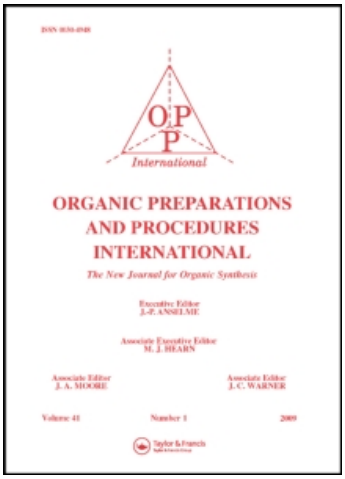

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CONVENIENT SYNTHESIS OF 1-AMINOALKYLPHOSPHONATES UNDER SOLVENT-FREE CONDITIONS

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CONVENIENT SYNTHESIS OF 1-AMINOALKYLPHOSPHONATES UNDER SOLVENT-FREE CONDITIONS

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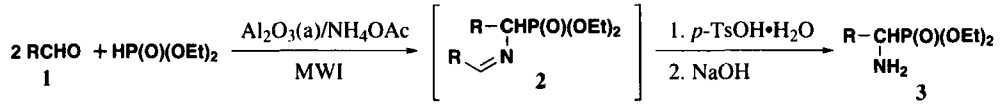
1-Aminophosphonic acids are probably the most important substitutes for the corresponding α-amino acids in biological systems.[1-4] Indeed, a number of potent antibiotics,[5] enzyme inhibitors,[6] and pharmacological agents[7] are 1-aminophosphonic acids, or derivatives, thereof. Of the number of methods for the synthesis of 1-aminoalkyl phosphonates developed during past two decades,[8] the condensation of amines and carbonyl compounds followed by the nucleophilic addition of a dialkyl or diaryl phosphite to the resulting imine is the most convenient one.[9-15] The formation of 1-hydroxyphosphonates or a product of its rearrangement frequently accompanies the formation of 1-aminoalkyl phosphonates.[16] Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\bullet}Et_2O$, $ZnCl_2$, $MgBr_2$, and $InCl_3$ have been used as catalyst. The most typical procedure for unsubstituted amino phosphonates is a Strecker-type reaction[17]which involves the treatment of an aldehyde with ammonia and dialkyl phosphite. This reaction, however, does not give highyield nor can it be carried out on a large scale since it is performed in a sealed vessel at 100°C.

In recent years, the use of reagents and catalysts immobilized on solid supports has received considerable attention. Such reagents not only simplify purification processes but also help prevent release of reaction residues into the environment. Reagents supported on organic polymers and within and/or on the surface of inorganic matrices have all been reported.[18] The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques.[19] It has been demonstrated that application of microwave irradiation (MWI) to organic reactions not only results in reduced reaction times but also in improved yield compared to those obtained under conventional conditions. Under microwave conditions, reactions are performed using minimal amounts of solvent or, in some cases, in the absence of solvent. Consequently such processes result in formation of reduced quantities of waste and combined with the rapid reaction times and improved yields normally observed, may therefore be considered as more environmentally acceptable. In the



a) R = C_6H_5- b) R = *p*-$CH_3C_6H_4$- c) R = *p*-ClC_6H_4- d) R = *p*-BrC_6H_4- e) R = *p*-$CH_3OC_6H_4$-
f) R = *p*-$(CH_3)_2CHC_6H_4$- g) R = *m*-BrC_6H_4- h) R = *m*-ClC_6H_4- i) R = α-naphthyl j) R = β-naphthyl
k) R= C_6H_{13}-

context of our studies on microwave assisted reactions for the synthesis of organophosphorus compounds,[20] we now report a more practical alternative for the synthesis of 1-aminoalkylphosphonates from aldehydes using alumina supported ammonium acetate under microwave irradiation without solvent and catalyst.

Table 1. (1-Aminoalkyl) Phosphonates by Microwave Irradiation on Alumina-supported Ammonium Acetate under MWI

Cmpd.[a]	Yield (%)	Time (min)	^{1}H-NMR (δ)	^{31}P-NMR (δ)
3a[23b]	77	1	1.13 (3H, t, J = 7.1 Hz), 1.23 (3H, t, J = 7.1), 1.98(2H, br, -NH_2), 3.83 (1H, m), 3.95 (1H, m), 4.00 (2H, m), 4.21 (1H, d, J = 17.2 Hz), 7.23-7.42 (5H, m)	25.05
3b[23c]	68	2	1.18 (3H, t, J = 7.1 Hz), 1.27 (3H, t, J = 7.1), 1.83(2H, br, -NH_2), 2.33(3H, s) 3.84 (1H, m), 3.97 (1H, m), 4.05 (2H, m), 4.21 (1H, d, J = 16.7 Hz), 7.14 (2H, d, 7.8 Hz), 7.33 (2H, d, 7.8 Hz)	25.34
3c[23b]	65	1	1.11 (3H, t, J = 7.1 Hz), 1.16 (3H, t, J = 7.1), 2.13 (2H, br, -NH_2), 3.81 (1H, m), 3.90 (1H, m), 3.94 (2H, m), 4.13 (1H, d, J = 17.2 Hz), 7.20 (2H, d, 7.8 Hz), 7.29 (2H, d, 7.8 Hz)	24.35
3d[23b]	55	1	1.16 (3H, t, J = 7.1 Hz), 1.22 (3H, t, J = 7.1), 2.45 (2H, br, -NH_2), 3.84 (1H, m), 3.93-4.02 (3H, m), 4.17(1H, d, J = 17.2 Hz), 7.26 (2H, d, 7.8 Hz), 7.42 (2H, d, 7.8 Hz)	24.16
3e[23b]	53	2	1.18-1.31 (6H, m), 2.83 (2H, -NH_2), 3.79 (3H, s) 3.84-4.05 (4H, m), 4.21(1H, d, J = 17.3 Hz), 6.88 (2H, d, 7.8 Hz), 7.37 (2H, d, 7.8Hz)	24.64
3f[20b]	65	2	1.14 (3H, t, J = 7.1 Hz), 1.20 (6H, d, 6.9 Hz), 1.24 (3H, t, J = 7.1), 1.88 (2H, br, -NH_2), 2.84-2.87(1H, m), 3.85 (1H, m), 3.94 (1H, m), 4.02 (2H, m), 4.19 (1H, d, J = 17.2 Hz), 7.17 (2H, d, 7.8 Hz), 7.33 (2H, d, 7.8 Hz)	25.40
3g[20b]	52	1	1.16-1.26 (6H, m), 3.98-4.07 (4H, m), 4.86 (1H, d, J = 17.2 Hz), 5.48 (2H, br, -NH_2), 7.12-7.72 (4H, m)	24.13
3h[20b]	60	1	1.16-1.28 (6H, m), 2.28 (2H, br, -NH_2), 3.94-4.08 (4H, m), 4.88 (1H, d, J = 17.2 Hz), 7.12-7.72 (4H, m)	24.23
3i[20b]	72	2	1.17-1.25 (6H m), 1.98 (2H, br, -NH_2), 3.65 (1H, m), 3.81 (1H, m), 4.06 (2H, m), 5.09 (1H, d, J = 17.2 Hz), 7.43-7.83 (7H, m)	25.43
3j[23d]	70	2	1.10 (3H, t, J = 7.1 Hz), 1.20 (3H, t, J = 7.1), 2.15 (2H, br, -NH_2), 3.81 (1H, m), 3.90 (1H, m), 3.99 (2H, m), 4.37 (1H, d, J = 17.2 Hz), 7.39-7.85 (7H, m)	24.97
3k[23c]	50	1	0.89 (3H, t, J = 7.0 Hz); 1.31 (6H, t, J = 6.9), 1.52-1.75 [10H, m, 5(-CH_2-)], 1.98 (2H, br, -NH_2), 3.00 (1H, m, PCH), 3.95-4.12 (4H, m)	28.05

a) All compounds are known (*lit.* reference given after compound number) and are colorless oils.

It is found that acidic alumina-supported ammonium acetate promotes the synthesis of 1-aminophosphonates from aldehydes and diethyl phosphite under microwave irradiation. Thus treatment of benzaldehyde (**1a**) with diethyl phosphite in the presence of acidic alumina-supported ammonium acetate, gave a 92% yield of diethyl N-(phenylmethylene)-1-aminophenyl methylphosphonate (**2a**). ^{1}H-NMR spectrum of **2a** exhibits a doublet at δ 8.42 indicative for the coupling HC(imine)-P ($^4J_{HP}$ = 4.7 Hz) moiety in the molecule.[21] The reaction of **2a** with *p*-toluenesulfonic acid monohydrate in ether and followed neutralization of ammonium tosylate, gave 1-(aminophenylmethyl)phosphonate (**3a**) (*Table 1*).

The reactions were clean with no tar formation, and interestingly, none of the 1-hydroxyalkylphosphonates was observed.[22] Neutral and basic alumina, and magnesium oxide are not as effective as acidic alumina. Other ammonium salts such as ammonium chloride, ammonium bromide, ammonium fluoride and ammonium hexafluorophosphate are not effective and did not give any product. We also found that 1-hydroxyalkylphosphonates can be converted, albeit in lower yields to corresponding 1-aminoalkylphosphonates in the presence of a mixture of ammonium acetate and acidic alumina under solvent-free conditions using microwave irradiation. Investigation of the mechanism of this conversion (TLC) showed that the 1-hydroxyalkylphosphonates decomposed in the mixture of alumina/ammonium acetate under microwave irradiation to give the aldehyde and diethyl phosphite which then react as described earlier.

In summary, simple work-up, rapid reaction rates, mild reaction conditions, moderate to good yields, relatively clean reactions with no tar formation make this method an attractive and a useful contribution to present methodologies.

EXPERIMENTAL SECTION

All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained by a Buchi 510 and are uncorrected. A commercially available pulse microwave at 2450 MHz (600 W) was used in all experiments. The infrared (IR) spectra were determined using a FT-IR Brucker-Vector 22. NMR spectra were taken with a DMX-500 Bruker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. Silica gel column chromatography was carried out with Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC. Aluminium oxide 90 active acidic (activity stage I) was used for the reactions (Merck No. 1078)

General Procedure for Synthesis of 1-Aminoalkylphosphonates.- This solvent-free reaction method is operationally simple. Thirty mmol of the reagent were obtained by grinding ammonium acetate (30 mmol, finely ground) and alumina (Al_2O_3, acidic, 5.75 gr) in a mortar until a fine and homogeneous powder was obtained (5-10 min). The aldehyde (60 mmol) was added to this reagent (it is necessary to grind the solid aldehydes before addition of diethyl phosphite). Diethyl phosphite (30 mmol) was then added dropwise after which the mixture was irradiated by microwave for 1-2 min using 600 W (a kitchen-type microwave was used in all experiments). The reaction mixture was disolved in diethyl ether (100 mL) and *p*-TsOH•H_2O (30 mmol) was added to ethereal solu-

tion. After completion of the formation of the salt (1 hr), the tosylate of **3** was collected and neutralized with NaOH (10%). Chromatography on a plug of silica gel with EtOAc/*n*-hexane (9:1) and evaporation of the solvent under reduced pressure gave the pure products as oils in 50-77% yields. All products gave satisfactory spectral data in accord with the assigned structures. All products are known and some spectroscopic data are given in the *Table*: [23, 20b]

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