# Surface-Mediated Solid Phase Reactions: A Simple and New Method for the Synthesis of α-Aminophosphonates under Solvent-Free Conditions

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Alumina-supported ammonium formate was found to be an efficient reagent for the synthesis of 1-aminophosphonates from aldehydes and diethyl phosphite. This method is an easy, rapid and high-yielding reaction for the synthesis of 1-aminophosphonates.

In recent years, considerable interest has been focused on the synthesis of phosphonic acids, particularly the α-substituted analogs that are an important class of compounds with applications as antibiotics, antiviral agents and enzyme inhibitors. Among the α-functionalized phosphonic acids, α-aminophosphonic acid derivatives are gaining in interest in medicinal chemistry. α-Aminophosphonic acids are analogues of naturally occurring α-amino acids in biological systems. Extensive investigations over the last twenty years have shown they are of particular importance in biological and medicinal research.[1] In this connection, the uses of α-aminoalkylphosphonates as enzyme inhibitors,[2] antibiotics and pharmacological agents,[3] herbicides,[4] and haptens of catalytic antibodies[5] are well documented. Although there are many classical methods for synthesizing α-aminophosphonic acids, these involve either long reaction times, expensive reagents, or the use of conditions which are amenable to aliphatic aminophosphonic acids rather than aromatic aminophosphonic acids.[6] The most typical procedure is a Strecker-type reaction[7] which involves the treatment of an aldehyde with ammonia and dialkyl phosphite. This method, however, is not high yielding nor suitable for large-scale production since the reaction is performed in a sealed vessel with heating at 100 °C.

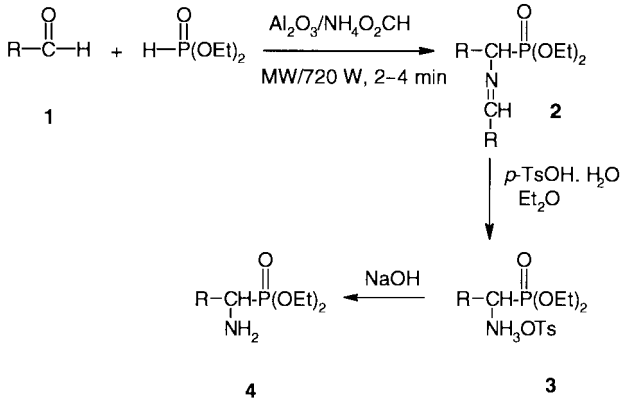
Surface-mediated solid phase reactions are of growing interest[8] because of their advantages of ease of set up, mild conditions, rapid reactions, selectivity, increased yields of the products and low cost compared with their homogeneous counterparts. As a part of our efforts to explore the use of surface-mediated reactions for the synthesis of organophosphorus compounds,[9–12] in this report, a new method for the synthesis of α-aminophosphonates on a solid surface is described. It was found that acidic alumina supported ammonium formate under solvent-free conditions is capable of the synthesis of α-aminophosphonates from aldehydes and diethyl phosphite under mild reaction conditions (Scheme 1, Table 1).

The aldehyde **1** is treated with diethyl phosphite in the presence of acidic alumina-supported ammonium formate, giving imine derivatives of 1-aminoalkylphosphonate **2** (Scheme 1). $^1$H NMR spectrum of **2** exhibits a doublet at 8.25 ppm due to coupling constant, which is indicative for the coupling HC–P ($J_{HP}$ = 5 Hz) moiety in the molecule.[13] The reaction of **2** with *p*-toluenesulfonic acid monohydrate in ether and followed neutralization of ammonium salt **3**, gave the desired 1-aminoalkylphosphonates (**4**). The overall yields of these reactions are shown in Table 1.

**Table 1**. The Synthesis of 1-Aminophosphonates (**4**) in the Presence of Acidic Alumina-Supported Ammonium Formate under Solvent-Free Conditions.

| Product **4** | R- | Time/min | Yield[a]/% |
|---|---|---|---|
| **a** | $CH_3$- | 2 | 68 |
| **b** | *n*-$C_5H_{11}$- | 3 | 66 |
| **c** | *n*-$C_4H_9$- | 3 | 70 |
| **d** | $C_6H_5$- | 2 | 78 |
| **e** | *p*-$CH_3OC_6H_4$- | 3 | 75 |
| **f** | *o*-$ClC_6H_4$- | 2 | 65 |
| **g** | *m*-$ClC_6H_4$- | 2 | 72 |
| **h** | *p*-$ClC_6H_4$- | 2 | 78 |
| **i** | *p*-$FC_6H_4$- | 2 | 65 |
| **j** | *m*-$CH_3C_6H_4$- | 4 | 65 |
| **k** | Ph–CH=CH- | 2 | 63 |
| **l** | Furfuryl | 2 | 68 |
| **m** | α-Naphthyl | 2 | 70 |
| **n** | β-Naphthyl | 2 | 75 |

[a]Isolated yield.




**Scheme 1.**

As shown in Table 1, aliphatic aldehydes with diethyl phosphite, in the presence of alumina supported ammonium formate, afford the desired products in excellent yields (**4a–4c**). The *o*-, *m*- and *p*-substituted benzaldehydes also react with diethyl phosphite in the presence of alumina supported ammonium formate with microwave irradiation, 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**).

The reactions were clean with no tar formation and interestingly, no product from the 1-hydroxyphosphonate was observed.[14] Indeed, a wide range of aldehydes were converted to corresponding 1-aminoalkylphosphonates using this reaction.

Neutral and basic aluminas and magnesium oxide are not effective as acidic alumina and usually give low yields of the corresponding amine since they produce 1-hydroxyphosphonates as the major product instead.

This solvent-free reaction method is operationally simple. The reagent (30 mmol) was 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 grained before adding the diethyl phosphite). Diethyl phosphite was added to this mixture and the whole was irradiated by microwave for 3–6 min using 720 W (A kitchen-type microwave was used in all experiments). The reaction mixture is washed with diethyl ether (200 mL). *p*-TsOH·$H_2O$ (30 mmol) was added to the ethereal solution with stirring. After completion of the reaction (1 h), the solid was filtered and neutralized with NaOH (10%). Chromatography through a plug of silica gel with EtOAc/*n*-hexane (1:9) and evaporation of the solvent under reduced pressure gave the pure product as oil in 63–78% yields.[15]

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

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**References and Notes**

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15 All products gave satisfactory spectral data in accord with the assigned structures. For **4d** as an example $^1$H NMR ($CDCl_3$/TMS): δ 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) $cm^{-1}$.