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Microwave-assisted synthesis of 1-aminoalkyl phosphonates under solvent-free conditions

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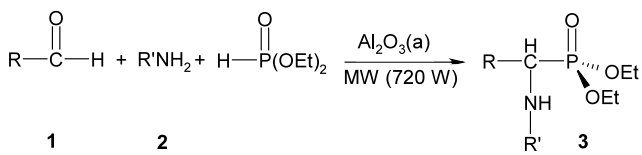
Abstract—A simple, efficient and general method has been developed for the synthesis of 1-aminoalkyl phosphonates through a one-pot reaction of aldehydes with amines in the presence of acidic alumina under solvent-free conditions using microwave irradiation. It was also found that acidic alumina supported ammonium formate under solvent-free conditions is capable of the synthesis of 1-aminophosphonates from aldehydes and diethyl phosphite under mild reaction conditions. © 2001 Published by Elsevier Science Ltd.

1-Aminoalkyl phosphonates have received an increasing amount of attention since they are key substrates in the synthesis of phosphonopeptides.[1] The use of 1-aminoalkyl phosphonates as enzyme inhibitors,[2] antibiotics and pharmacological agents,[3] herbicides,[4] and haptens of catalytic antibodies[5] are well documented. A number of synthetic methods for the synthesis of 1-aminoalkyl phosphonates has been developed during past two decades.[6] Of these methods, the Kabachnik–Fields[7–12] synthesis of 1-aminoalkyl phosphonates, catalyzed by a base or an acid, is the most convenient. The key step in the Kabachnik–Fields synthesis of 1-aminoalkyl phosphonates is the nucleophilic addition of an amine to a carbonyl compound followed by the addition of a dialkyl or diaryl phosphite to the resulting imine. The formation of 1-hydroxyphosphonates or a product of its rearrangement frequently accompanies the formation of 1-aminoalkyl phosphonates.[13] Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, $MgBr_2$, and $InCl_3$ have been used as catalysts. However, these reactions cannot be carried out in a one-step operation with the carbonyl compound, amine and dialkyl phosphite because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.[14]

Surface-mediated solid-phase reactions are of growing interest[15] 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. Acceleration of organic reactions by microwave dielectric heating has been widely exploited. Microwave irradiation using solvent-free conditions has also shown its utility in organic synthesis.[16] As a part of our efforts to explore the utility of surface-mediated reactions for the synthesis of organophosphorus compounds,[17–20] we describe herein a new method for the synthesis of 1-aminoalkyl phosphonates on a solid surface under microwave irradiation. It was found that acidic alumina under solvent-free conditions was capable of producing high yields of 1-aminoalkyl phosphonates under mild reaction conditions (Scheme 1 and Table 1).

As shown in Table 1, the reaction of a mixture of aniline, an aldehyde and diethyl phosphite in the presence of acidic alumina under microwave irradiation, afforded the desired products in excellent yields (**3a–f**). *m*-Nitroaniline also reacted with aldehydes in the presence of diethyl phosphite on alumina under microwave irradiation to give the desired compounds in high yields



Scheme 1.

Keywords: 1-aminoalkyl phosphonates; aldehydes; alumina; microwave; amines.

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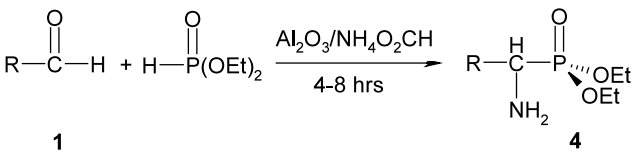
Table 1. Synthesis of 1-aminoalkyl phosphonates (**3**) on acidic alumina using microwave irradiation under solvent-free conditions

3	R	R′	Time (min)	Yield[a] (%)
a	C_6H_5-	C_6H_5-	6	87
b	p-$CH_3C_6H_4$-	C_6H_5-	6	85
c	p-$(CH_3)_2CHC_6H_4$-	C_6H_5-	6	70
d	p-$NO_2C_6H_4$-	C_6H_5-	3	90
e	n-C_4H_9-	C_6H_5-	5	65
f	C_6H_5-CH=CH-	C_6H_5-	5	85
g	C_6H_5-	m-$NO_2C_6H_4$-	5	70
h	p-$CH_3C_6H_4$-	m-$NO_2C_6H_4$-	5	85
I	p-$(CH_3)_2CHC_6H_4$-	m-$NO_2C_6H_4$-	6	80
j	C_6H_5-	Cyclohexyl	6	75
k	C_6H_5-CH=CH-	Cyclohexyl	6	95
l	C_6H_5-CH=CH-	$HOCH_2CH_2$-	6	95
m	C_6H_5-	$HOCH_2CH_2$-	6	80

[a] Isolated yields.

(**3g–i**). The reactions also proceeded with high yields with cyclohexylamine and ethanolamine (**3j–m**).

This solvent-free synthesis method is operationally simple: 30 mmol of amine was added to a mixture of an aldehyde (30 mmol) and alumina (Al_2O_3, acidic, 5.75 g). Diethyl phosphite was added, then the mixture was irradiated by microwave for 3–6 min using 720 W (a kitchen-type microwave was used in all experiments). The reaction mixture was extracted with CH_2Cl_2 (200 mL), the extracts were dried (Na_2SO_4) and the solvent was evaporated to give the crude products. Pure products were obtained by crystallization from CH_2Cl_2/n-hexane or by distillation under reduced pressure in 70–95% yield.[21]



1 4

Scheme 2.

It was also found that acidic alumina supported ammonium formate under solvent-free conditions is capable of the synthesis of 1-aminophosphonates from aldehydes and diethyl phosphite under mild reaction conditions (Scheme 2, Table 2).

As shown in Table 2, aliphatic aldehydes with diethyl phosphite, in the presence of alumina supported ammonium formate, afford the desired products in excellent yields (**4a–c**). The o-, m- and p-substituted benzaldehydes also react with diethyl phosphite in the presence of alumina supported ammonium formate at room temperature, to give the desired compounds in high yields (**4d**, **4j**). The reactions also proceed with good yields with cinnamaldehyde as an α,β-unsaturated aldehyde and furfural as a heterocyclic aldehyde (**4k**, **4l**). Polynuclear aromatic aldehydes also afford the 1-aminoalkylphosphonates in good yields (**4m**, **4n**).[22]

The reactions were clean with no tar formation and, interestingly, no product from the 1-hydroxyphosphonate was observed.[13] Indeed, a wide range of aldehydes and amines was converted into the corresponding 1-aminophosphonates using this reaction procedure. Neutral and basic alumina and magnesium oxide are not as effective as acidic alumina and usually give low yields of the required product; instead they produce 1-hydroxyphosphonates as the major products.

In summary, a simple work-up, low consumption of solvent, relatively fast reaction rates, mild reaction conditions, good yields, and the selectivity of the reactions make these methods an attractive and useful contribution to present methodologies.

Acknowledgements

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Table 2. The synthesis of 1-aminophosphonates **4** in the presence of acidic alumina-supported ammonium formate under solvent-free conditions

Product **4**	R-	Time (h)	Yield [a] (%)	Product **4**	R-	Time (h)	Yield[a] (%)
a	CH_3-	8	75	**h**	p-ClC_6H_4-	5	80
b	n-C_5H_{11}-	8	66	**i**	p-FC_6H_4-	8	76
c	n-C_4H_9-	8	73	**j**	m-$CH_3C_6H_4$-	8	73
d	C_6H_5-	6	75	**k**	Ph-CH=CH-	4	70
e	p-$CH_3OC_6H_4$-	8	59	**l**	Furfuryl	6	70
f	o-ClC_6H_4-	5	68	**m**	α-Naphthyl	7	65
g	m-ClC_6H_4-	8	76	**n**	β-Naphthyl	7	75

[a] Isolated yields.

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21. All products gave satisfactory spectral data in accord with the assigned structures. For **3a**, as an example, ^{1}H 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}.
22. This solvent-free reaction method is operationally simple: 30 mmol of the reagent is prepared by the combination of ammonium formate (30 mmol, finely ground) and alumina (Al_2O_3, acidic, 5.75 g) in a mortar and pestle by grinding them together until a fine, homogeneous, powder is obtained (5–10 min). The aldehyde (60 mmol) is added to this reagent (solid aldehydes need to be ground before adding the diethyl phosphite). Diethyl phosphite is added slowly and after 4–8 h (Table 1) of vigorous stirring, the reaction mixture is extracted with diethyl ether (200 ml). *p*-TsOH·H_2O (30 mmol) was added to the ethereal solutions with stirring. After completion of the reaction (1 h), the solid was filtered and neutralized with NaOH (10%). Chromatography on a plug of silica gel with EtOAc/*n*-hexane (1:9) and evaporation of the solvent under reduced pressure gave the pure product as an oil in 59–80% yields. All products gave satisfactory spectral data in accord with the assigned structures. For **4d** as an example, ^{1}H NMR ($CDCl_3$/TMS): 1.15 (3H, t, $J=7.1$ Hz), 1.28 (3H, t, $J=7.1$), 2.75 (2H, br, -NH_2); 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), 4.88 (1H, d, $J=17.8$ Hz), 7.45 (5H, m); IR (neat): 3377, 3295 (–NH_2), 1237 (P=O), 1103–997 (P–O–Et) cm^{-1}.