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A Novel Synthesis of Diethyl 1-Aminoarylmethylphosphonates on the Surface of Alumina

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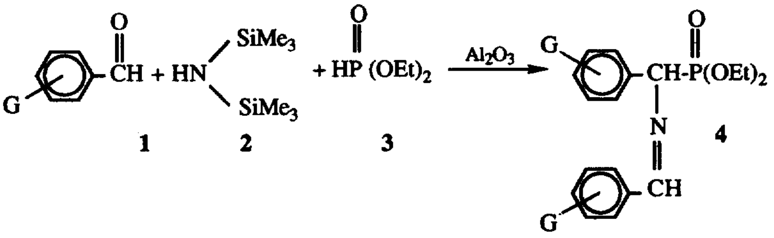
Abstract: A novel route has been devised for the preparation of a series of diethyl 1-aminoarylmethylphosphonates. The route involves facile reaction among aromatic aldehydes, diethyl hydrogen phosphite and HMDS on the surface of alumina. © 1997 Published by Elsevier Science Ltd.

Significant interest has developed in the application of 1-aminoalkylphosphonic acids as analogues of naturally occuring α-amino acids.[1] Indeed a number of potent antibiotics,[2] enzyme inhibitors,[3] and pharmacological agents[4] are 1-aminophosphonic acids as well as their derivatives, notably peptides. These important compounds have also been used in ingenious way as peptidomimetics.[5] Aminophosphonic acids are also found as constituents of natural products.[6] Several approaches to the synthesis of these material are available: a) addition of P-H function to imines and enamines,[7] b) addition of P-H function to nitriles,[8] c) Arbuzof and Michaelis-Becker reactions[9], d) condensation of X-NH_2 with acyl phosphorus species,[10] e) Curtius and Hoffmann rearrangement of substituted phosphonoacetic ester,[11,12] f) conversion of the corresponding 1-hydroxyalkanephosphonates to 1-aminoalkylphosphonates,[13,14] and e) alkylation of nucleophilic precursors such as Schiff bases.[15]

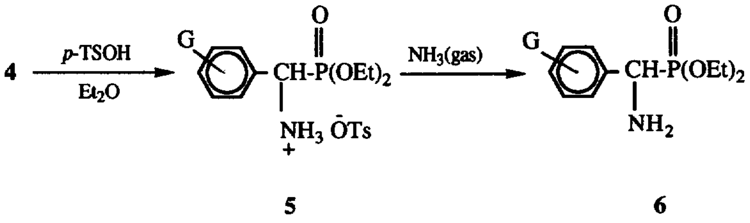
In this work we have used technique of surface-mediated solid phase reaction which is growing interest because of their advantages of ease of set up, mild conditions, rapid reactions, selectivity, increased yields of the products and low cost compared with their homogeneous counterparts. Thus the aromatic aldehydes **1** is treated with hexamethyldisilazane (HMDS, **2**) in presence of diethyl hydrogen phosphite (**3**) on the surface of acidic alumina. The products are benzylidene derivatives of 1-aminoarylmethylphosphonate **4**, Scheme1. ^{1}H-NMR spectrum of **4** exhibits a doublet at 8.2 ppm due to coupling constant which is indicative for the coupling HC-P (J_{HP}=5Hz) moiety in the molecule[16].

Removal of benzylidene group is occured by treatment of **4** with p-toluenesulfonic acid monohydrate in ether and followed by neutralization of the ammonium salts **5** with ammonia to give the desired 1-aminoarylmethylphosphonates (**6**), Scheme 2. The overall yields of these reactions are shown in Table 1.



Scheme 1

The aromatic aldehydes with ortho substituents and *p*-nitrobenzaldehyde do not produce the corresponding 1-aminoarylmethylphosphonates at all (Table 1, entries **6k-6n**). This observation may show the effect of steric and electronic factors in the synthesis of these compounds.



Scheme 2

Table 1. Preparation of Diethyl 1-Aminoarylmethylphosphonates(6).

Entery	Ar	Time (hr)	Yield[a] (%)	Entery	Ar	Time hr	Yield[a] (%)
6a	C_6H_5-	1	50	**6h**	1-$C_{10}H_7$-	0.67	65
6b	*p*-ClC_6H_4-	2.5	42	**6i**	2-$C_{10}H_7$-	0.41	65
6c	*p*-$CH_3C_6H_4$-	0.5	65	**6j**	*p*-$O_2NC_6H_4$-	3	-
6d	*p*-$CH_3C_6H_4$-	1	55	**6k**	*o*-$O_2NC_6H_4$-	3	-
6e	*m*-$CH_3C_6H_4$-	1.5	50	**6l**	*o*-ClC_6H_4-	3	-
6f	*p*-BrC_6H_4-	2	47	**6m**	*o*-$CH_3OC_6H_4$-	3	-
6g	*p*-$(CH_3)_2CHC_6H_4$-	0.84	60	**6n**	2,4-$Cl_2C_6H_3$-	3	-

a. Isolated Yield.

Neutral and basic alumina, and magnesium oxide are not as effective as acidic alumina and usually give low yields of the corresponding amines, instead they produce diethyl 1-hydroxyarylmethylphosphonates as major product.

Simple work up, low consumption of solvent, fast reaction rates, mild reaction condition, good yields, and selectivity of the reaction make this method an attractive and a useful contribution to the present methodologies.[17]

Experimental

General: All chemicals were commercial products and distilled or recrystallized before use. IR 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 GC-MS Shimadzu GP 1000 spectrometer.

General Procedure for Preparation of Diethyl 1-Aminoarylmethylphosphonates on the Surface of Alumina:

Acidic alumina (1 gr) and HMDS(1.61 gr, 0.01mol) were mixed at room temperature. The liquid aldehyde (0.02mol) was added dropwise to the mixture with stirring. After completion of aldehyde addition, acidic alumina (2 gr) was added while resultant mixture was stirred. An exothermic reaction took place at this step thus stirring of mixture was continued for 15 min until its temperature reached to room temperature. Diethyl hydrogen phosphite (1.38 gr, 0.01 mol) was added to the reaction vessel and the mixture was stirred for 0.5-2 hrs. The resultant solid mass was washed with ether (4 X 25 ml). The ethereal solutions were combined together and then p-TsOH, H_2O (1.9 gr, 0.01 mol) was added with stirring. After completion of the reaction, which was monitored by TLC, ammonia gas was bubbled through the solution for 5 min and the resultant mixture was stirred for 15 min. The crude product was obtained by filtration and evaporation of the solvent under the reduced pressure. Chromatography on plug of silica gel with EtOAc/n-hexane (1:9) and evaporation of the solvent under the reduced pressure gave the pure product as an oil in 42-65% yields.

For the solid aromatic aldehydes, prior to addition of acidic alumina and other reagents they are dissolved in minimum amount of tetrachlorid carbon.

ACKNOWLEDGEMENT

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17. All products gave satisfactory spectral data in accord with the assigned structures. For **3b** as an example: ^{1}H-NMR ($CDCl_3$/TMS): 1.15-1.30(2t, 6H,2-$OCH_2\underline{CH_3}$); 2.72(br, 2H, -$N\underline{H_2}$);3.96-4.65(2q,4H, 2-$O\underline{CH_2}CH_3$); 4.19-4.23(d, 1H, J_{HP}=16.78HZ, C$\underline{H}$-P); 7.13-7.33(m, 4H) ppm; ^{31}P-NMR(H_3PO_4): 23.51ppm; IR(CCl_4): 3350-3430(-NH_2), 1610(N-H), 1245(P=O), 1000-1100, 970(P-O-Et)cm^{-1}.

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