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TRIPHENYLPHOSPHINE: AS A PROFICIENT CATALYST FOR ONE POT SYNTHESIS OF α-HYDROXY PHOSPHONATES UNDER NEAT CONDITION

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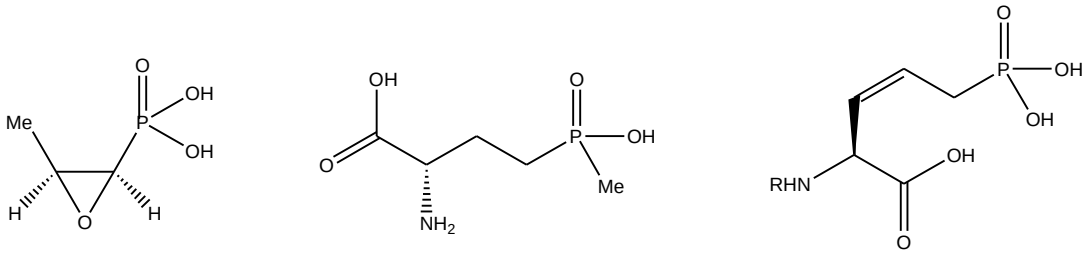
ABSTRACT:
A very easy and useful method was reported for one pot synthesis of α-hydroxy phosphonates using aromatic aldehyde and diethyl phosphite catalysed by triphenylphosphine (PPh_3) in under solvent less condition. The reaction proceeds with short reaction time, eco-friendly catalyst, easy work-up procedure, high yielding of products.

KEY WORDS:
α-hydroxy phosphonates, mild reaction condition, short reaction time, easy work-up procedure, high yielding of products.

1. INTRODUCTION:

It is very familiar that organophosphorus compound have great importance in the field industrial, agricultural and medicinal chemistry based on their physical and biological properties in addition to their use as a synthetic intermediates for synthesis of various bioactive molecules[1-3]. Among many organophosphorus compound α-amino and α-hydroxy phosphonates reveal variety of fascinating and utilizable applications[4-8]. Over a past decade, synthesis of α-hydroxy phosphonates received very much attention due to their potential biological activities such as anti-viral[9], anti-bacterial[10], anti-cancer[11] anti-oxident[12]. In addition to these α-hydroxy phosphonates are act as key precussor for synthesis of α-keto[13], α-amino[14], α-halo[15], α-acetoxy phosphonates[16], 1-2 diketone[17].

α-hydroxy phosphonates are structural counterpart of α-hydroxyphosphonic acids[18], and can act as enzyme inhibitor for human protein tyrosine phosphatase (PTP)[19], farnesyl protein transferase (FPT)[20], purine nucleoside phosphorylase (PNP)[21], and human renin[22]. Phosphonates are prime natural product[23]and their reagents are versatile synthetic important precursors for various biologically active analogs[24].



Fosfomycin Phosphinothricin Rhizocticin A, R-Arg

Figure-1

α-hydroxy phosphonates are firstly synthesized by the Pudovik reaction, in which the C–P bond is composed by the integration of a dialkyl phosphite to an unsaturated system and the Abramov reaction in which the C–P bond is composed by the integration of a trialkyl phosphite to an unsaturated system. Hydrophosphylation of carbonyl compound is conventionally mediated by a base-catalyzed reaction. Commonly synthesis of α-hydroxy phosphonates involves reaction between substituted aldehyde and diethyl phosphite with different bases such as ethyl magnesium bromide[25], LDA[26], KF on alumina[27], quinine[28], Magnesium oxide[29]. In addition to this reaction of substituted aldehyde and ketones with trialkyl phosphite are reported in presence of acid catalyst such as $LiClO_4.Et_2O$[30], guanidine hydrochloride[31]. There are some drawbacks in the existing methodologies such as requirement of elevated temperature, severe reaction condition, strong acid and base, slow reaction rate, mixture of product, use of toxic catalyst and inadequate yield. Hence, the development of an affordable protocol for a synthesis of α- hydroxyphosphonate with facile accessibility, a low toxicity solid acid catalyst and the capability to work under neat conditions is highly preferred for the synthesis of α-hydroxyphosphonates.

Over a last few years, the utilization of solid acid catalysts has received consequential attention in synthesis of organic compound as a result of their growing and environmental advantage. These types of reagents not only make simpler purification processes but also help in minimizing the liberation of toxic reaction residues into the environment. Triphenylphosphine is non-corrosive, inexpensive, eco-friendly catalyst can be used for synthesis of different multicomponent reaction[32].

2. EXPERIMENTAL:

3.1 General :

All the chemicals, reagents and solvents were purchased from Merk, Loba and Avra make. They are utilized without further purification. The melting point were recorded on digital melting/boiling point apparatus of Labtronics make which expressed in degree centigrade (°C) and found uncorrected. Thin layer chromatography was accomplished on precoated plates of TLC silica gel 60 F_{254}. 20% ethyl acetate in hexane solvent was used for TLC. Visualization was made with UV light (254 or 365nm). IR spectra were obtained on Shimatzu Infra Red Spectrophotometer at Jijamata College of Arts and Science, Bhende, Ahmednagar and absorptions (ν_{max})were reported in wave numbers (cm^{-1}). The ^1H NMR spectra were recorded on at Indian Institute of Science Bangalore using Bruker- 500 MHz spectrometer in $CDCl_3$ solvent using TMS as an internal standard and chemical shifts were measured in δ parts per million (ppm) and coupling constants (J) were measured in hertz (Hz).

3.2 The spectral analysis of some of the representative compounds were given here:

Compound 3a: Diethyl hydroxyl (phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.26-7.49 (m, 5H, Ar-H), 5.00-5.03 (d, 1H, J= 10.8 Hz, CH-PO-), 3.94-4.10 (m, 4H, OCH_2), 1.19-1.28 (m, 6H, OCH_2CH_3).

Compound 3b: Diethyl hydroxyl (4-methyl phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm: 7.16-7.37 (m, 4H, Ar-H), 4.95-4.98 (d, 1H, J=10.4 Hz CH-PO-), 3.93-4.09 (m, 4H, OCH_2), 2.34 (s, 3H, Ar-CH_3), 1.20-1.29 (m, 6H, OCH_2CH_3)

Compound 3c: Diethyl hydroxyl (4-methoxy phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm: 6.89-7.41 (m, 4H, Ar-H), 4.93-4.96 (d, 1H, J=10Hz, CH-PO-), 3.91-4.10 (m, 4H, OCH_2), 3.81 (s, 3H, OCH_3), 1.20-1.30 (m, 6H, OCH_2CH_3)

Compound 3d: Diethyl hydroxyl (3-nitro phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm: 7.53-8.37 (m, 4H, Ar-H), 5.13-5.16 (d, 1H, J=11.2 Hz, CH-PO-), 4.08-4.14 (m, 4H, OCH_2), 3.59 (s, 1H, OH), 1.25-1.57 (m, 6H, OCH_2CH_3)

Compound 3e: Diethyl hydroxyl (2-fluoro phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm: 7.02-7.68 (m, 4H, Ar-H), 5.36-5.39 (d, 1H, J=11.2 Hz, CH-PO-), 3.99-4.22 (m, 4H, OCH_2), 1.21-1.31 (m, 6H, OCH_2CH_3)

Compound 3f: Diethyl hydroxyl (4-fluoro phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm: 7.44-7.48 (m, 2H, Ar-H), 7.02-7.07 (m, 2H, Ar-H), 4.98-5.01 (d, 1H, J=10.4 Hz, CH-PO-), 3.97-4.10 (m, 4H, OCH_2), 1.21-1.29 (m, 6H, OCH_2CH_3)

Compound 3g: Diethyl hydroxyl (4-chloro phenyl) methyl phosphonates:

^{1}H NMR (400 MHz, $CDCl_3$,) δ ppm: 7.23-7.46 (m, 4H, Ar-H), 4.81-4.79 (d, 1H, J=10.8 Hz, CH-PO-), 3.99-4.26 (m, 4H, OCH_2), 1.24-1.35 (m, 6H, OCH_2CH_3)

3. RESULT AND DISCUSSION:

3.1 General procedure for synthesis of α-hydroxy phosphonates:

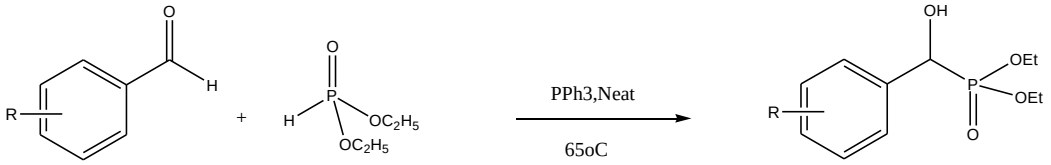
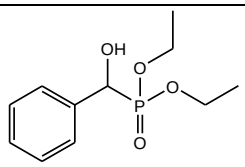
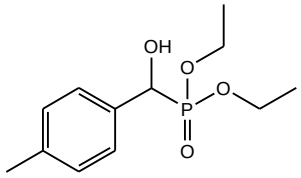
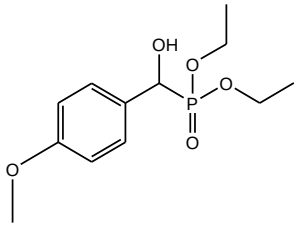
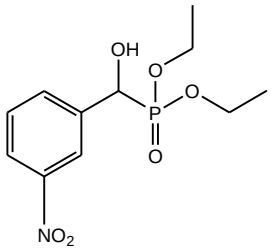
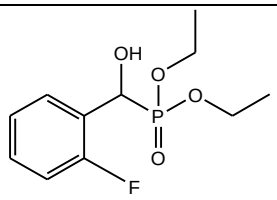
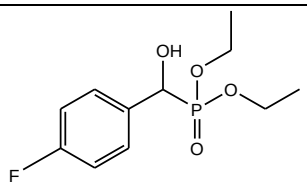


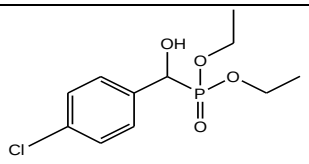
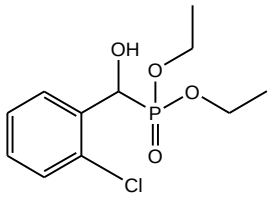
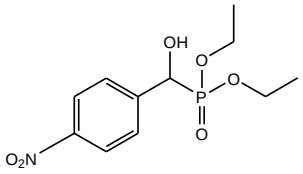
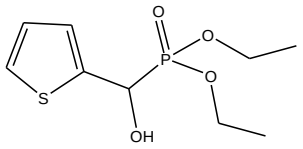
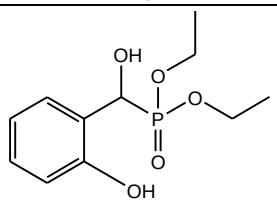
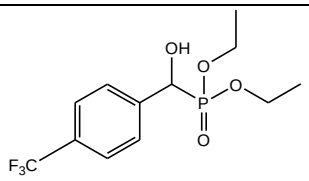
figure-2

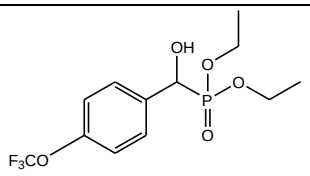
Scheme-1 Synthesis of hydroxy phosphonates

In a 50 ml round bottom flask, the mixture of aromatic aldehyde, diethyl phosphite and triphenylphosphine (20%) was heated at 65^0C for 2 hrs under neat condition and the progress of reaction reaction was monitored by TLC. After completion of reaction, water was discharged to the reaction mixture and extracted with ethyl acetate, then organic layer were dry over an.Na_2SO_4 and concentrated under reduced pressure to obtain solid. The crude product was recrystallized in ethanol solvent to afford the pure product. Using established protocol, aromatic aldehyde with electron donating and withdrawing group at respective position was used for synthesis of α-hydroxy phosphonates and w3wresult are summarized in table-1

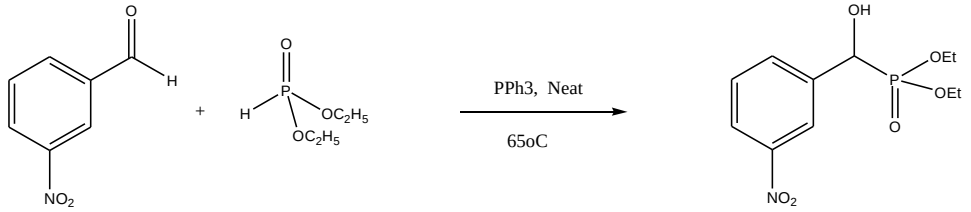
Table-1: Synthesis of α -hydroxy phosphonates derivatives.

Entry	**Aldehyde**	**Compound**	**M.P.ºC found**	**M.P. ºC Reported[ref]**	**Yield (%)**
1	Benzaldehyde	 3a	74-75	75-77[29]	88
2	4-Methyl benzaldehyde	 3b	95-96	94-95[29]	86
3	4-Methoxy benzaldehyde	 3c	120-122	120-121[29]	88
4	3-Nitro benzaldehyde	 3d	80-82	81-82[29]	90
5	2-Fluro benzaldehyde	 3e	88-89	-	85
6	4- Fluro benzaldehyde	 3f	78-79	-	88

7	4-Chloro benzaldehyde	 3g	68-70	67-68[29]	84
8	2-Chloro benzaldehyde	 3h	75-77	74-75[29]	82
9	4- Nitro benzaldehyde	 3i	88-90	87-88[29]	88
10	Thiophene 2-aldehyde	 3j	semi-solid nature	-	82
11	Salicyldehyde	 3k	semi-solid nature	-	82
12	4-trifluromethyl benzaldehyde	 3l	90-92	-	86

13	4-trifluromethoxy benzaldehyde	 3m	semi-solid nature	-	82

In a first endeavour, we begin with our protocol containing 3-nitro benzaldehyde (0.66 mmol) and diethyl phosphite (0.66 mmol) and triphenylphosphine (10 mol%) was stirred in ethanol for overnight at room temperature. After examine TLC, it is observed that, reaction completed 80%, so we decided for the optimization of concentration of catalyst and reaction condition. So we modified the above procedure by heating 3-nitro benzaldehyde (0.66 mmol) and diethyl phosphite (0.66 mmol) and triphenylphosphine (5 mol%) for 2 hrs at 65^0C under neat condition and the progress of reaction reaction was monitored by TLC. The residue wash with water and extracted with ethyl acetate (3x 10 ml) then organic layer were dry over an.Na_2SO_4 and concentrated under reduced pressure to obtain solid. The crude product was recrystallized in ethanol solvent to afford the pure product.



1a 2a 3a

figure-3

3.2 Optimization of catalyst :

In initial part of our experiment, nucleophilic addition of diethyl phosphite towards 3-nitro benzaldehyde in 1:1 mol ratio was performed in presence of catalyst such as $AlCl_3$, $ZnCl_2$, NH_4Br, $BaCl_2$, and $BaNO_3$, $NiCl_2$. These catalyst even though facilitate the formation of α - hydroxy phosphonates but relatively slower rate with poor yield. Nevertheless when PPh_3 was utilized, the reaction proceeds with faster rate with high yielding of product. (table-2, entry-11).

Table-2: synthesis of Diethyl hydroxyl (3-nitro phenyl) methyl phosphonates : Optimization of catalyst[a] :

Entry	**Catalyst**	**Concentration (mol%)**	**Time (hrs)**	**Yield (%)[b]**
1	-	-	10	15
2	$AlCl_3$	5	8	20
3	$ZnCl_2$	5	8	22
4	NH_4Br	5	8	28
5	$BaCl_2$	5	8	35
6	$BaNO_3$	5	8	40
7	$NiCl_2$	5	8	48
8	PPh_3	5	2	60
9	PPh_3	10	2	75
10	PPh_3	15	2	82
11	PPh_3	20	2	90

[a]Reaction condition : 3-nitro phosphonates, (0.66 mmol), diethyl phosphite , (0.66 mmol) heating at 65^0C under neat condition.

[b]Isolated yields

3.3 Optimization of solvent :

To further improvement of reaction condition by optimizing solvent for nucleophilic addition of diethyl phosphite towards 3-nitro benzaldehyde in 1:1 mol ratio was investigated in presence of catalyst PPh_3 (20 mol%) under different solvent such as Toluene, THF, 1,4-dioxane, Ethanol, Acetonitrile. The reaction performed very well with faster rate and excellent yield under neat condition.(table-3, entry-6). It may be due to under solvent-free conditions, the concentration of catalyst leads to higher reaction rates than the same reaction in the presence of solvent.

Table-3:synthesis of Diethyl hydroxyl (3-nitro phenyl) methyl phosphonates: optimization of solvent[a] :

Entry	Solvent	Time (hrs)	Yield (%)[b]
1	Toluene,	2	60
2	THF,	2	65
3	1,4-dioxane,	2	70
4	Ethanol,	2	78
5	Acetonitrile	2	80
6	Neat	2	90

[a]Reaction condition : 3-nitro phosphonates, (0.66 mmol), diethyl phosphite , (0.66 mmol), PPh_3 (20mol%) heating at 65^0C.

[b]Isolated yields

4. CONCLUSION:

In conclusion , we have developed facile, more efficient and extremely simple one-pot protocol under solvent free condition for phosphorylation of aromatic aldehyde with moderate good yield using triphenylphosphine as a catalyst. The main advantage of present synthetic protocol is mild, solvent free, eco-friendly catalyst and easy work-up procedure. It is expected that present methodology will find application in organic synthesis.

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