CHAPTER-V

A highly efficient, eco-friendly one-pot synthesis of α-aminophosphonates over high surface area CuO nanopowder
INTRODUCTION

This section deals with the one-pot three component synthesis of α-aminophosphonates over high surface area crystalline CuO nanopowder under solvent less condition.

Importance of α-aminophosphonates

The synthesis of α-aminophosphonate derivatives has gained much interest in recent years in organic and medicinal chemistry due to their important biological and pharmacological properties.1 As structural analogues of amino acids (peptidomimetics), their biological activity is mainly exhibited through metabolic regulation and ability to inhibit various metalloenzymes having an amino acid as substrate.2 In addition, a number of these compounds may act as antibiotic,3 antimicrobial,4 antitumor5 and antiviral agents.6 In agrochemistry some of the derivatives of α-aminophosphonate are used as fungicidal7 and herbicidal agents.8 Another important aspect is their ability to form various types of metal complexes, which also exhibit biological activity.9 Thus, some complexes of platinum group metals have shown remarkable antitumor activity.10 The high phosphonate affinity to bone and other calcified tissues may be utilized for the drug design against bone diseases.11 The high potency of aminophosphonates have prompted researchers to find new methodologies for its synthesis.

A brief review on the synthesis of α-aminophosphonates

In this section some interesting examples of recent years have been incorporated based on the synthesis of α-aminophosphonate nucleus.

M. H Sarvari applied the commercially available titania (TiO₂) as a heterogeneous and reusable catalyst in the synthesis of α-aminophosphonates under solvent free conditions.12 The one-pot three component coupling of amines, carbonyl compounds and diethyl phosphite was proved to be efficient for the synthesis at thermal conditions generating high yields (Scheme 1). Bulk CuO, ZnO and MgO were found to be inactive under the said conditions.
Variety of carbonyl compounds and amines (aromatic and aliphatic) were compatible in the reaction.

\[
\begin{align*}
\text{R}_1^\text{C}=\text{O} + \text{R}_2^3\text{NH} + \text{HPO(OEt)}_2 & \xrightarrow{\text{TiO}_2 (20\text{ mol})} \text{EtO}^\text{R}_1\text{R}_2\text{NHR}^3 \\
\text{no solvent, } 50 \degree \text{C} & \end{align*}
\]

Scheme 1

SbCl\(_3\) adsorbed on Al\(_2\)O\(_3\) was found to be an efficient and recyclable catalyst in promoting three-component coupling reactions of aldehydes (aromatic and aliphatic), amines (aryl amines, aliphatic amines and esters of S-\(\alpha\)-amino acids) and dialkylphosphites to afford the corresponding \(\alpha\)-aminophosphonates in high yields (Scheme 2). Kapoor and his co-workers\(^{13}\) carried out the reactions at ambient conditions in acetonitrile.

\[
\begin{align*}
\text{R}_1^\text{C}=\text{H} + \text{R}_2^3\text{NH} + \text{HPO(OR')}_2 & \xrightarrow{\text{SbCl}_3/\text{Al}_2\text{O}_3} \text{R}^\text{O}_1\text{RO}_2\text{P}^\text{NHR}^2 \\
\text{CH}_3\text{CN, } \text{rt} & \end{align*}
\]

Scheme 2

The application of another heterogeneous catalyst TaCl\(_3\)/SiO\(_2\) in the synthesis of aminophosphonate derivatives was demonstrated by S. Chandrasekhar et al\(^{14}\). Several aromatic aldehydes and aromatic amines were treated with diethyl phosphite in DCM to afford the product in high yield (Scheme 3). TaCl\(_3\)/SiO\(_2\) coordinates with the nitrogen of the imine and facilitates the nucleophilic addition of diethyl phosphate to yield the amino phosphonates.
The use of heteropoly acid (HPA) catalysts has also received considerable attention because of their environmental compatibility, reusability, operational simplicity, greater selectivity, non-toxicity, non-corrosiveness and ease of isolation. 12-Tungstophosphoric acid, the strongest HPA in the Keggin series, have been extensively studied as super acid catalyst by Heydari et al\textsuperscript{15} in the synthesis of α-aminophosphonates by one-pot coupling of different aldehydes, amines and P(OMe)\textsubscript{3}. Short reaction times with excellent yields are the characteristic features of this methodology (Scheme 4).

The same research group\textsuperscript{16} explored the utility of a task-specific ionic liquid (TSIL) as a Bronsted acid catalyst for the reaction between various aldehydes/ketones, amines and trimethyl phosphite in aqueous medium to afford the corresponding α-aminophosphonates in high yield (Scheme 5). Very short time was required to complete the reaction at room temperature. The catalyst was reused several times without loss of its activity.
Another application of ionic liquid catalyzed solvent-free synthesis was carried out by Bommera and his co-workers. (Bromodimethyl)sulfonium bromide was a competent catalyst at room temperature affording α-aminophosphonates in very short time (Scheme 6).

Heydari and his co-workers followed a different approach for this synthesis in a metal catalyst free, homogeneous and recyclable medium. They used trifluoroethanol as a catalytic solvent which is highly acidic in nature. Moreover, its strong hydrogen bonding ability and low boiling point are interesting features behind its use. At room temperature three component coupling occurred within short reaction time to produce high yield of the α-aminophosphonates (Scheme 7).

Very recently, Kidwai et al. utilized Cu-nanoparticles as an efficient, novel and recyclable catalyst for a multi-component coupling reaction using aldehyde, amine and diethyl...
phosphite. This method provides a wide range of substrate applicability, devoid of co-catalyst/heavy metals, with an excellent yield of α-aminophosphonates (Scheme 8). The catalyst could be recovered and reused up to four runs with almost consistent activity.

Scheme 8

Organocatalysis has emerged as an important area of research over the last few years. Compared with biocatalysts and metal catalysts, organocatalysts are usually more stable, more environmentally friendly, more readily available and less expensive. Vahdat et al developed an oxalic acid catalyzed methodology for the one-pot synthesis of α-aminophosphonates. Under solvent free thermal conditions different aldehydes, amines and trimethyl phosphate reacted with excellent yields (Scheme 9).

Scheme 9

Another organocatalytic application for this synthesis was demonstrated by Gill et al. They synthesized α-aminophosphonates by the reaction of aldehydes and amines with triethyl phosphite in the presence of the easily available, inexpensive, and nontoxic catalyst thiamine hydrochloride (VB1) under the influence of ultrasound irradiation in aqueous medium with short reaction times (4-6 min) and high yields (85-95%) (Scheme 10).
Nagarkar and his group\textsuperscript{22} utilized CeO\textsubscript{2} nanoparticles for the development of the same reaction under ultrasonication technique. Nano CeO\textsubscript{2} has been found to be an excellent catalyst for the green synthesis of \(\alpha\)-aminophosphonates under ultrasound irradiation and solvent-free condition to afford good to excellent yield (Scheme 11).

Microwave induced rapid synthesis of aminophosphonates was carried out by Zhang et al.\textsuperscript{23} The reaction was performed under solvent free and catalyst free condition. Different aromatic aldehydes and aromatic amines were reacted with dimethyl phosphite to provide the product in excellent yield within 2 minutes of reaction time (Scheme 12).
A copper chelate of \( N,N',N'',N''' \)-tetramethylated quaternized form of tetrapyridinoporphyrazine proved to an efficient catalyst in aqueous medium in the three component coupling reaction to produce \( \alpha \)-aminophosphonates as shown by Sobhani and his group.\(^{24}\) At 80 °C different aromatic aldehyds and aromatic amines reacted together with trialkyl or dialkyl phosphite leading to the product in high yield (Scheme 13)

\[
\begin{align*}
&\text{R}^1\text{CHO} + \text{R}^2\text{NH}_2 + \text{P(OR)}_3 \quad \text{or} \quad \text{HPO(OR)}_3 \\
&\xrightarrow{[\text{Cu(3,4-untppa)}][\text{MeSO}_4]_2} \quad \text{water} \quad 80^\circ\text{C} \\
&\text{R}^1\text{P=O} + \text{R}^2\text{NH} \quad \text{R}^1\text{O} \quad \text{RO} \quad \text{OR}
\end{align*}
\]

Scheme 13

A new approach for the synthesis of \( N \)-trimethylsilyloxy-\( \alpha \)-amino phosphonates was reported by Heydari and his group\(^{25}\) using LiClO\(_4\)/diethyl ether (LPDE) as a catalyst at room temperature. Different aldehydes, phenylhydroxylamine and dimethyl(trimethylsilyl)phosphite in diethyl ether were reacted to generate the product in 15 minutes in high yield (Scheme 14).

\[
\begin{align*}
&\text{R}^1\text{CHO} + \text{PhNHOH} + \text{MeO}P\text{OSiMe}_3 \quad \text{LPDE, rt} \quad 15\text{ min} \\
&\xrightarrow{\text{LPDE, rt}} \quad \text{NOSiMe}_2 \quad \text{N} \quad \text{MeO} \quad \text{OMe} \quad \text{MeO} \quad \text{OMe}
\end{align*}
\]

Scheme 14

Das et al\(^{26}\) treated \( N \)-tosyl aldimines with dialkyl trimethylsilyl phosphites at 0 °C in the presence of iodine as a catalyst in dichloromethane and obtained the corresponding \( N \)-sulfonated \( \alpha \)-amino phosphonates in excellent yields within 1.5 to 2.5 h (Scheme 15). This
was the first example of the use of silylated phosphites to prepare tosylated aminophosphonates.

**Scheme 15**

In the same year the same group\(^\text{27}\) developed another method for the preparation aminophosphonates by the treatment of N-benzylxocarbonylamino sulphones with triethyl phosphite catalyzed over InCl\(_3\) in DCM at room temperature in high yield. The corresponding N-benzylxocarbonylamino sulphones or α-amido sulphones were prepared separately from aldehydes by reaction with ammonium carbamate and Na salt of aryl sulphonamide in presence of aqueous HCOOH (Scheme 16).

**Scheme 16**

Das et al\(^\text{28}\) carried out a distinct approach for the synthesis of α-aminophosphonates starting with nitro compounds followed by reduction to amines using In metal in dilute aqueous hydrochloric acid at room temperature. The amine, generated in situ, was reacted with different carbonyl compounds and phosphates in the usual manner to generate the aminophosphonate derivative within 0.5-1.5 h (Scheme 17).
3D mesoporous aluminosilicate nanocage catalyst (Al-KIT-6) provided excellent yields of \( \alpha \)-aminophosphonates with a high selectivity in a short reaction time due to its high acidity, 3D pores, and a huge space in the nanocages as was demonstrated by Vinu et al.\textsuperscript{29} Different aldehydes, amines and diethyl phosphite coupled together at room temperature to generate the product (Scheme 18).

Subba Reddy and his group\textsuperscript{30} introduced nano ferric oxide as a magnetically separable catalyst for the synthesis of \( \alpha \)-aminophosphonates in solvent free conditions (Scheme 19). The major advantages of the three component coupling method are high yields, short reaction times, magnetically recyclable catalyst, and solvent-free reaction conditions. A wide variety of aldehydes and amines are compatible in this reaction.
A mild and efficient method has been devised by K. P. Boroujeni\textsuperscript{31} for the preparation of $\alpha$-aminophosphonates from three component condensation of an aldehyde, an amine, and diethyl phosphite in the presence of catalytic amounts of cross-linked polystyrene supported aluminium triflate (Ps-Al(OTf)\textsubscript{3}) under solvent-free conditions in good to excellent yields (Scheme 20). The catalyst is stable and can be easily recovered and reused without appreciable change in its efficiency.

\textbf{Scheme 20}
“A highly efficient, eco-friendly one-pot synthesis of \( \alpha \)-aminophosphonates over high surface area CuO nanopowder”

> RESULTS AND DISCUSSION

A very simple protocol was followed by the candidate. A mixture of an aldehyde, an amine and trimethyl phosphite was stirred in the presence of CuO nanopowder at solventless and ambient condition to produce a wide range of \( \alpha \)-aminophosphonates.

\[
\text{RCHO} + \text{R'NH}_2 + \text{P(OMe)}_3 \xrightarrow{\text{CuO nanopowder, solvent less, rt}} \text{OMe}
\]

> Advantage of using CuO nanopowder in this methodology

In recent years nanomaterials have attracted a great deal of attention in organic synthesis due to their high surface to volume ratio leading to larger number of active sites and their reusability. Notably, there are not many reports available in the literature for the use of non-silicious and non-supported metal oxide nanopowders in multicomponent organic synthesis.\textsuperscript{32} Crystalline CuO nanopowder proved to be an efficient catalyst under solvent free condition for the synthesis of \( \alpha \)-aminophosphonates in excellent yields. The advantage of using CuO nanopowder are as follows; a) its high surface area (101 m\(^2\)/g) compared to bulk commercial CuO (4.1 m\(^2\)/g) leading to larger number of active sites, b) the catalyst is recyclable up to 4 runs without substantial loss of activity, c) dry condition not required, d) reaction takes place smoothly, e) no side products are obtained, and f) very mild conditions are applied in the reaction. The latter ensures the use of a large number of functional groups. Therefore, CuO nanopowder is a “green catalyst” for the formation of \( \alpha \)-aminophosphonates in solvent free condition.
Physical Characterization of the CuO nanopowder

The catalyst was prepared following a triblock-copolymer templated sol-gel approach. It was characterized by SEM, X-ray diffraction study and BET surface area analysis. It is quite predictable from the SEM image of the catalyst that the material is crystalline in nature and the particle sizes are below 50 nm (Fig. 5.1). The particles are of almost of equal shape and size. To determine the crystalline nature and exact particle size, X-ray diffraction study was performed. In the wide angle study as shown in Fig. 5.2, characteristic peaks due to crystal planes appeared which confirmed its high crystalline nature. The peaks correspond to (110), (002), (111/200), (202), (020), (113), (311), (220), (311) and (222) planes of monoclinic CuO which are consistent with standard JCPDS reported values. The FWHM (Full Width at Half Maxima) values of the sharp peaks were used to determine the crystallite sizes applying Sherrer's formula \( D_p = \frac{0.94\lambda}{B\cos\theta} \) where \( D_p \) is the diameter of the particle, \( \lambda \) is the wavelength of radiation (\( \lambda = 154 \) nm), \( B \) is the corresponding FWHM value, \( \theta \) is the diffraction angle and accordingly, the particle sizes were found to lie between 18-20 nm. BET method was applied to measure the surface area which was found to be 101 m\(^2\)/g. In UV-Vis absorption spectrum the material showed a strong absorption band at 375 nm, a characteristic band for CuO nanopowder. It exhibited a blue shift due to quantum confinement effect due to very small particle size (Fig. 5.3).

Optimization of reaction conditions

In the initial study for standardization, a screening was performed with a variety of solvents taking benzaldehyde, aniline and P(OMe)\(_3\) as substrates (Table 1). Different conventional organic solvents like diethyl ether, dichloromethane, tetrahydrofuran and toluene generated low to moderate yields (entries 1-4) using CuO nanopowder as catalyst. The best result was achieved under solventless condition (entry 5) when the reaction was completed within 1h in 96% yield. A screening of catalysts was also performed using the same reaction under solventless condition. It seems pertinent to mention that the reaction did not proceed in the
absence of the catalyst. A variety of Cu salts were examined in this process. The reaction failed with Cu granules and CuO wire (entry 7-8). Bulk CuO and other homogeneous Cu catalysts like CuSO₄, Cu(OAc)₂ afforded low to moderate yields (entries 9-11). High yields were obtained with CuO supported mesoporous SBA15 and TiO₂ but the reaction took comparatively longer time for completion (entries 12-13). The corresponding products were characterized by ¹H NMR, ¹³C NMR, IR spectral and elemental analysis.

Table 1. Optimization of reaction conditions in synthesis of α-aminophosphonates*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Diethyl ether</td>
<td>CuO nanopowder</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>Dichloromethane</td>
<td>CuO nanopowder</td>
<td>6</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>Tetrahydrofuran</td>
<td>CuO nanopowder</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>CuO nanopowder</td>
<td>6</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>solvent less</td>
<td>CuO nanopowder</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>solvent less</td>
<td>no catalyst</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>solvent less</td>
<td>Cu granules</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>solvent less</td>
<td>CuO wire</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>solvent less</td>
<td>bulk CuO powder</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>solvent less</td>
<td>CuSO₄·5H₂O</td>
<td>6</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>solvent less</td>
<td>Cu(OAc)₂·H₂O</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>solvent less</td>
<td>CuO/SBA15 (20)</td>
<td>2.5</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>solvent less</td>
<td>CuO/TiO₂ (20)</td>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>

*Reaction Condition: 1.0 eq benzaldehyde, 1.0 eq aniline, 1.3 eq P(OMe)₃, room temperature stirring, 20 mg catalyst, wt % loading in parenthesis, isolated yield.
Fig. 5.1. SEM analysis of the CuO nanopowder

Fig. 5.2. X-Ray Diffraction study of the CuO nanopowder
After optimizing the reaction conditions (Table 1, entry 5), the scope and limitations of the protocol were investigated by treating a diverse range of aldehydes, both aromatic and aliphatic, with aniline and P(OMe)$_3$ in water. The results have been summarized in Table 2. Regardless of the nature of the functional groups attached to the aldehydes, all the reactions proceeded smoothly generating the corresponding α-aminophosphonates in good yields (entries 1-8). However, aromatic aldehydes containing hydroxy groups took relatively longer time for completion (entry 9-10). Methoxy aldehydes and naphthylaldehyde produced excellent yields in short time (entry 11-13). The reaction was successful with aliphatic aldehydes (entries 14-15) too. Furthermore, the reaction of different amines, both aromatic and aliphatic, with benzaldehyde and P(OMe)$_3$ (Table 3) were studied. In these cases good conversions were observed. Interestingly, aliphatic amines, viz., cyclohexylamine, pyrrolidine, piperidine and morpholine, showed faster reaction rates compared to aromatic amines possibly due to their higher basicity. The formation of α-hydroxyphosphonate as a byproduct was not observed in any of the reactions.
Table 2. One-pot synthesis of α-aminophosphonates with various aldehydes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>3a</td>
<td>1.0</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂C₆H₄</td>
<td>3b</td>
<td>0.7</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>3-NO₂C₆H₄</td>
<td>3c</td>
<td>0.5</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl C₆H₄</td>
<td>3d</td>
<td>0.5</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>4-Me C₆H₄</td>
<td>3e</td>
<td>1.0</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>4-CN C₆H₄</td>
<td>3f</td>
<td>0.7</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>4-OMe C₆H₄</td>
<td>3g</td>
<td>0.5</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>3-OMe C₆H₄</td>
<td>3h</td>
<td>1.0</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>4-OH C₆H₄</td>
<td>3i</td>
<td>2.0</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>4-OH-3-OMe C₆H₅</td>
<td>3j</td>
<td>2.0</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>3,4-di OMe C₆H₃</td>
<td>3k</td>
<td>1.0</td>
<td>89</td>
</tr>
<tr>
<td>12</td>
<td>3,4,5-tri OMe C₆H₂</td>
<td>3l</td>
<td>1.2</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>1-naphthyl</td>
<td>3m</td>
<td>0.5</td>
<td>94</td>
</tr>
<tr>
<td>14</td>
<td>CH₃CH(CH₃)</td>
<td>3n</td>
<td>0.7</td>
<td>85</td>
</tr>
<tr>
<td>15</td>
<td>CH₃CH₂</td>
<td>3o</td>
<td>1.0</td>
<td>91</td>
</tr>
</tbody>
</table>

*Reaction Condition: 1.0 eq aldehyde, 1.0 eq aniline, 1.3 eq P(OMe)₃, 20 mg catalyst, solvent less room temperature stirring; isolated yield.
Table 3. One-pot synthesis of α-aminophosphonates with various amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>Product</th>
<th>Time(h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>4a</td>
<td>0.5</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>2-Me C₆H₄</td>
<td>4b</td>
<td>0.5</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>4-Me C₆H₄</td>
<td>4c</td>
<td>0.7</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl C₆H₄</td>
<td>4d</td>
<td>0.5</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>4-Br C₆H₄</td>
<td>4e</td>
<td>1.0</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>4-OMe C₆H₄</td>
<td>4f</td>
<td>1.0</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>3-NO₂ C₆H₄</td>
<td>4g</td>
<td>1.2</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>C₆H₅CH₂</td>
<td>4h</td>
<td>0.7</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>cyclohexyl</td>
<td>4i</td>
<td>1.0</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>pyrrolidine</td>
<td>4j</td>
<td>0.5</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>piperidine</td>
<td>4k</td>
<td>0.3</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>morpholine</td>
<td>4l</td>
<td>0.3</td>
<td>88</td>
</tr>
</tbody>
</table>

*Reaction Condition: 1.0 eq benzaldehyde, 1.0 eq amine, 1.3 eq P(OMe)₃, 20 mg catalyst, solvent less room temperature stirring; isolated yield.
Reusability study of the catalyst

From the context of green approach, reusability study of the catalyst is an important criterion. This was performed through condensation of benzaldehyde, aniline, and P(OMe)₃. Under the stabilized condition the reaction was carried out in the presence of nano CuO catalyst. After completion of the reaction, the reaction mixture was centrifuged at 3000 rpm for 10 min and the supernatant layer was decanted. The deposited catalyst was collected after washing several times with acetone to remove all the organic substances. It was then dried at 80 °C for 4h and was reused 4 consecutive times with fresh batch of reactants following the same process. With all the batches the reaction proceeded smoothly with almost reproducible results each time (Fig. 5.4) which confirmed the reusability of the catalyst.

Fig. 5.4. Reusability study of CuO nanopowder with entry 1, Table 2.

Mechanistic evaluation of the reaction

From the mechanistic point of view it is believed that the nanosized Cu³⁺O, an efficient Lewis acid, is the main active site in the reaction. It promoted the formation of imines by condensation of aldehyde and amine. The activated imine then reacted with trimethyl phosphite to generate an intermediate complex. After removal of methanol and on hydrolysis
the corresponding α-aminophosphonate was produced. CuO catalyst was removed from the product and recycled with fresh batch of reactants. A probable mechanistic pathway has been proposed in Fig. 5.5.

Fig. 5.5. Probable mechanism for the CuO nanopowder catalyzed synthesis of α-aminophosphonates.

> EXPERIMENTAL

• General

$^1$H NMR and $^{13}$C NMR spectral analysis was carried out on Bruker-Avance Digital 300 MHz Spectrometer. TMS was used as internal standard. Infrared spectra were recorded in KBr pellet in reflection mode on a Perkin Elmer RX-1 FTIR spectrophotometer. SEM images
were obtained from a Hitachi S-3400N microscope at an operating voltage of 15 kV. The sample was coated with gold for effective imaging before being charged. X-Ray powder diffraction study was carried out on a Philips PW-1830 X-Ray diffractometer at a voltage of 35 kV and a current of 25 mA using CuKα radiation (λ=154 nm) at the scanning rate of 1°/minute in the 2θ range 10-80°. Melting points (uncorrected) were determined on a Köfler Block apparatus. E. Merck aluminium-backed silica gel plates coated with silica gel G were used for analytical TLC and monitored under UV light (254 and 360 nm) and also by exposing to iodine chamber. Synthetic grade chemicals from Sigma-Aldrich and E-Merck were used for the preparation of the catalyst and from Spectrochem for carrying out the organic reactions. For column chromatography neutral alumina (fine mesh) was used from Merck. All the solvents used in the reaction were distilled and dried over Na₂SO₄.

- **Typical procedure for the synthesis of CuO nanopowder**
  The catalyst was synthesized by a sol-gel EISA method (Evaporation Induced Self Assembly) templated over the non-ionic pluronic block copolymer P123 (EO20PO70EO20, M = 5800, Sigma-Aldrich). 1.0 gm of the template was dissolved in 10 mL anhydrous ethanol at room temperature to a clear solution. Then quantitative amount of Cu(NO₃)₂·3H₂O (1.2 gm, 5 mmol, E-Merck) was added. The blue solution was stirred at room temperature for 2 h. The homogeneous gel was then aged at 40 °C for 24 h for slow solvent evaporation. It was then dried at 100°C for 36 h to obtain a green mass. Finally, it was calcined at 500°C for 4 h in air by slowly increasing the temperature from room temperature (ramping rate of 5 °C/ min) to produce the black CuO nanopowder.

- **Typical procedure for the synthesis of α-aminophosphonates**
  A mixture of aldehyde (1.0 mmol), amine (1.0 mmol), trimethylphosphite (1.3 mmol) and 20 mg catalyst was stirred at room temperature in the absence of any solvent for certain periods as indicated in Tables 2 and 3. After completion of the reaction, (monitored by TLC) the
reaction mixture was diluted with dichloromethane and centrifuged to separate the catalyst for reuse. The organic layer was decanted and added to water. It was then extracted with dichloromethane (3 x 10 mL). This extract was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography using neutral alumina with ethyl acetate/hexane as eluant. All the isolated compounds were characterized by mp, FT IR, $^1$H NMR, $^{13}$C NMR and elemental analysis (C, H, and N).

> CONCLUSION

An efficient, atom economical and eco-friendly protocol for the one pot three component syntheses of α-aminophosphonates over CuO nanopowder as catalyst has been developed. The striking features of this protocol include (i) room temperature reaction under solvent free condition, (ii) operational simplicity, (iii) highly expeditious, (iv) high yields and (v) recyclable catalyst.

> PUBLICATION

“A Highly Efficient, one-pot synthesis of α-aminophosphonates over CuO nanopowder”

Bikash Karmakar, Sanjay Paul and Julie Banerji*

SPECTROSCOPIC DATA OF SOME CHARACTERISTIC COMPOUNDS

Dimethyl-α-(N-anilino)-α-(phenyl)methylphosphonate

Yield 252 mg; white solid; mp 88 °C; IR (KBr): 3305, 3025, 2955, 1601, 1499, 1241, 1034, 763.5, 699 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.49 (d, J = 11.0 Hz, 3H), 3.72 (d, J = 10.6 Hz, 3H), 4.78 (m, 1H), 4.85 (m, 1H), 6.59 (d, J = 8.1 Hz, 2H), 6.7 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.5 Hz, 2H), 7.25-7.37 (m, 3H), 7.46 (d, J = 7.5 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 53.7, 54.7, 56.7, 113.87, 127.73, 128.05, 128.7, 129.16, 135.61, 145.98; Anal. calcd for C₁₅H₁₈N₂O₃P: C, 61.85; H, 6.18; N, 4.81%. Found: C, 61.91; H, 6.22; N, 4.72%.

Dimethyl-α-(N-anilino)-α-(4-nitrophenyl)methylphosphonate

Yield 200 mg; yellow solid; mp 95 °C; IR (KBr): 3308, 3066, 2951, 1602, 1525, 1344, 1247, 1050, 853, 695 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.62 (d, J = 10.8 Hz, 3H), 3.79 (d, J = 10.8 Hz, 3H), 4.82 (m, 1H), 4.92 (m, 1H), 6.54 (d, J = 8.4 Hz, 2H), 6.75 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 2H), 7.66 (d, J = 7.5 Hz, 2H), 8.21 (d, J = 8.7 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 54.1, 54.6, 56.6, 113.85, 119.3, 123.9, 128.61, 129.39, 143.63, 145.4, 147.72; Anal. calcd for C₁₅H₁₈N₂O₃P: C, 53.57; H, 5.06; N, 8.33%. Found: C, 53.63; H, 5.11; N, 8.38%.

Dimethyl-α-(N-anilino)-α-(3-nitrophenyl)methylphosphonate

Yield 196 mg; yellow crystalline solid; mp 98 °C; IR (KBr): 3290, 3033, 1602, 1526, 1349, 1243, 1043, 836 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.62 (d, J = 10.8 Hz, 3H), 3.8 (d, J = 10.8 Hz, 3H), 4.85-4.97 (m, 2H), 6.57 (d, J = 7.8 Hz, 2H), 6.74 (t, J =
7.4 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 8.34 (d, J = 1.8 Hz, 1H); $^1$C NMR (CDCl$_3$, 75.5 MHz): δ 53.8, 54.0, 55.2, 56.0, 113.9, 114.7, 127.32, 128.85, 128.93, 129.14, 146.1, 159.4; Anal. calcd for C$_{15}$H$_7$N$_2$O$_5$P: C, 53.57; H, 5.06; N, 8.33%. Found: C, 53.49; H, 5.17; N, 8.45%.

> **Dimethyl-α-(N-anilino)-α-(4-Chlorophenyl)methylphosphonate**

Yield 211 mg; white solid; mp 60 °C; IR (KBr): 3319, 3029, 2953, 1603, 1497, 1233, 1030, 756 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 3.55 (d, J = 10.8 Hz, 3H), 3.77 (d, J = 10.5 Hz, 3H), 4.74 (m, 1H), 4.80 (m, 1H), 6.56 (d, J = 8.7 Hz, 2H), 6.72 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.9 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.4 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): δ 53.8, 54.0, 56.2, 113.85, 118.11, 128.9, 129.1, 129.23, 133.9, 134.23, 145.75; Anal. calcd for C$_{15}$H$_7$NO$_5$PCl: C, 55.30; H, 5.22; N, 4.30%. Found: C, 55.36; H, 5.17; N, 4.21%.

> **Dimethyl-α-(N-anilino)-α-(4-Methylphenyl)methylphosphonate**

Yield 211 mg; white solid; mp 114 °C; IR (KBr): 3312, 3028, 2953, 1603, 1508, 1231, 1031, 755 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 2.31 (s, 3H), 3.49 (d, J = 10.5 Hz, 3H), 3.76 (d, J = 10.8 Hz, 3H), 4.72 (d, J = 7.5 Hz, 1H), 4.81 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 7.8 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 7.11 (m, 4H), 7.35 (d, J = 7.8 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): δ 21.1, 53.8, 54.4, 56.4, 113.9, 127.6, 127.7, 129.14, 129.45, 132.4, 137.8, 146.12; Anal. calcd for C$_{16}$H$_{20}$NO$_5$P: C, 62.95; H, 6.56; N, 4.59%. Found: C, 62.87; H, 6.61; N, 4.55%.
> **Dimethyl-α-(N-anilino)-α-(4-Cyanophenyl)methylphosphonate**

Yield 230 mg; white solid; mp 121 °C; IR (KBr): 3331, 2954, 2225, 1602, 1506, 1243, 1032, 839, 747 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.58 (d, J = 10.8 Hz, 3H), 3.76 (d, J = 10.8 Hz, 3H), 4.79 (bs, 1H), 4.87 (s, 1H), 6.52 (d, J = 8.4 Hz, 2H), 6.72 (t, J = 7.4 Hz, 1H), 7.10 (d, J = 7.2 Hz, 2H), 7.56-7.64 (m, 4H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 54.0, 54.7, 56.7, 111.96, 113.8, 118.48, 119.17, 128.48, 129.34, 132.43, 141.6, 145.5; Anal. calcd for C₁₆H₁₅N₂O₄P: C, 60.76; H, 5.38; N, 8.86%. Found: C, 60.71; H, 5.33; N, 8.92%.

> **Dimethyl-α-(N-anilino)-α-(4-Methoxyphenyl)methylphosphonate**

Yield 222 mg; white solid; mp 123 °C; IR (KBr): 3292, 2952, 1603, 1504, 1242, 1025, 842, 757 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.50 (d, J = 10.5 Hz, 3H), 3.76 (d, J = 10.5 Hz, 3H), 3.78 (s, 3H), 4.71 (s, 1H), 4.79 (s, 1H), 6.60 (d, J = 7.8 Hz, 2H), 6.70 (t, J = 6.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 2H), 7.11 (t, J = 7.9 Hz, 2H), 7.39 (d, J = 7.2 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 53.75, 54.0, 55.2, 56.0, 113.9, 114.7, 127.32, 128.85, 128.93, 129.14, 146.1, 159.4; Anal. calcd for C₁₆H₂₀N₂O₄P: C, 59.81; H, 6.23; N, 4.36%. Found: C, 59.73; H, 6.19; N, 4.42%.

> **Dimethyl-α-(N-anilino)-α-(3-Methoxyphenyl)methylphosphonate**

Yield 203 mg; white solid; mp 65 °C; IR (KBr): 3308, 3011, 2949, 1598, 1493, 1262, 1231, 1033, 753 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.51 (d, J = 10.5 Hz, 3H), 3.78 (d, J = 10.8 Hz, 3H), 3.80 (s, 3H), 4.73 (m, 1H), 4.80 (m, 1H), 6.61 (dd, J = 3.5 Hz, 7.8 Hz, 2H), 6.68-6.74 (m, 1H), 6.82 (d, J = 8.1 Hz, 1H); ¹³C NMR
(CDCl₃, 75.5 MHz): δ 53.83, 54.71, 55.32, 56.7, 113.39, 113.46, 113.86, 118.58, 120.14, 129.2, 129.7, 137.24, 146.2, 159.9.

> **Dimethyl-α-(N-anilino)-α-(4-Hydroxyphenyl)methylphosphonate**

Yield 196 mg; pale yellow solid; mp 86 °C IR (KBr): 3365, 3119, 1604, 1511, 1218, 1035, 843, 753 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.54 (d, J = 10.5 Hz, 3H), 3.77 (d, J = 10.5 Hz, 3H), 4.71 (s, 1H), 4.8 (s, 1H), 6.61 (d, J = 8.1 Hz, 2H), 6.71 (d, J = 8.4 Hz, 3H), 7.11 (t, J = 7.8 Hz, 2H), 7.25 (d, J = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 51.9, 54.03, 54.3, 114.0, 121.9, 125.7, 129.7, 130.1, 131.2, 135.0, 149.2; Anal. calcd for C₁₅H₁₈N₀₄P: C, 58.63; H, 5.86; N, 4.56%. Found: C, 58.57; H, 5.79; N, 4.65%.

> **Dimethyl-α-(N-anilino)-α-(3,4-Dimethoxyphenyl)methylphosphonate**

Yield 187 mg; white solid; mp 78 °C; IR (KBr): 3293, 3108, 2953, 1601, 1513, 1457, 1241, 1036, 756 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.52 (d, J = 10.5 Hz, 3H), 3.76 (d, J = 10.5 Hz, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.69 (s, 1H), 4.77 (s, 1H), 6.61 (d, J = 8.2 Hz, 2H), 6.71 (t, J = 7.4 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 7.1 (t, J = 9.3 Hz, 2H), 7.0 (m, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 53.83, 54.71, 55.32, 56.7, 113.39, 113.46, 113.86, 118.58, 120.14, 129.2, 129.7, 137.24, 146.2, 159.9; Anal. calcd for C₁₇H₂₂NO₄P: C, 58.12; H, 6.27; N, 3.99%. Found: C, 58.07; H, 6.15; N, 4.11%.

> **Dimethyl-α-(N-anilino)-α-(3,4,5-Trimethoxyphenyl)methylphosphonate**

Yield 175 mg; white solid; mp 138 °C; IR (KBr): 3303, 2951, 1598, 1505, 1457, 1246, 1125, 1054, 829, 751 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.52 (d, J = 10.5 Hz, 3H), 3.76 (d, J =
10.5 Hz, 3H), 3.81 (s, 3H), 3.84 (s, 6H), 4.65 (d, J = 7.5 Hz, 1H), 4.75 (d, J = 8.8 Hz, 1H),
6.62 (d, J = 8.1 Hz, 2H), 6.7 (s, 2H), 6.74 (t, J = 8.8 Hz, 1H),
7.13 (t, J = 7.8 Hz, 2H); 13C NMR (CDCl3, 75.5 MHz): δ 53.7, 53.8, 55.0, 56.2, 59.0, 60.2, 113.84, 118.7, 129.2, 131.2, 146.04, 146.3; Anal. calcd for C18H24NO5P: C, 56.7; H, 6.3; N, 3.67%. Found: C, 56.62; H, 6.34; N, 3.61%.

➤ Dimethyl-α-(N-anilino)-α-(1-naphthyl)methylphosphonate

Yield 208 mg; white solid; mp 132 °C; IR (KBr): 3308, 3027, 1949, 1601, 1236, 1054, 1026, 830 cm⁻¹; 1H NMR (CDCl3, 300 MHz): δ 3.15 (d, J = 10.5 Hz, 3H), 3.81 (d, J = 10.8 Hz, 3H), 5.06 (t, J = 8.7 Hz, 1H), 5.67 (dd, J = 7.7 Hz, 7.7 Hz, 1H), 6.55 (d, J = 8.1 Hz, 2H), 6.66 (t, J = 7.3 Hz, 1H), 7.05 (t, J = 7.9 Hz, 2H), 7.45 (t, J = 7.7 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.79 (d, J = 9.1 Hz, 2H), 7.91 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 8.7 Hz, 1H); 13C NMR (CDCl3, 75.5 MHz): δ 50.2, 52.2, 53.7, 113.6, 118.1, 118.4, 122.6, 125.5, 125.6, 125.7, 126.5, 128.6, 128.7, 129.2, 131.3, 131.4, 133.8, 145.9; Anal. calcd for C19H20NO3P: C, 66.86; H, 5.86; N, 4.10%. Found: C, 66.91; H, 5.83; N, 4.06%.

➤ Dimethyl-α-(N-anilino)-α-(isopropyl)methylphosphonate

Yield 303 mg; white solid; mp 74 °C; IR (KBr): 3345, 2962, 1603, 1500, 1239, 1048, 827, 749 cm⁻¹; 1H NMR (CDCl3, 300 MHz): δ 1.09 (m, 6H), 2.17-2.31 (m, 1H), 3.32-3.49 (m, 1H), 3.65 (d, J = 10.2 Hz, 3H), 3.72 (d, J = 10.5 Hz, 3H), 6.66 (d, J = 8.1 Hz, 2H), 6.74 (t, J = 8.5 Hz, 1H), 7.16 (t, J = 7.8 Hz, 2H); 13C NMR (CDCl3, 75.5 MHz): δ 18.0, 20.39, 20.55, 52.3, 53.27, 57.05, 113.2, 118.0, 129.3, 147.45;
Anal. calcd for C_{12}H_{20}NO_{3}P: C, 56.03; H, 7.78; N, 5.45%. Found: C, 56.11; H, 7.71; N, 5.43%.

- **Dimethyl α-anilino-α-(ethyl)methylphosphonate**
  Yield 340 mg; white crystals; mp 40 °C; IR (KBr): 3432, 3029, 2373, 1629, 1456, 1236, 1040, 702 cm⁻¹; ′H NMR (CDCl₃, 300 MHz): δ 1.03 (t, J = 7.4 Hz, 3H), 1.62-1.76 (m, 1H), 1.91-2.05 (m, 1H), 2.15 (s, 1H), 3.52 (d, J = 10.4 Hz, 3H), 3.73 (d, J = 10.8 Hz, 3H), 6.65 (d, J = 8.1 Hz, 2H), 6.71 (t, J = 7.2 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H); ′C NMR (CDCl₃, 75.5 MHz): δ 10.6, 23.9, 51.1, 52.6, 53.6, 113.2, 118.2, 129.3, 147.0. Anal. Calcd for C₁₁H₁₇NO₃P: C, 54.54; H, 7.02; N, 5.76%. Found: C, 54.39; H, 7.45; N, 5.67%.

- **Dimethyl α-anilino-α-cyclohexylphosphonate**
  Yield 245 mg; white solid; IR (KBr): 3324.1, 2948.2, 2861.5, 1601.3, 1497.4, 1319.8, 1226.8, 1016.8, 822.2, 758.1, 580.5 cm⁻¹; ′H NMR (CDCl₃, 300 MHz): δ 1.25-2.24 (m, 10H), 3.68 (d, J = 10.2 Hz, 6H), 6.84 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.8 Hz, 2H), 7.18 (t, J = 7.8 Hz, 2H); ′C NMR (CDCl₃, 75.5 MHz): δ 19.9, 25.2, 30.3, 52.9, 118.41, 119.53, 128.77, 145.55; Anal. Calcd for C₁₄H₂₂NO₃P: C, 59.36; H, 7.77; N, 4.95%. Found: C, 59.42; H, 7.69; N, 4.93%.

- **Dimethyl α-anilino-α-cyclopentylphosphonate**
  Yield 243 mg; reddish heavy oil; IR (KBr): 3310.3, 2952.2, 2372.7, 1601.6, 1496.6, 1323.1, 1227.7, 1045.5, 1018.9, 825.0, 754.0 cm⁻¹; ′H NMR (CDCl₃, 300 MHz): δ 1.71-1.76 (m, 4H), 2.03-2.19 (m, 4H), 3.71 (d, J = 10.2 Hz, 6H), 6.78 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 7.8 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H); ′C NMR (CDCl₃, 75.5 MHz): δ...
Dimethyl-α-(N-2-methylanilino)-α-(phenyl)methylphosphonate

Yield 238 mg; white powder; mp 48 °C; IR (KBr): 3418, 3028, 2956, 1596, 1507, 1543, 1240, 1047, 832 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 2.2 (s, 3H), 3.40 (d, \(J = 10.5\) Hz, 3H), 3.68 (d, \(J = 10.5\) Hz, 3H), 4.56 (br s, 1H), 4.71 (s, 1H), 6.32 (d, \(J = 7.8\) Hz, 1H), 6.57 (t, \(J = 7.4\) Hz, 1H), 6.87 (t, \(J = 7.8\) Hz, 1H), 6.97 (d, \(J = 7.2\) Hz, 1H), 7.17-7.28 (m, 3H), 7.38 (d, \(J = 6.1\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75.5 MHz): \(\delta\) 17.5, 53.8, 54.7, 56.7, 111.3, 118.2, 123.0, 126.9, 127.6, 128.0, 128.7, 130.2, 135.7, 144.0; Anal. calcd for C\(_{16}\)H\(_{20}\)NO\(_3\)P: C, 62.95; H, 6.58; N, 4.59%. Found: C, 62.89; H, 6.55; N, 4.67%.

Dimethyl-α-(N-4-methylanilino)-α-(phenyl)methylphosphonate

Yield 254 mg; white powder; mp 80 °C; IR (KBr): 3427, 3297, 2952, 1614, 1518, 1268, 1027, 824 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 2.18 (s, 3H), 3.48 (d, \(J = 10.5\) Hz, 3H), 3.76 (d, \(J = 10.8\) Hz, 3H), 4.69 (t, \(J = 9.4\) Hz, 1H), 4.81 (d, \(J = 6.0\) Hz, 1H), 4.61 (d, \(J = 8.1\) Hz, 2H), 6.91 (d, \(J = 8.1\) Hz, 2H), 7.28-7.36 (m, 3H), 7.46 (d, \(J = 7.2\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 75.5 MHz): \(\delta\) 20.32, 53.8, 55.01, 57.0, 114.04, 127.8, 128.0, 128.02, 129.69, 135.74, 143.73; Anal. calcd for C\(_{16}\)H\(_{20}\)NO\(_3\)P: C, 62.95%; H, 6.58; N, 4.59%. Found: C, 63.02; H, 6.54; N, 4.53%.

Dimethyl-α-(N-4-chloroanilino)-α-(phenyl)methylphosphonate

Yield 229 mg; white powder; mp 112 °C; IR (KBr): 3410, 3291, 2953, 1597, 1497, 1239, 1032, 829 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300...
Dimethyl-α-(N-4-bromoanilino)-α-(phenyl)methylphosphonate

Yield 304 mg; white powder; mp 60 °C; IR (KBr): 3310, 3006, 2952, 1593, 1492, 1238, 1029, 818 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.38 (d, J = 10.5 Hz, 3H), 3.68 (d, J = 10.8 Hz, 3H), 4.66 (dd, J = 7.8 Hz, 7.8 Hz, 1H), 4.83 (t, J = 8.6 Hz, 1H), 6.40 (d, J = 8.7 Hz, 2H), 7.1 (d, J = 8.7 Hz, 2H), 7.19–7.29 (m, 3H), 7.37 (d, J =7.5 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 53.8, 54.7, 56.7, 110.3, 115.5, 127.4, 128.2, 128.8, 131.9, 135.0, 145.1; Anal. calcd for C₁₅H₁₇BrNO₃P: C, 48.65; H, 4.59; N, 3.78%. Found: C, 48.72; H, 4.62; N, 3.69%.

Dimethyl-α-(N-4-methoxyanilino)-α-(phenyl)methylphosphonate

Yield 211 mg; white powder; mp 58°C; IR (KBr): 3297.3, 2951.2, 2837.3, 1515.2, 1454.5, 1240.4, 1036.6, 820.2, 786.1, 639.4, 573.6 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.48 (d, J = 10.5 Hz, 3H), 3.75 (s, 3H), 3.82 (d, J = 10.8 Hz, 3H), 4.68 (d, J = 5.4 Hz, 1H), 4.75 (t, J = 6.0 Hz, 1H), 6.55 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 7.29–7.36 (m, 3H), 7.45 (d, J = 7.5 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 53.71, 53.87, 55.63, 57.66, 114.76, 115.31, 127.81, 128.03, 128.68, 135.75, 140.1, 152.79; Anal. calcd for C₁₆H₂₀NO₄P: C, 59.81; H, 6.23; N, 4.36%. Found: C, 59.73; H, 6.29; N, 4.31%.
> **Dimethyl-α-(N-3-nitroanilino)-α-(phenyl)methylphosphonate**

Yield 267 mg; bright yellow crystals; mp 130 °C; IR (KBr): 3281, 3082, 2954, 1622, 1533, 1347, 1234, 1030, 819 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 3.40 (d, \(J = 10.6\) Hz, 3H), 3.72 (d, \(J = 10.6\) Hz, 3H), 4.73 (m, 1H), 5.53 (t, \(J = 8.6\) Hz, 1H), 6.81 (d, \(J = 7.5\) Hz, 1H), 7.17 (m, 1H), 7.27 (m, 3H), 7.42 (m, 5H); \(^13\)C NMR (CDCl\(_3\), 75.5 MHz): \(\delta\) 53.7, 54.1, 56.4, 108.0, 113.0, 119.4, 127.8, 128.4, 128.9, 129.7, 134.5, 147.1, 149.2; Anal. calcd for C\(_{15}\)H\(_{17}\)N\(_2\)O\(_3\)P: C, 53.57; H, 5.06; N, 8.33%. Found: C, 53.51; H, 5.11; N, 8.39%.

> **Dimethyl-α-(N-cyclohexylamino)-α-(phenyl)methylphosphonate**

Yield 260 mg; Yellow oil; IR (neat): 3441.9, 2925.7, 1620.5, 1395.5, 1034.3 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.02-2.17 (m, 11H), 2.33 (bs, 1H), 3.50 (d, \(J = 10.5\) Hz, 3H), 3.77 (d, \(J = 10.5\) Hz, 3H), 4.23 (d, \(J = 22.0\) Hz, 1H), 7.27-7.41 (m, 5H); \(^13\)C NMR (CDCl\(_3\), 75.5 MHz): \(\delta\) 24.4, 24.85, 26.02, 31.9, 34.3, 53.4, 53.9, 56.3, 58.3, 127.8, 128.36, 128.47, 136.41; Anal. calcd for C\(_{15}\)H\(_{24}\)NO\(_3\)P: C, 60.61; H, 8.08; N, 4.79%. Found: C, 60.58; H, 8.12; N, 4.79%.

> **Dimethyl-α-(N-Pyrrolido)-α-(phenyl)methylphosphonate**

Yield 223 mg; Yellow oil; IR (neat): 3409.3, 2957.5, 1654.9, 1460, 1231.6, 1083.1, 1049.4, 767.0, 554.5 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.73 (s, 4H), 2.62 (s, 4H), 3.42 (d, \(J = 10.2\) Hz, 3H), 3.72 (d, \(J = 10.2\) Hz, 3H), 3.81 (s, 1H), 7.29-7.39 (m, 3H), 7.46 (d, \(J = 7.5\) Hz, 2H); \(^13\)C NMR (CDCl\(_3\), 75.5 MHz): \(\delta\) 23.2, 52.8, 52.9, 53.3, 53.4, 127.97, 128.24, 129.82, 136.3; Anal. calcd for C\(_{15}\)H\(_{20}\)NO\(_3\)P: C, 57.99; H, 7.43; N, 5.20%. Found: C, 57.91; H, 7.36; N, 5.24%.
DimethyI-α-(N-Piperido)-α-(phenyl)methylphosphonate

Yield 230 mg; Pale white solid; mp 69 °C; IR (KBr): 3407.5, 1649.8, 1459.3, 1227.9, 1080.1, 1050.2, 791.0, 709.2, 555.5 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.2-1.28 (m, 2H), 1.49-1.54 (m, 4H), 2.29-2.34 (m, 2H), 2.7-2.77 (m, 2H), 3.40 (d, J = 10.5 Hz, 3H), 3.82 (d, J = 10.2 Hz, 3H), 3.89 (s, 1H), 7.26-7.32 (m, 3H), 7.39 (d, J = 6.6 Hz, 2H); ¹³C NMR (CDCl₃, 75.5 MHz): δ 24.0, 26.42, 52.44, 52.6, 52.64, 54.1, 128.0, 130.41, 130.53, 132.2; Anal. calcd for C₁₄H₂₂NO₃P: C, 59.36; H, 7.77; N, 4.95%. Found: C, 59.31; H, 7.71; N, 4.89%.
Fig. 5.6.1 $^1$H NMR (CDCl$_3$) spectrum of Dimethyl-$\alpha$-(N-anilino)-$\alpha$-(phenyl) methylphosphonate

Fig. 5.6.2 $^1$H NMR (CDCl$_3$) spectrum of Dimethyl-$\alpha$-(N-anilino)-$\alpha$-(4-nitrophenyl) methylphosphonate
Fig. 5.6.3 $^1$H NMR (A) (CDCl$_3$) and IR (B) (KBr) spectra of Dimethyl-$\alpha$-(N-anilino)-$\alpha$-(3-nitrophenyl) methylphosphonate
Fig. 5.6.4 $^1$H NMR (CDCl$_3$) spectrum of Dimethyl-$\alpha$-(N-anilino)-$\alpha$-(4-chlorophenyl) methylphosphonate

Fig. 5.6.5 $^1$H NMR (CDCl$_3$) spectrum of Dimethyl-$\alpha$-(N-anilino)-$\alpha$-(4-methylphenyl) methylphosphonate
Fig. 5.6.6 $^1$H NMR (CDCl$_3$) spectrum of Dimethyl-\(\alpha\)-(N-anilino)-\(\alpha\)-(4-cyanophenyl) methylphosphonate

Fig. 5.6.7 $^1$H NMR (CDCl$_3$) spectrum of Dimethyl-\(\alpha\)-(N-anilino)-\(\alpha\)-(4-methoxylphenyl) methylphosphonate
Fig. 5.6.8 $^1$H NMR (A) (CDCl$_3$) and IR (B) (KBr) spectra of Dimethyl-α-(N-anilino)-α-(3-methoxyphenyl) methylphosphonate
Fig. 5.6.9 $^1$H NMR (A) and $^{13}$C NMR (B) (CDCl$_3$) spectra of Dimethyl-α-(N-anilino)-α-(3,4-dimethoxyphenyl) methylphosphonate
Fig. 5.6.10. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-α-(N-anilino)-α-(3,4,5-trimethoxyphenyl) methylphosphonate

Fig. 5.6.11. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-α-(N-anilino)-α-(naphthyl) methylphosphonate
Fig. 5.6.12. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-α-(N-anilino)-α-(isopropyl) methylphosphonate

Fig. 5.6.13. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-α-(N-anilino)-α-(ethyl)methylphosphonate
Fig. 5.6.14. $^1$H NMR (A) and $^{13}$C NMR (B) (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-2-methylanilino)-$\alpha$-(phenyl) methylphosphonate.
Fig. 5.6.15. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-4-methylanilino)-$\alpha$-(phenyl) methylphosphonate

Fig. 5.6.16. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-4-chloroanilino)-$\alpha$-(phenyl) methylphosphonate
Fig. 5.6.17. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-4-bromoanilino)-$\alpha$-(phenyl)methylphosphonate

Fig. 5.6.18. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-4-methoxyanilino)-$\alpha$-(phenyl)methylphosphonate
Fig. 5.6.19. $^{13}$C NMR (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-3-nitroanilino)-$\alpha$-(phenyl) methylphosphonate

Fig. 5.6.20. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-$\alpha$-(N-cyclohexylamino)-$\alpha$-(phenyl) methylphosphonate
Fig. 5.6.21. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-α-(N-piperido)-α-(phenyl) methylphosphonate

Fig. 5.6.22. $^1$H NMR (CDCl$_3$) spectra of Dimethyl-α-(N-morpholino)-α-(phenyl) methylphosphonate
References


