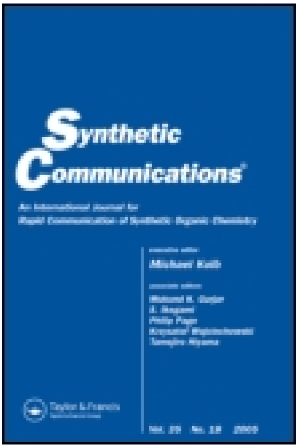

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Surface-Mediated Solid Phase Reactions: Preparation Of Diethyl 1-Hydroxyarylmethylphosphonate on the Surface of Magnesia

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SURFACE-MEDIATED SOLID PHASE REACTIONS: PREPARATION OF DIETHYL 1-HYDROXYARYLMETHYLPHOSPHONATES ON THE SURFACE OF MAGNESIA

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Abstract: Magnesia is found to be an effective catalyst for synthesis of diethyl 1-hydroxyarylmethylphosphonates from aromatic aldehydes and diethyl hydrogen phosphite.

Surface-mediated solid phase reactions are of growing interest[1] because of their ease of set-up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts. As a part of our efforts to explore the novel utilities of surface-mediated reactions in this report a new method for the preparation of diethyl 1-hydroxyarylmethylphosphonates is described.

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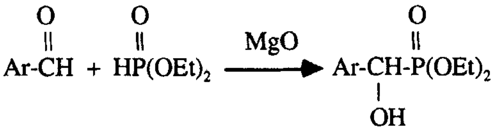
1-Hydroxyalkanephosphonic esters are compounds of significant biological and pharmaceutical interest[2,3]. It is a useful reagent for the synthesis of enol ethers[4] and 1-chloroalkanephosphonates[5] that are reagents for the preparation of α-chloro-α,β-unsaturated acids[6], diethyl 1,2-epoxyalkylphosphonates[7-10], and 1-(methylthio)-methylphosphonate[11] as well as derivatives of alkylidenediphosphonates and vinylphosphonates[12]. They are prepared by thermal non-catalyzed addition[13-15] and base or acid catalyzed addition[16-24] of dialkyl hydrogen phosphite to aldehydes[24]. All these methods often suffer from one of the following drawbacks: a) low yields and b) side reactions. Alumina is used also as catalyst for preparation of 1-hydroxyalkanephosphonic esters[25,26]. we describe here a new and easy method for synthesis of diethyl 1-hydroxyarylmethylphosphonates from aldehydes and diethyl hydrogen phosphite on magnesia surface without solvent (Scheme 1):



$$\mathrm{Ar\text{-}\overset{\overset{O}{\|}}{C}H} + \mathrm{H\overset{\overset{O}{\|}}{P}(OEt)_2} \xrightarrow{\mathrm{MgO}} \mathrm{Ar\text{-}\underset{\underset{OH}{|}}{C}H\text{-}\overset{\overset{O}{\|}}{P}(OEt)_2}$$

1 2

Scheme 1

As it is shown in Table 1, *o,m,p*-substituted benzaldehydes (2b-2l) with diethyl hydrogen phosphite in the presence of magnesia afford the desired products in excellent yields. These results clearly show that the reactions seem to be faster with higher yields when the aromatic part of the aldehyde molecules carry electron-withdrawing groups. Cinnamaldehyde (2n) as a α,β-unsaturated aldehyde and furfural (2m) as a heterocyclic aldehyde also reacted with diethyl hydrogen phosphite in the presence of magnesia at room temperature to produce the desired compounds in high yields. The reaction also proceeded with high yields in polynuclear aromatic aldehydes (2p, 2q). The physical characteristics of the compounds are shown in Table 2.

Table 1. Preparation of Diethyl 1-Hydroxyarylmethylphosphonates(2).

	Ar	Time (hr)	Yield%		Ar	Time (hr)	Yield%
2a	C_6H_5-	0.25	95	2i	*o*-$O_2NC_6H_4$-	0.03	90
2b	*p*-$CH_3C_6H_4$-	0.5	90	2j	*m*-$O_2NC_6H_4$-	0.17	90
2c	*p*-$CH_3OC_6H_4$-	1	95	2k	*p*-$(CH_3)_2NC_6H_4$-	1	90
2d	*m*-$CH_3OC_6H_4$-	1	90	21	2,4-$Cl_2C_6H_3$-	0.17	100
2e	*m*-HOC_6H_4-	3	80	2m		4	95
2f	*p*-ClC_6H_4-	0.33	90	2n	$C_6H_5CH=CH$-	1.5	80
2g	*o*-ClC_6H_4-	0.5	90	2p	α-$C_{10}H_7$-	0.83	85
2h	*p*-$O_2NC_6H_4$-	0.17	100	2q	β-$C_{10}H_7$-	2	80

To sum up, the important features of this methodology are as; a) the addition of external base is usually not required; b) side reactions are not observed; c) reactions are fast; d) reaction condition is mild; e) work-up is easy; and f) high yields are mostly obtained. We believe that this method is a useful addition to the present methodology for the preparation of 1-hydroxyarylmethylphosphonates.

EXPERIMENTAL

General:

All chemicals were commercial products and distilled or crystallized before use. Infrared spectra were measured using a perkin Elmer 738 spectrometer. ^{1}H-NMR and ^{31}P-NMR spectra were recorded by a varian XL-400 MHz instrument. Mass spectra are obtained on a GC-MS Shimadzu GP1000 spectrometer. All melting points were determined by a Buchi 510.

Table 2: The physical characteristics of Diethyl 1-Hydroxyarylmethylphosphonates (2).

Product	M.P (°C)	IR(Nujol) ν_{max}(cm^{-1})	^{1}H-NMR($CDCl_3$/TMS) δ(ppm)	^{31}P-NMR ($CDCl_3$ /H_3PO_4) δ(ppm)	M.S m/e(M$^+$)
2a	75-77^a	3260(O-H), 1230(P=O), 1050(P-O-C)	1.15((2t, 6H,O-$CH_2\underline{CH_3}$), 3.9(m,4H,2-$O\underline{CH_2}CH_3$) 4.1 (bs,1H,-$\underline{OH}$), 4.85(d,1H,-$\underline{CH}$-P, J_{HP}=12Hz), 7.2(m,5H,-$C_6\underline{H_5}$)	19.42	224
2b	94-95^a	3260 (O-H), 1240(P=O), 1030(P-O-C)	1.2(2t,6H,-$OCH_2\underline{CH_3}$), 2.3(s,3H,-$\underline{CH_3}$) 3.9(m,4H,-$O\underline{CH_2}CH_3$), 4.8(bs,1H,-$\underline{OH}$) 4.9(d,1H,-$\underline{CH}$-P, J_{HP}=12Hz), 7.2(m,4H,-$C_6\underline{H_4}$-CH_3)	19.74	258
2c	120-121.5^a	3250(O-H), 1235(P=O), 1035(P-O-C)	1.2(2t,6H,-$OCH_2\underline{CH_3}$), 3.7(s, 3H,-$O\underline{CH_3}$) 3.8(m,4H,-$O\underline{CH_2}CH_3$), 4.18(bs,1H,-$\underline{OH}$) 4.85(d,1H,-$\underline{CH}$-P,J_{HP}=12Hz), 7.1(m,4H,-$C_6\underline{H_4}$-OCH_3)	20.16	274
2d	140^b	3260(O-H), 1230(P=O) 1040(P-O-C)	1.20(2t,6H,-$OCH_2\underline{CH_3}$),3.7(s,3H,-$O\underline{CH_3}$) 3.9(m,4H,-$O\underline{CH_2}CH_3$),4.85(bs,1H,-$\underline{OH}$) 4.9(d,1H,-$\underline{CH}$-P,J_{HP}=12Hz),7.05(m,4H,-$C_6\underline{H_4}$-OCH3)	19.13	274
2e	97-98.5	3300-3100(O-H),1210(P=O) 1050(P-O-C)	1.15(2t,6H,-$OCH_2\underline{CH_3}$),4.0(m,4H,-$O\underline{CH_2}CH_3$) 4.1(bs,1H,-$\underline{OH}$),4.8(d,1H,-$\underline{CH}$-P,J_{HP}=11Hz),7.2(m, 4H,-$C_6\underline{H_4}OH$),8.4(s,1H,-$\underline{OH}$)	19.23	260
2f	67-68^a	3215(O-H),1210(P=O) 1040(P-O-C)	1.15(2t,6H,-$OCH_2\underline{CH_3}$),3.9(m,4H,-$O\underline{CH_2}CH_3$) 5.4(bs,1H,-$\underline{OH}$),5.55(d,1H,-$\underline{CH}$-P,J_{HP}=12Hz),7.2-7.8 (m,4H-$C_6\underline{H_4}Cl$)	18.65	278

2g	74-75	3220(O-H),1235(P=O) 1035(P-O-C)	$1.35(2t,6H,-OCH_2\underline{CH_3}),4.1(m,4H,-O\underline{CH_2}CH_3)$ $5.55(d,1H,-\underline{CH}-P,J_{HP}=13Hz),5.6(bs,1H,-\underline{OH}),7.4$ $(m,4H,-C_6\underline{H_4}Cl)$	18.61	278
2h	87-88	3240(O-H),1205(P=O) 1035(P-O-C)	$1.27(2t,6H,-OCH_2\underline{CH_3}),4.1(m,4H,-O\underline{CH_2}CH_3)$ $5.2(d,1H,-\underline{CH}-P,J_{HP}=14Hz),5.9(bs,1H,-\underline{OH})$ $7.2-8(m,4H,-C_6\underline{H_4}-NO_2)$	18.43	257
2i	114-116	3220(O-H),1240(P=O) 1050(P-O-C)	$1.25(2t,6H,-OCH_2\underline{CH_3}),4.1(m,4H,-O\underline{CH_2}CH_3)$ $5.2(d,1H,-\underline{CH}-P,J_{HP}=13),5.7(bs,1H,-\underline{OH}),$ $7.8(m,4H,-C_6\underline{H_4}NO_2)$	18.52	257
2j	81-82	3220(O-H),1220(P=O) 1030(P-O-C)	$1.25(2t,6H,-OCH_2\underline{CH_3}),4.1(m,4H,-O\underline{CH_2}CH_3)$ $5.2(d,1H,-\underline{CH}-P,J_{HP}=13),5.7(bs,1H,-\underline{OH}),$ $7.2-8(m,4H,-C_6\underline{H_4}NO_2)$	18.52	257
2k	80-81	3220(O-H),1220(P=O) 1045(P-O-C)	$1.25(2t,6H,-OCH_2\underline{CH_3}),2.9(5,6H,-N\underline{(CH_3)}_2$ $4.0(m,4H,-\underline{CH_2}CH_3),\ 3.9(bs,1H,-OH)$ $4.85(d,1H,-\underline{CH}-P,J_{HP}=11\ Hz),7.1(m,4H,-C_6\underline{H_4}N(CH_3)_2)$	21.37	287
2l	90-91	3220(O-H),1210(P=O) 1045(P-O-C)	$1.25(2t,6H,-OCH_2\underline{CH_3}),4.1(m,4H,-O\underline{CH_2}CH_3),$ $4.8(bs,1H,-\underline{OH}),5.8(d,1H,-\underline{CH}-P,J_{HP}=20Hz),$ $7.2(m,3H,C_6\underline{H_3}CL_2)$	19.64	313

(continued)

Table 2: Continued.

Product	M.P (°C)	IR(Nujol) ν_{max}(cm^{-1})	^{1}H-NMR(CDCl$_3$/TMS) δ(ppm)	^{31}P-NMR (CDCl$_3$ /H$_3$PO$_4$) δ(ppm)	M.S m/e(M$^+$)
2m	174^b	3280(O-H),1230(P=O) 1050(P-O-C)	1.35(2t,6H,-OCH$_2\underline{\mathrm{CH}_3}$),4.2(m,4H,-O$\underline{\mathrm{CH}_2}CH_3$), 5.2(bs,1H,-$\underline{\mathrm{OH}}$),5.1(d,1H,-$\underline{\mathrm{CH}}$-P,J$_{HP}$=14Hz), 6.47(m,2H,C$_4\underline{\mathrm{H}_3}$O),7.4(m,1H,C$_4H_3$O)	19.59	234
2n	105-106^a	3250(O-H),1230(P=O) 1045(P-O-C)	1.15(2t,6H-OCH$_2\underline{\mathrm{CH}_3}$),4.0(m,4H,-O$\underline{\mathrm{CH}_2}CH_3$), 4.3(bs,1H,-$\underline{\mathrm{OH}}$),4.4(dd,1H,-$\underline{\mathrm{CH}}$-P,J$_{HP}$=18, J$_{HH}$=6Hz) 6.08(dd,1H,PhCH=$\underline{\mathrm{CH}}$,J$_{HH}$=6Hz, 16Hz), 6.4(dd,1H, 1.15(2t,6H,-OCH$_2\underline{\mathrm{CH}_3}$),4.0(m,4H,-O$\underline{\mathrm{CH}_2}CH_3$)	19.49	294
2p	77-78	3210(O-H),1220(P=O) 1030(P-O-C)	1.15(2t,6H-OCH$_2\underline{\mathrm{CH}_3}$),4.0(m,4H,-O$\underline{\mathrm{CH}_2}CH_3$), 4.4(bs,1H,-$\underline{\mathrm{OH}}$),4.8(d,1H,-$\underline{\mathrm{CH}}$-P,J$_{HP}$=12Hz) 7.2-7.7(m,7H,-C$_{10}\underline{\mathrm{H}_7}$)	19.56	270
2q	88-89	3215(O-H),1220(P=O) 1030(P-O-C)	1.15(2t,6H-OCH$_2\underline{\mathrm{CH}_3}$),4.0(m,4H,2-O$\underline{\mathrm{CH}_2}CH_3$), 4.5(bs,1H,-$\underline{\mathrm{OH}}$),4.8(d,1H,-$\underline{\mathrm{CH}}$-P,12Hz) 7.2-7.7(m,7H,-C$_{10}\underline{\mathrm{H}_7}$)	19.53	270

a. Melting points are in agreement with the reported melting points in literature [13,27].
b. Boiling points.

General procedure for preparation of Diethyl 1-Hydroxyarylmethylphosphonates from Liquid Aldehydes:

Magnesia (0.8 gr, 0.02 mol) was added to a mixture of diethyl hydrogen phosphite (2.76 gr, 0.02 mol) and the aldehyde (0.02 mol). This mixture was stirred at room temperature for 2min-4hr (Table 1). The solid mixture was washed with dichloromethane (4x25 ml) and the crude product was isolated in a pure state by simple filtration chromatography through a short plug of silica gel and then was crystallized from dichloromethane/hexane.

For solid aldehydes, prior to addition of magnesia, the mixture of diethyl hydrogen phosphite and the aldehyde must be stirred and heated at 60°C.

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