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"CALCIUM OXIDE CATALYZED SYNTHESIS OF ALPHA HYDROXYL PHOSPHONATES AT AMBIENT TEMPERATURE AND SOLVENT FREE CONDITION"

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ABSTRACT :

Eco-friendly synthesis of biologically important class of compound, α-hydroxyphosphonates is carried out by using Calcium oxide as reusable catalyst from variety of aldehydes and dialkyl phosphites at room temperature under solvent free conditions in high purity and excellent yields.

KEYWORDS : *α-hydroxyphosphonates, Calcium oxide, solvent-free, dialkyl phosphites.*

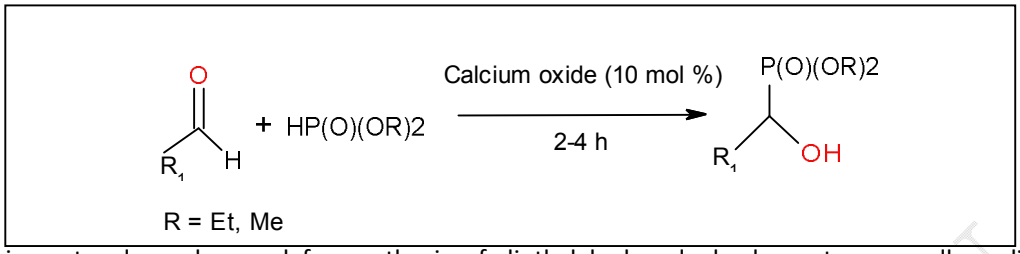
INTRODUCTION:

α-Hydroxy phosphonates are biological precursors of α-hydroxy phosphonic acid and it has been reported that derivatives of α-hydroxy phosphonic acid act as very important enzyme inhibitors [1-3]. For example, they are inhibitors of important medicinal enzymes as rennin [4-6] or human immunodeficiency virus (HIV) protease and polymerase.[7] They also show anti-virus [8] and anti-cancer activities.[9] Thus synthesis of α-hydroxyphosphonates using simple and scalable method is area of interest for many organic chemists. α-Aminophosphonates, another precursor for α-hydroxy phosphonic acid and its derivatives has received lot of attention and variety of methods are reported for the synthesis of same,[10-23] however very few methods have been reported for the synthesis of α-hydroxyphosphonates.

Amongst the various base catalyzed protocols, diethyl amine catalyzed protocol is easiest and most economical.[24] However, if suffers from the drawbacks of longer reaction time and the use of organic solvent. This observation prompted us to develop a new protocol for the synthesis of α-hydroxyphosphonates under solvent-free conditions using an inexpensive catalyst. Accordingly, a variety of bases were screened for the possible synthesis of α-hydroxyphosphonate using 4-chlorobenzaldehyde and diethyl phosphite as model substrates under solvent-free conditions. The results summarized in Table – 1 clearly revealed the suitability of Calcium oxide as a catalyst as well as it demonstrates that a compromise has to be made between the time required and the amount of catalyst to be used for the synthesis of α-hydroxyphosphonates.

RESULTS AND DISCUSSION:

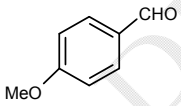
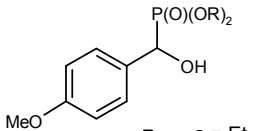
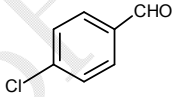
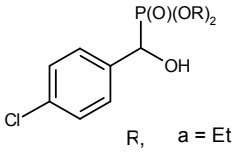
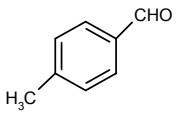
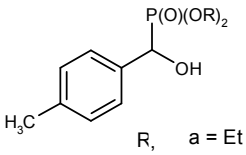
The choice of Calcium oxide also offers the advantage of easier work up. This is because after completion of the reaction, on addition of organic solvent corresponding α-hydroxyphosphonate separated out as a solution of organic solvent and solid catalyst which can be collected by simple filtration. It was then planned to explore the scope as well as the generality of the protocol under the optimized reaction conditions. (10 mol % Calcium oxide, rt, solvent-free) Accordingly a variety of aromatic (bearing electron donating, electron withdrawing groups) heterocyclic, aliphatic as well as conjugated aldehydes were efficiently converted to corresponding α-hydroxyphosphonates.

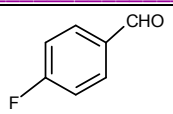
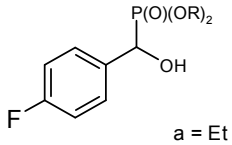
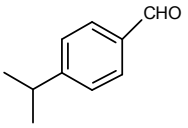
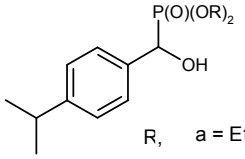
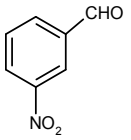
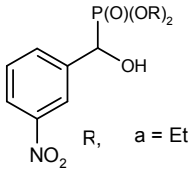


This protocol can be used for synthesis of diethyl hydroxyl phoshponates as well as dimethyl hydroxyl phoshponates by employing diethyl ethyl phosphite and dimehtyl phosphite respectively, as a source of nuclophile. When we screened variety of basic catalysts available such as CsOH, NaOH supported on silica gel, $Al(OH)_3$, KOH supported on silica gel we found that Calcium oxide is most economical and commercially available catalyst which can catalyze this reaction. We also tried to explore the suitable reaction conditions and when reaction was carried out using different solvents like dichloromethane, methyl alcohol, acetonitrile, hexane, ethyl acetate etc. it was found that reaction gives maximum yield when solvent free conditions are used.

Considering the eco- benign nature of the protocol as it employs solvent free conditions for synthesis which is carried out at room temperature we tied to extend this protocol to different aldehydes and ketones. It was observed that reactions with aldehydes were swift and excellent yields were obtained in short reaction time. However the reactions of ketones were very slow and only 20-30 % conversion could be achieved even after prolonged reaction time. In case of ketones heating of reaction mixture at 50^0C could increase the yield only up to 40 %. Thus we can conclude that there is need to develop protocol for synthesis of α-hydroxyphosphonate using ketones as a source of carbonyl compounds.

Table 1. Calcium oxide catalyzed synthesis α-hydroxyphosphonates

Entry	Aldehyde	Alkyl Phosphite	Product	Time (h)	Yield[a,b] (%)
a		a) DEP b) DMP		2 2.5	92 94
b		a) DEP b) DMP		1.5 2	89 92
c		a) DEP b) DMP		4 3	88 89

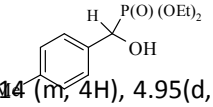
d		DEP	 a = Et	2.5	92
e		a) DEP b) DMP	 R, a = Et b = Me	4 4	94 87
f		a) DEP b) DMP	 R, a = Et b = Me	3 3.5	82 81

a: Yields refer to pure isolated products. b: All products gave satisfactory spectral (IR, NMR. MS) analysis DEP = Diethyl phosphite ($HP(O)(OEt)_2$) , DMP = Dimethyl phosphite ($HP(O)(OMe)_2$)

Typical procedure for the synthesis of α-hydroxyphosphonates- A mixture of an aldehyde (2 mmol), diethyl phosphite (2 mmol) and calcium oxide (10 mol %, 40 mg) was stirred together at ambient temperature for an appropriate time (Table 1). Upon completion of the reaction (TLC), dichloromethane (10 mL) was added and the solid product was filtered, washed with dichloromethane (2×5 mL) the solvent was evaporated and the resultant solid was chromatographed over silica gel (hexane-ethyl acetate, 9:1, v/v) to afford pure α-hydroxyphosphonate. All the products were characterized by spectral methods. The spectral data of the synthesized α-aminophosphonates as well as α-hydeoxyphosphonates is summarized below.

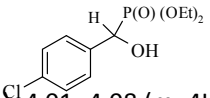
SPECTRAL DATA A-HYDROXYPHOSPHONATES.

Dethyl-1-hydroxy-1-(4-methoxyphenyl) methyl phosphonate (6a)



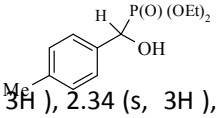
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19-1.31(m, 6H), 3.81 (s, 3H), 3.96 - 4.14 (m, 4H), 4.95(d, J_{PH} = 10 Hz, 1H), 6.90 (d *J* = 8 Hz, 2H), 7.41(d, *J* = 8 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 16.46, 55.25, 63.24, 68.78, 71.98, 113.72, 128.54, 159.53; **GCMS:** m/z = 136, 135, 107, 92, 77, 63, 51.

Diethyl [(hydroxyl)(4-cholrophenyl) methyl] phosphonate (6b)



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, *J* = 8 Hz, 3H) 1.26 (t, *J* = 8 Hz, 3H), 4.01- 4.08 (m, 4H), 4.59 (bs, 1H), 5.00 (d, $^1J_{PH}$ = 12 Hz, 1H), 7.31 (d, *J* = 6 Hz, 2H), 7.41 (d, *J* = 6 Hz, 2H). **GCMS:** m/z = 142, 141, 140, 139 (100%), 111, 75.

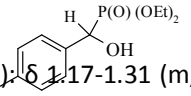
Diethyl [(hydroxyl)(4-methylphenyl) methyl] phosphonate (6c)



^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, *J* = 8 Hz, 3H), 1.27 (t, *J* = 8 Hz, 3H), 2.34 (s, 3H), 3.95- 4.21 (m, 5H), 4.98 (d, J_{PH} = 12 Hz, 1H), 7.16 (d *J* = 8 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H); **^{13}C NMR** (75 MHz,

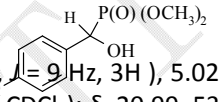
$CDCl_3$): δ 16.18, 20.04, 63.11, 68.79, 71.98, 122.02, 128.72, 133.70, 137.52; **GCMS:** m/z =120, 119, 91, 65, 51.

Dethyl-1-hydroxy-1-(4-isopropylphenyl) methyl phosphonate (6d)



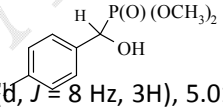
IR (neat): 3290 (br), 1234, 1046, 1025 cm^{-1}, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.17-1.31 (m, 6H), 2.89 (septet, *J* = 6.9 Hz, 1H), 3.96 - 4.08 (m, 4H), 4.98 (d, $^1J_{PH}$ = 10.5 Hz, 1H), 5.41(bs, 1H), 7.19 (d, *J* = 7.8 Hz, 2H); 7.38 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 16.20, 23.59, 23.82, 33.69, 63.13(d, $^2J_{PC}$ = 7.0 Hz), 63.45(d, $^2J_{PC}$ = 7.0 Hz), 126.20, 127.06, 133.78, 148.62; **GCMS:** m/z = 148, 133, 105 (100%), 91, 77, 51.

Dmethyl-1-hydroxy-1-(4-methylphenyl) methyl phosphonate(6f)



^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.66 (d, *J* = 9Hz, 3H), 3.72(d, *J* = 9 Hz, 3H), 5.02 (d, J_{PH} =10 Hz, 1H), 7.18 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 2H) ; **^{13}C NMR** (75 MHz, $CDCl_3$): δ 20.99, 53.34, 53.49, 53.64, 53.77, 68.75, 71.65, 126.94, 128.79, 133.52, 137.64.

Dimethyl-1-hydroxy-1-(4-methylphenyl) methyl phosphonate, (6l)



^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.66 (d, *J* = 8 Hz, 3H), 3.72 (d, *J* = 8 Hz, 3H), 5.01 (d, $^1J_{PH}$ = 10 Hz, 1H), 7.18 (d, *J* = 8 Hz, 2H), 7.37 (dd, *J* = 8Hz, 2Hz, 2H).

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