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A convenient synthesis of 1-aminophosphonates from 1-hydroxyphosphonates

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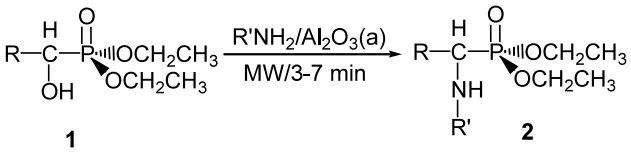
Abstract—A simple, efficient, and general method has been developed for the synthesis of 1-aminophosphonates from 1-hydroxyphosphonates under solvent–free conditions using microwave irradiation. 1-Aminophosphonates were obtained in high yield and mild conditions by reaction of diethyl 1-hydroxyalkylphosphonates with amines in the presence of acidic alumina. © 2003 Elsevier Science Ltd. All rights reserved.

1-Aminophosphonic acids are probably the most important substitutes for the corresponding amino acids in biological systems.[1–4] Indeed a number of potent antibiotics,[5] enzyme inhibitors,[6] and pharmacological agents[7] are 1-aminophosphonic acids as well as their derivatives, notably peptides. Aminophosphonic acids are also found as constituents of natural products. These important compounds have been synthesized by various routes: (a) addition of P–H function to imines and enamines,[8] (b) addition of P–H function to nitriles,[9] (c) Arbuzov and Michaelis–Beacker reactions,[10] (d) condensation of X-NH_2 with acyl phosphorus species,[11] (e) Curtius and Hoffmann rearrangement of substituted phosphonoacetic esters[12] and (f) alkylation of nucleophilic precursors such as Schiff bases.[13] Despite this wide range of synthetic methods for synthesis of 1-aminophosphonates, little attempt has been made to convert readily accessible 1-hydroxyphosphonates to 1-aminophosphonates.[14,15] Surface-mediated solid-phase reactions are of growing interest[16] because of their ease of set up and work-up, mild reaction conditions, rate of reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts. The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[17] Syntheses which normally require long periods, can be achieved conveniently and very rapidly in a microwave oven. As a part of our efforts to explore the utility of surface-mediated reactions for the synthesis of organophosphorus compounds,[18–21] we report here a new method for the preparation of 1-aminophosphonates from 1-hydroxyphosphonates in the presence of a mixture of an amine and acidic alumina under solvent-free conditions using microwave irradiation producing high yields of 1-aminophosphonates (Scheme 1, Table 1).

As shown in Table 1, the reaction of a mixture of aniline, diethyl 1-hydroxyphosphonates[22] in the presence of acidic alumina under microwave irradiation, afforded the desired products in good yields (**2a**–**2e**). *m*-Nitroaniline also reacted to give the desired compounds in good yields (**2f**–**2h**). The reactions also proceeded with good yields with cyclohexylamine (**2i**–**2k**). The reaction of (*S*)-(−)-phenylethylamine with diethyl 1-hydroxyphenyl methylphosphonate gave the desired compound in good yield. The reactions were clean with no tar formation.[23] The reactions failed after 48 h without microwave irradiation.

In summary, a simple work-up, low consumption of solvent, fast reaction rates, mild reaction conditions, good yields, relatively clean reactions with no tar formation make this method an attractive and a useful contribution to present methodologies. Indeed, a wide range of 1-hydroxyphosphonates were converted to the corresponding 1-aminophosphonates using this method.



1 **2**

Scheme 1.

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Table 1. Reaction of a mixture of amine and diethyl 1-hydroxyphosphonates in the presence of acidic alumina under microwave irradiation

1	R	R′	Reaction time (min)	Yield (%)[a] 2
a	C_6H_5-	C_6H_5-	5	55
b	*p*-$CH_3C_6H_4$-	C_6H_5-	5	62
c	C_6H_5-CH=CH-	C_6H_5-	4	65
d	*p*-$NO_2C_6H_4$-	C_6H_5-	3	57
e	*n*-C_4H_9-	C_6H_5-	5	50
f	C_6H_5-	*m*-$O_2NC_6H_4$-	7	53
g	*p*-$CH_3C_6H_4$-	*m*-$O_2NC_6H_4$-	7	55
h	C_6H_5-CH=CH-	*m*-$O_2NC_6H_4$-	7	56
i	C_6H_5-	Cyclohexyl	5	60
j	*p*-$CH_3C_6H_4$-	Cyclohexyl	5	58
k	C_6H_5-CH=CH-	Cyclohexyl	5	60
l	C_6H_5-	(*S*)-(−)-1-Phenylethyl-	6	65[b]

[a] Isolated yields.
[b] Diastereomeric ratio is 65:35 based on ^{31}P NMR.

Further investigations of the mechanism of this reaction are now in progress.

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22. Procedure for the preparation of 1-hydroxyphosphonates: Magnesium oxide (2 g) was added to a stirred mixture of diethyl phosphite (0.02 mol) and aldehyde (0.02 mol) at rt. After 2 h the mixture was washed with dichloromethane (4×50 mL), dried with $CaCl_2$, and solvent evaporated to give the crude products. Products were crystallized from CH_2Cl_2/*n*-hexane (1:2) or distilled under reduced pressure. All products gave satisfactory

spectral data in accord with the assigned structures. For **1c** as an example: White crystals (82%); mp 105–106°C (*n*-hexane/CH_2Cl_2); ^1H NMR ($CDCl_3$/TMS): 1.15 (3H, t, $J=7.1$ Hz), 1.28 (3H, t, $J=7.1$), 3.94 (1H, ddq, $J=7.1$, 11.2, 8.1 Hz), 4.09 (1H, ddq, $J=7.1$, 8.1, 11.2 Hz), 4.18 (2H, m), 4.3 (1H, br, OH), 4.4 (1H, dd, $J_{HP}=18$, $J_{HH}=6$ Hz), 6.08 (1H, dd, $J=6$, 16 Hz), 6.4 (1H, d, $J=16$), 6.9–7.4 (5H, m); ^{31}P NMR ($CDCl_3/H_3PO_4$): 19.49; IR (KBr): 3250 (-OH), 1230 (P=O), 1045 (P-O-Et) cm^{-1}.

23. This solvent-free reaction method is operationally simple. 1-Hydroxyphosphonate (2 mmol) was combined with alumina (Al_2O_3, acidic, 1.5 g) in a mortar and pestle by grinding them together until a fine, homogeneous powder was obtained (5–10 min). Amine (3 mmol) was added to this mixture and the mixture was irradiated by microwaves for 3–7 min at 720 W (a kitchen-type microwave was used in all experiments). The mixture (including alumina) was chromatographed through a plug of silica gel with EtOAc/*n*-hexane and evaporation of the solvent under reduced pressure gave the pure product in 50–65% yields. All products gave satisfactory spectral data in accord with the assigned structures. For **2a** as an example ^1H NMR ($CDCl_3$/TMS-500 MHz): 1.12 (3H, t, $J=7.1$ Hz), 1.29 (3H, t, $J=7.1$), 3.68 (1H, ddq, $J=7.1$, 11.2, 8.1 Hz), 3.95 (1H, ddq, $J=7.1$, 8.1, 11.2 Hz), 4.14 (2H, m), 4.75 (1H, br, -NH), 4.78 (1H, d, $J=17.9$ Hz), 6.61 (2H, d, $J=8.5$ Hz), 6.70 (1H, t, $J=7.4$), 7.11 (2H, t, $J=7.4$), 7.27 (1H, m), 7.34 (2H, t, $J=7.4$), 7.49 (2H, m); IR (neat): 3295 (-NH), 1233 (P=O), 1103–997 (P-O-Et) cm^{-1}.