

One-Pot Synthesis of Diethyl 1-Hydroxyphosphonic Esters on The Surface of Basic Methal Oxides Under Solvent Free Conditions

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This paper is dedicated to Professor Habib Firouzabadi for his great contribution in organic chemistry on the occasion of his 65th birthday and his honourable retirement.

The effect of a series of metal oxides on synthesis of diethyl 1-hydroxyphosphonates under solvent free condition was studied and the results showed that calcium oxide was the most efficient reagent than the others for preparation of the title compounds.

Keywords: Diethyl 1-Hydroxyphosphonate, Metal oxide, Calcium oxide, Solvent free, Diethyl phosphite

INTRODUCTION

1-Hydroxyphosphonic esters have received great attention both as substrates for preparation of other 1-substituted phosphonates [1], and also their potential biological activity. For example, representatives of this class act as inhibitors of farnesyl protein transferase (FPTase) [2], rennin [3], HIV protease [4], and 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase [5].

In addition of thermal non-catalyzed [6] and acid catalyzed [7] preparations of 1-hydroxyalkyl- or arylphosphonates, base-catalyzed addition of dialkyl phosphites to aldehydes have been also applied [8,1b]. Among the base-catalyzed methods, those in combination with the technique of surface-mediated solid phase under solvent free conditions, are of growing interest [9]; mainly for the following reasons: a) more selectivity, b) milder condition, c) simple work up, d) increasing yield, e) lower reaction time, f) lower price, and g) less toxicity. Several base-catalyzed approaches using basic alumina, and magnesia as catalyst have been already reported by us [9] for the production of the title compounds.

Considering the results with basic alumina and magnesia, we have been encouraged to investigate the effect of other metal oxides for finding a more efficient and suitable catalyst.

EXPERIMENTAL

Chemical and Apparatus

All chemicals were obtained from Merck, Flucka Chemical Companies. IR spectra were obtained on Shimadzu FTIR-8300 spectrometer. The ¹H-NMR (250MHz) and ¹³C-NMR (62.5MHz) were run on a Bruker Avance DPX, 250 MHz, FT-NMR spectrometer (δ in ppm, J in Hz). Mass spectra were recorded on a GC MS Shimadzu GP 1000 spectrometer. Melting points were recorded on a Buchi B-510 apparatus in open capillary tubes and are uncorrected.

General Procedure for Preparation of Diethyl 1-Hydroxyphosphonates from Liquid Aromatic or Aliphatic Aldehydes on the Metal Oxide Surface:

The metal oxide (5.1 mmol) was added to a stirred mixture of diethyl phosphite (5.1 mmol) and aromatic aldehyde (5 mmol) at room temperature. The reagents were completely

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adsorbed on the metal oxide surface. Progress of the reaction was followed by TLC. After a reaction time of 3 min to 24 h (depends on aldehyde and metal oxide, Table 4), the product was extracted with dichloromethane (4x5 ml) and filtered from a short pad of MgSO₄ through celite. The filtrate was evaporated under reduced pressure to give the crude phosphonic ester which was purified by crystallization from dichloromethane/*n*-hexane or by silica gel column chromatography.

General Procedure for Preparation of Diethyl 1-Hydroxyphosphonates from Solid Aromatic Aldehydes on the Metal Oxide Surface:

Diethyl phosphite (0.7g, 5.1mmol) was added to solid aldehyde (5.1mmol) and was heated at 60°C and stirred until the aldehyde is dissolved. Then the metal oxide (5.1mmol) was added to this mixture. After 2 min to 24h (Table 4), the mixture was washed with dichloromethane (4x5 ml) and filtered. The pure product was obtained by evaporation of dichloromethane and then crystallization or silica gel column chromatography.

RESULTS AND DISCUSSION

In continuation of our previous work [9] and the report on the sequence of strength of basicity of some metal oxides [10], we decided to use several of metal oxides for preparation of 1-hydroxyphosphonates in order to introduce the more efficient catalyst for this purpose.

The studied oxides in this investigation were CaO, MgO, BaO, ZnO, SnO₂, Co₃O₄, TiO₂, CdO, and MnO₂. The catalytic effect of the above oxides were studied, at first, on the reaction of 4-methylbenzaldehyde with diethyl phosphite and then on 3-methoxy- and 4-nitrobenzaldehyde by effective catalysts. The results showed that among these metal oxides only ZnO, CdO, BaO, MgO, and CaO are effective and CaO is the most effective one among all (Table 1).

The reaction of diethyl phosphite with 4-methylbenzaldehyde and 3-nitrobenzaldehyde in the presence of calcium oxide was carried out in solvents such as dichloromethane and chloroform and also under solvent free conditions at room temperature. The results showed that the solvent free reaction afforded the highest yields and shortest reaction times (Table 2)

Table 1. The Effect of Metal Oxide Catalysts on the Preparation of 1-Hydroxyphosphonates at Room Temperature

Aldehyde	Catalyst	Reaction Time (hr)	Yield (%)
4-Methylbenzaldehyde	TiO ₂	12	NR*
	MnO ₂	12	NR*
	SnO ₂	12	NR*
	Co ₃ O ₄	12	NR*
	ZnO	5	77
	CdO	1	95
	BaO	1	50
	MgO	0.5	90
	CaO	0.05	95
3-Methoxybenzaldehyde	ZnO	24	75
	CdO	24	90
	BaO	12	65
	MgO	1	90
	CaO	1	96
4-Nitrobenzaldehyde	ZnO	0.33	99
	CdO	0.25	99
	BaO	0.83	75
	MgO	0.16	100
	CaO	0.08	100

* No Reaction

Table 2. The Effect of Solvent on the Reaction of Diethyl Phosphite with Aldehydes over Calcium Oxide at Room Temperature.

Aldehyde	Solvent	Reaction time (h)	Yield (%)
4-Methylbenzaldehyde	None	0.05	95
	CH ₂ Cl ₂	5	80
	CHCl ₃	3	80
3-Nitrobenzaldehyde	None	0.08	100
	CH ₂ Cl ₂	2	80
	CHCl ₃	2	75

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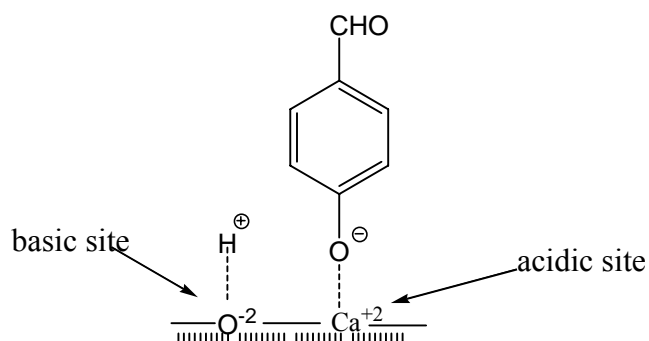
The effect of four different molar ratios of calcium oxide relative to the aldehyde and diethyl phosphite respectively was also studied on the reaction time. The best results were obtained when equimolar of them were used (Table 3).

Table 3. The Effect of Molar Ratio of Calcium Oxide to Aldehyde and Diethyl Phosphite Respectively on the Reaction Times for Preparation of 1- Hydroxyphosphonates

Aldehyde	Molar ratio*	Reaction time (min)
4-Methylbenzaldehyde	0.35:2:2	15
	1:2:2	5
	2:2:2	3
	3:2:2	3
3-Nitrobenzaldehyde	0.35:2:2	14
	1:2:2	5
	2:2:2	2
	3:2:2	2

* CaO:Aldehyde:HPO(OEt)₂

With the optimized conditions in hand, we studied the generality of this method on various aldehydes, including α,β -unsaturated, and aromatic aldehydes. Except of 2-hydroxy benzaldehyde and 4-hydroxybenzaldehyde (Table 4, entries 7 and 11) that their reactions did not proceed at all presumably due to poisoning of the acidic and basic sites of the catalyst (Scheme 1), the reaction of other type of substrates was occurred smoothly and efficiently (Table 4).

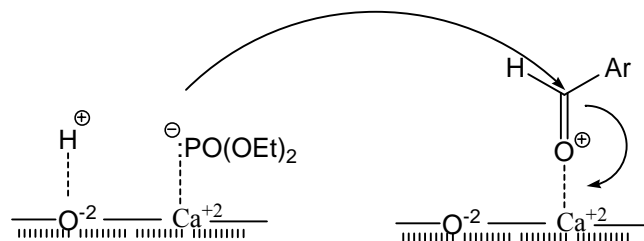


Scheme 1. Calcium oxide poisoning by 4- hydroxybenzaldehyde

In most cases, the products were isolated simply by extraction with CH₂Cl₂ and the crude products were purified by recrystallization from CH₂Cl₂/n-hexane or by silica gel column chromatography. All products were fully characterized by comparison of their spectral IR, ¹H-NMR, ¹³C-NMR, MS and physical data, M.p. and B.p. with the authentic samples [9].

Comparison of the recorded data on using MgO [9b] for the synthesis of 1-hydroxyphosphonates with those of CaO shows the reactions proceed generally in shorter times and with higher yields when CaO catalyst is utilized. This is parallel to the higher strength of basic sites and the more number of basic sites per unit weight of CaO relative to MgO, which reported in the literature [10].

Considering the acidic and basic sites on the surface of metal oxides [10], which can be pictured according to Scheme 2 for calcium oxide, we suggest the following probable mechanism for the reaction of aldehydes with diethyl phosphite:



Scheme 2. The probable mechanism for formation of diethyl 1-hydroxyphosphonates

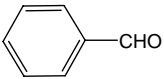
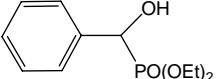
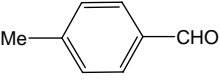
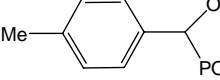
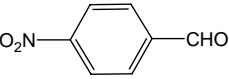
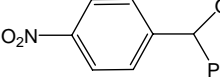
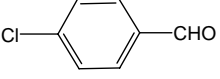
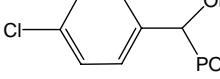
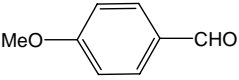
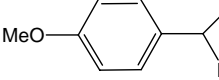
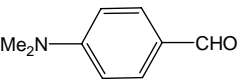
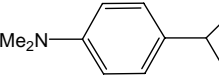
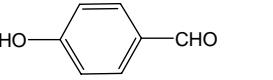
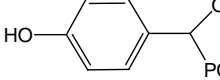
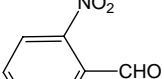
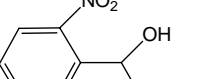
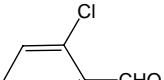
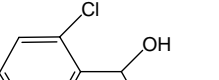
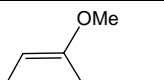
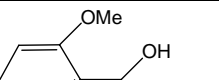
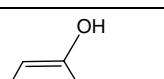
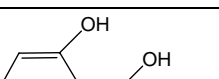
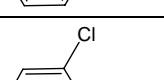
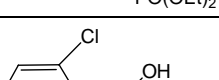
CONCLUSION

In summary, we have described a mild and efficient protocol for the synthesis of diethyl 1-hydroxyphosphonates with excellent yields and short times under solvent free conditions. The simple experimental procedure combined with easy work up makes this method quite simple, convenient, economical and environmentally benign for the preparation of the title compounds.

ACKNOWLEDGMENT

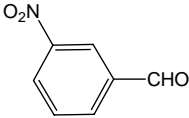
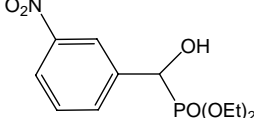
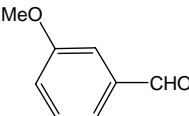
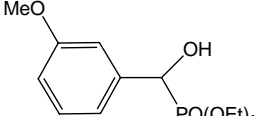
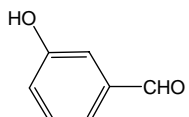
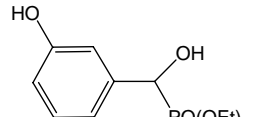
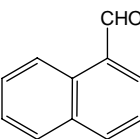
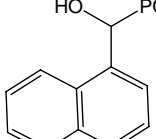
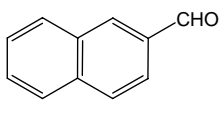
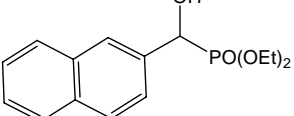
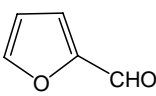
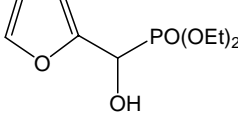
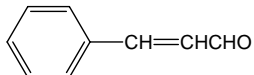
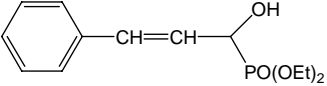
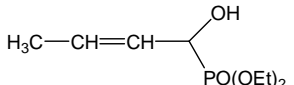
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Table 4. The Preparation of Diethyl 1-Hydroxyphosphonates from the Reaction of Aldehydes and Diethyl Phosphite in the Presence of Calcium Oxide at Room Temperature

Entry	reactant	Product	Reaction time(min)	Yield(100%)*
1			10	90
2			3	95
3			5	100
4			30	87
5			90	96
6			40	90
7			180	0
8			4	98
9			10	99
10			15	94
11			180	0
12			5	99

One-Pot Synthesis of Diethyl 1-Hydroxyphosphonic Esters

Table 4. Continued

Entry	reactant	Product	Reaction time(min)	Yield(100%)*
13			2	99
14			60	98
15			10	91
16			45	98
17			10	99
18			25	90
19			45	96
20	$\text{H}_3\text{C}-\text{CH}=\text{CHCHO}$		15	98

* Isolated yield

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