *et al.*: Angew. Chem. Int. Ed., 2008, **47**, 392. https://doi.org/10.1002/anie.200704116

[43] Kumar A., Jamwal S., Khan S. *et al.*: Phosphorus Sulfur, 2017, **192**, 381. https://doi.org/10.1080/10426507.2016.1247085

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МЕТОДОЛОГІЯ ДОСЛІДЖЕННЯ ГІДРОФОСФОНІЛЮВАННЯ АЛЬДЕГІДНИХ ПОХІДНИХ З $H_6P_2W_{18}O_{62}\cdot 14H_2O$, ЯК ВІДНОВЛЮВАЛЬНОГО КАТАЛІЗАТОРА

Анотація. *Розроблено каталітичний процес гідрофонфонілювання альдегідів загальної формули* $H_6P_2W_{18}O_{62}\cdot 14H_2O$. *Для отримання α-гідроксифосфонатів різні альдегіди піддавали взаємодії з діетилфосфітом у присутності 1 % гетерополікислоти як каталізатора. Синтезовані сполуки охарактеризовані за допомогою ІЧ-спектроскопії та методів* ^1H *ЯМР,* ^{13}C *ЯМР і* ^{31}P *ЯМР. Показано, що головною перевагою розробленого процессу є прості та м'які умови синтезу, незначний час реакції, відсутність розчинників, доступність та можливість відновлення каталізатора.*

Ключові слова: *альдегід, діетилфосфіт, реакція Пудовика, α-гідроксифосфонат.*