Silica-Supported Ammonium Hydrogen Carbonate as an Efficient Reagent for One-Pot Synthesis of 1-Aminophosphonates from Aldehydes

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Abstract: Silica-supported ammonium hydrogen carbonate was found to be an efficient reagent for the synthesis of 1-aminophosphonates under microwave irradiation in solvent-free conditions. This method is an easy, rapid, one-pot, and good-yielding reaction for the synthesis of 1-aminophosphonates.

Key words: 1-aminophosphonates, silica, microwave-assisted, ammonium hydrogen carbonate, aldehydes

1-Aminophosphonates are probably the most important amino acid derivatives in biological systems.1–4 Indeed a number of potent antibiotics,5 enzyme inhibitors,6 and pharmacological agents7 are 1-aminophosphonic acids as well as their derivatives, notably peptides. Most synthetic methods reported utilize reactions of imines with phosphorus nucleophiles.8–13 Although there are many classical methods reported to utilize reactions of imines with phosphorus nucleophiles,5–13 although there are many classical methods for synthesizing 1-aminophosphonic acids, these involve either long reaction times, expensive reagents, required an additional deprotection step, or the use of conditions which are amenable to aliphatic aminophosphonic acids rather than aromatic aminophosphonic acids.14 On the other hand, the formation of 1-hydroxyphosphonates or a product of its rearrangement frequently accompanies the formation of 1-aminooalkyl phosphonates.15,16 The most typical procedure is a Strecker-type reaction17 which involves the treatment of an aldehyde with ammonia and dialkyl phosphite (Scheme 1).

Scheme 1

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. Despite the wide range of synthetic methods for the synthesis of 1-aminophosphonates, few attempts have been made at a one-pot synthesis of 1-aminophosphonates.17,18

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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 are the major route to one-pot synthesis. 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 to organic reactions not only results in reduced reaction times but also improves yield compared to those obtained under conventional reaction conditions. Under microwave conditions reactions are performed using minimal amounts of solvent and in some cases in the absence of solvent, consequently such processes result in formation of reduced quantities of waste. Combined with the rapid reaction times and improved yields normally observed, these processes may therefore be considered as environmentally acceptable.

We became interested in simply substituting ammonia by an ammonium salt in Strecker-type reaction (Scheme 2) for the synthesis of 1-aminophosphonates. We believe that an ammonium salt could act not only as an ammonia source but also as an acid catalyst for the formation and activation of the imine intermediate in Scheme 1. During our studies on the solvent-free reactions for the synthesis of organophosphorus compounds using immobilized reagents on inorganic solid phases,21–24 we recently found that ammonium formate is a suitable reagent for the synthesis of 1-aminophosphonates.25 Further investigations on the synthesis of 1-aminophosphonates using other ammonium salts we would also like to introduce here as a more practical alternative for the one pot synthesis of 1-aminophosphonates from aldehydes using of silica-supported ammonium hydrogen carbonate (a cheap reagent) under microwave irradiation in solvent-free conditions.

First the reaction of p-chlorobenzaldehyde (1e) and diethyl phosphite was tested as a model reaction (Table 1). When ammonium hydrogen carbonate was used as a reagent in ethanol for 24 hours, the reaction proceeded smoothly to afford 1-hydroxyphosphonate 3c as the major product (entry 1). The same results were obtained when ammonium hydrogen carbonate was immobilized on silica or acidic alumina in ethanol for 24 hours (entry 2 and 3). On the other hand, other solvents such as CHCl₃,
CH₂Cl₂, and methanol gave 1-aminophosphonate in very low yield.

It was interesting to find that the model reaction gave 1-aminophosphonate as the major product in the presence of ammonium hydrogen carbonate immobilized on acidic alumina or silica (entry 5 and 6) under microwave irradiation. Under the same reaction condition, in the absence of alumina or silica, ammonium hydrogen carbonate under microwave irradiation afforded moderate yield of phosphonates. Mechanistically, diethylphosphite attacks an imine, which is formed from the aldehyde and ammonia (from ammonium hydrogen carbonate) in situ, to generate 1-aminophosphonate as the major product under microwave irradiation. In contrast to the reaction under microwave conditions, reaction of diethyl phosphate should occur rapidly with aldehyde to afford 1-hydroxyphosphonate as the major product in organic solvents.

In contrast to ammonium hydrogen carbonate, other ammonium salts were found unsuitable for aminophosphonates in aldehydes. For example, formation of 2c could not be detected in the case of ammonium chloride, ammonium bromide, and ammonium hexafluorophosphate. Only a trace amount of 2c was formed when ammonium nitrate was employed. In order to carry out the model reaction in a homogeneous condition, we also examined this reaction with various ammonium salts in EtOH–H₂O and found exclusive formation of desired 1-hydroxyphosphonate (3c). The reactions of various aldehydes with diethyl phosphate in the presence of silica-supported ammonium hydrogen carbonate gave the corresponding 1-aminophosphonates in good yields as shown in Table 2 and Scheme 3. As shown in Table 2, benzaldehyde derivatives (1a–g) with diethyl phosphate, in the presence of silica-supported ammonium hydrogen carbonate, afford the desired products in good yields (2a–g). The α- and β-naphthalene carbaldehydes, as a polynuclear aromatic aldehydes, also react with diethyl phosphate in the presence of silica-supported ammonium hydrogen carbonate under microwave irradiation, to give the desired compound in good yield (2h, 2i). The reactions also proceeded with good yields with heterocyclic aldehydes (2j). Heptanal as an aliphatic aldehyde with diethyl phosphate, in the presence of silica-supported ammonium hydrogen carbonate, afforded the desired products in good yield (2k).

In summary, a simple work-up, low consumption of solvent, fast reaction rates, mild reaction conditions, good yields, cheap starting materials, and relatively clean reactions with no tar formation make this method an attractive and a useful contribution to present methodologies. Further investigations of the mechanism of this reaction are now in progress.

All chemicals were obtained from commercial sources and distilled or recrystallized before use. A commercially available pulse microwave (domestic) at 2450 MHz (600 W) was used in all experiments. The infrared (IR) spectra were determined using a FT-IR Brucker 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.

**Table 1** The Reaction of p-Chlorobenzaldehyde and Diethyl Phosphite as a Model Reaction in the Presence of Ammonium Hydrogen Carbonate at Various Conditions for the Synthesis of 1-Aminophosphonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Reaction Condition</th>
<th>Yield%</th>
<th>Ratio 2e/3e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₄HCO₃</td>
<td>A</td>
<td>75</td>
<td>10:90</td>
</tr>
<tr>
<td>2</td>
<td>NH₄HCO₃/Al₂O₃</td>
<td>A</td>
<td>77</td>
<td>15:85</td>
</tr>
<tr>
<td>3</td>
<td>NH₄HCO₃/SiO₂</td>
<td>A</td>
<td>78</td>
<td>14:86</td>
</tr>
<tr>
<td>4</td>
<td>NH₄HCO₃</td>
<td>B</td>
<td>38</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>NH₄HCO₃/Al₂O₃</td>
<td>B</td>
<td>60</td>
<td>90:10</td>
</tr>
<tr>
<td>6</td>
<td>NH₄HCO₃/SiO₂</td>
<td>B</td>
<td>68</td>
<td>95:5</td>
</tr>
</tbody>
</table>

* Isolated yields.
* Based on isolated yields.
* A: Stirred in EtOH for 24 h.
* B: Microwave irradiation for 4 min.

**Scheme 2**

**Scheme 3**

Mechanistically, we simply substituted ammonia by an ammonium salt in solvent-free condition. Our hypothesis was that an ammonium salt could act not only as an ammonia source but also as an acid catalyst for the formation and activation of the intermediary imine. Furthermore, the reaction is not necessarily carried out in a sealed vessel when employing a nonvolatile ammonium salt.
Diethyl [Amino(phenyl)methyl]phosphonate (2a)  
Colorless oil.

1H NMR (CDCl₃–TMS, 500 MHz): δ = 1.13 (3 H, t, J = 7.1 Hz), 1.23 (3 H, t, J = 7.1 Hz), 1.98 (2 H, br, NH₂), 3.83 (1 H, m), 3.95 (1 H, m), 4.00 (2 H, m), 4.21 (1 H, d, J = 17.2 Hz), 7.23–7.42 (5 H, m).

31P NMR (CDCl₃–H₃PO₄, 202.4 MHz): δ = 25.05.

13C NMR (CDCl₃–TMS, 125.7 MHz): δ = 136.8, 127.4, 126.7, 126.6, 61.7 (d, JPC = 7.1 Hz), 61.6 (d, JPC = 7.1 Hz), 53.3 (d, JPC = 149.5Hz), 15.4 (d, JPC = 5.6 Hz), 15.3 (d, JPC = 5.6 Hz).

Diethyl [Amino(4-methylphenyl)methyl]phosphonate (2b)  
Colorless oil.

1H NMR (CDCl₃–TMS, 500 MHz): δ = 1.18 (3 H, t, J = 7.1 Hz), 1.27 (3 H, t, J = 7.1 Hz), 1.83 (2 H, br, NH₂), 2.33 (3 H, s) 3.84 (1 H, m), 3.97 (1 H, m), 4.05 (2 H, m), 4.21 (1 H, d, J = 16.7 Hz), 7.14 (2 H, d, J = 7.8 Hz), 7.33 (2 H, d, J = 7.8 Hz).

31P NMR (CDCl₃–H₃PO₄, 202.4 MHz): δ = 25.34.

13C NMR (CDCl₃–TMS, 125.7 MHz): δ = 137.3, 134.5, 128.9, 127.4, 62.6 (d, JPC = 6.9 Hz), 62.4 (d, JPC = 6.9Hz), 53.2 (d, JPC = 149.9 Hz), 20.9, 16.2 (d, JPC = 5.6 Hz), 16.1 (d, JPC = 5.6 Hz).

Diethyl [Amino(4-chlorophenyl)methyl]phosphonate (2c)  
Colorless oil.

1H NMR (CDCl₃–TMS, 500 MHz): δ = 1.11 (3 H, t, J = 7.1 Hz), 1.16 (3 H, t, J = 7.1 Hz), 2.13 (2 H, br, NH₂), 3.81 (1 H, m), 3.90 (1 H, m), 4.13 (1 H, d, J = 17.2 Hz), 7.20 (2 H, d, J = 7.8 Hz), 7.29 (2 H, d, J = 7.8 Hz).

31P NMR (CDCl₃–H₃PO₄, 202.4 MHz): δ = 24.35.

13C NMR (CDCl₃–TMS, 125.7 MHz): δ = 136.1, 133.3, 128.8, 128.2, 62.6 (d, JPC = 6.9 Hz), 62.4 (d, JPC = 6.9Hz), 53.4 (d, JPC = 149.9 Hz), 16.2 (d, JPC = 5.6 Hz), 16.1 (d, JPC = 5.6 Hz).

Diethyl [Amino(4-bromophenyl)methyl]phosphonate (2d)  
Colorless oil.

1H NMR (CDCl₃–TMS, 500 MHz): δ = 1.16 (3 H, t, J = 7.1 Hz), 1.22 (3 H, t, J = 7.1 Hz), 2.45 (2 H, br, NH₂), 3.84 (1 H, m), 3.93–4.02 (3 H, m), 4.17 (1 H, d, J = 17.2 Hz), 7.26 (2 H, d, J = 7.8 Hz), 7.42 (2 H, d, J = 7.8 Hz).

31P NMR (CDCl₃–H₃PO₄, 202.4 MHz): δ = 24.16.

13C NMR (CDCl₃–TMS, 125.7 MHz): δ = 136.6, 131.3, 129.1, 128.8, 62.7 (d, JPC = 6.9 Hz), 62.6 (d, JPC = 6.9Hz), 53.3 (d, JPC = 149.9 Hz), 16.2 (d, JPC = 5.6 Hz), 16.1 (d, JPC = 5.6 Hz).

Diethyl [Amino(4-isopropylphenyl)methyl]phosphonate (2g)  
Colorless oil.

1H NMR (CDCl₃–TMS, 500 MHz): δ = 1.14 (3 H, t, J = 7.1 Hz), 1.20 (6 H, d, J = 6.9 Hz), 1.24 (3 H, t, J = 7.1 Hz), 1.88 (2 H, br, NH₂), 2.84–2.87(1 H, m), 3.85 (1 H, m), 3.94 (1 H, m), 4.02 (2 H, m), 4.19 (1 H, d, J = 17.2 Hz), 7.17 (2 H, d, J = 7.8 Hz), 7.33 (2 H, d, J = 7.8 Hz).

31P NMR (CDCl₃–H₃PO₄, 202.4 MHz): δ = 25.40.

13C NMR (CDCl₃–TMS, 125.7 MHz): δ = 148.3, 134.8, 127.4, 126.3, 62.6 (d, JPC = 6.9 Hz), 62.4 (d, JPC = 6.9Hz), 53.5 (d, JPC = 149.9 Hz), 33.5, 3.7, 16.2 (d, JPC = 5.6 Hz), 16.1 (d, JPC = 5.6 Hz).

Diethyl [Amino(2-naphthyl)methyl]phosphonate (2i)  
Colorless oil.

1H NMR (CDCl₃–TMS, 500 MHz): δ = 1.10 (3 H, t, J = 7.1 Hz), 1.20 (3 H, t, J = 7.1 Hz), 2.15 (2 H, br, NH₂), 3.81 (1 H, m), 3.90 (1 H, m), 3.99 (2 H, m), 4.37 (1 H, d, J = 17.2 Hz), 7.39–7.85 (7 H, m).

One-Pot Synthesis of 1-Aminoalkyl Phosphonates from Aldehydes under Microwave Irradiation: General Procedure

The reagent (6 mmol) was prepared by grinding ammonium hydrogen carbonate (6 mmol) and silica (SiO₂, 2 g) in a mortar and pestle until a fine, homogeneous, powder is obtained (5–10 min). The aldehyde (10 mmol) was added to this reagent (solid aldehydes need to be ground before adding the diethyl phosphate). Diethyl phosphate (6 mmol) was added and this mixture was irradiated for 2–5 min using a 600 W microwave. Reaction mixture was washed with EtOAc (100 mL). The solvent was evaporated and HCl (5%, 50 mL) added and the reaction mixture was stirred for 10 min. The mixture was washed with Et₂O (3 × 50 mL) and the aqueous solution was neutralized with NH₄OH (10%). Extraction with Et₂O (3 × 50 mL), evaporation of solvent and chromatography on plug of silica gel with EtOAc–n-hexane (9:1) gave the pure product as an oil in 50–84% yields. All products gave satisfactory spectral data in accordance with the assigned structures and literature reports.²⁵–²⁷
13C NMR (CDCl₃–TMS, 125.7 MHz): δ = 135.2, 133.1, 132.8, 127.9, 127.8, 127.5, 126.4, 126.0, 125.9, 125.7, 62.7 (d, $J_C^P = 6.9$ Hz), 62.6 (d, $J_C^P = 6.9$ Hz), 53.6 (d, $J_C^P = 149.9$ Hz), 16.3 (d, $J_C^P = 5.6$ Hz).

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