



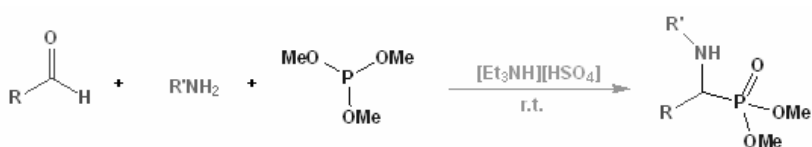
## SYNTHESIS OF $\alpha$ -AMINOPHOSPHONATES IN THE PRESENCE OF TRIETHYLAMMONIUM HYDROGEN SULFATE $[\text{Et}_3\text{NH}][\text{HSO}_4]$ AS A HIGHLY EFFICIENT IONIC LIQUID CATALYST

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Triethylammonium hydrogen sulfate was used as a cheap and mild acidic ionic liquid for efficient, one-pot, three-component reaction of aldehydes, amines and trimethyl phosphite. Thus  $\alpha$ -aminophosphonates were synthesized at room temperature in excellent yields. The ionic liquid catalyst is air and water stable, easy to prepare from amine and acid and easily separated from the reaction mixture.



### INTRODUCTION

Synthesis of  $\alpha$ -aminophosphonates have attracted intense interest due to structure analogues of amino acid and their diverse pharmacological properties like anticancer, antiviral, herbicides, fungicides, bactericides, peptide mimetics and enzyme inhibitors.<sup>1-5</sup>

In view of their versatile pharmaceutical importance, various methods have been developed for the synthesis of  $\alpha$ -aminophosphonates.<sup>6</sup> Of these, the Kabachnik–Fields reaction of aldehydes, amines, and phosphites is of great interest. Numerous protocols for this conventional synthesis include employment of various catalytic systems such as Lewis acids,<sup>7-9</sup> Brønsted acids,<sup>10</sup> heterogeneous catalysts,<sup>11-13</sup> metal triflates<sup>14-16</sup> and perchlorate<sup>17-19</sup> have been utilized. Owing to their synthetic and biological values, there is still need to develop new accessible, environmentally benign and efficient protocol for the preparation of  $\alpha$ -aminophosphonates.

Ionic Liquids (ILs) have attracted much attention in the scientific community during the past two decades. The application of ILs is growing continuously due to their attractive properties. They have very low vapor pressure and are nonexplosive and thermally stable in a wide temperature range.<sup>20</sup> So they are not volatile and therefore not harmful to environment; hence, green solvents are replacing volatile organic solvents and unsafe catalysts. They also obey the 12 principles of green chemistry such as atom economy, recyclability, safety etc.<sup>21</sup> Now ionic liquids have been used as environmentally benign solvents or catalysts for a number of chemical processes.<sup>20-21</sup> Some ionic liquids such as sulfonic acid functionalized ionic liquids,<sup>22-24</sup> 1-benzyl-3-methyl imidazolium hydrogen sulphate,<sup>25</sup> and  $[\text{bmim}][\text{AlCl}_4]$ <sup>26</sup> have been reported to catalyze the synthesis of  $\alpha$ -aminophosphonates, however, they suffer from various drawbacks such as high cost, difficulty in synthesis and separation, unstable to moisture, etc.

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In addition, ionic liquids have not been widely applied in industry due to high cost of ionic liquids, the difficulty in separation or recycling, the paucity of data with regard to their toxicity and biodegradability, and so on. To overcome these problems, some new ionic liquids have been prepared by a simple and atom economic acid–base neutralization reaction.<sup>27</sup>

## RESULTS AND DISCUSSION

Due to extending our interest to develop efficient methods for the synthesis of  $\alpha$ -aminophosphonates,<sup>28–31</sup> herein, we describe the utility of triethylammonium hydrogen sulfate for the Kabachnik–Fields reaction of aldehydes, amines, and trimethyl phosphite (Scheme 1).

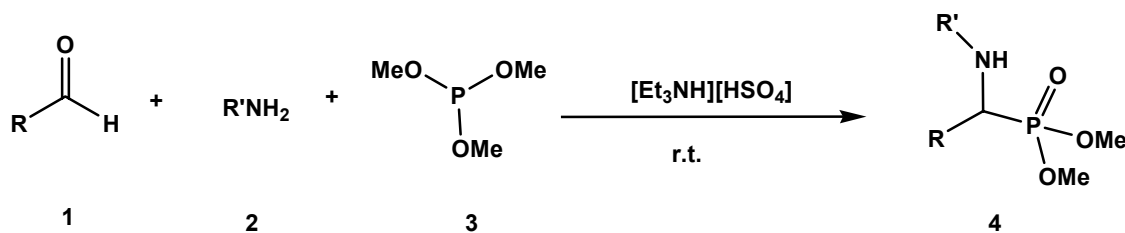
Triethylammonium hydrogen sulfate ( $[\text{Et}_3\text{NH}][\text{HSO}_4]$ ) was easily prepared from triethyl amine and sulfuric acid without using any solvent. This is a low cost due to using cheap amine and acid, mild, non-volatile and non-corrosive acidic ionic liquid and has been utilized as a catalyst for the cracking of dialkoxypropanes,<sup>27</sup> synthesis of quinoline,<sup>32</sup> thiazolidine and oxazolidine derivatives.<sup>33</sup>

To find out the suitable conditions for the reaction, a series of experiments were performed with the standard reaction of benzaldehyde, aniline, and trimethyl phosphite as a model reaction. The reactions were scrutinized using different conditions. The best results have been

obtained at room temperature with equal molar ratio (1 mmol) of benzaldehyde, aniline and trimethyl phosphite using 0.1 g of  $[\text{Et}_3\text{NH}][\text{HSO}_4]$ .

Under the optimal reaction conditions, a range of aldehydes were treated with different anilines and trimethyl phosphite in order to examine the scope of the three-component reaction. Several representative examples are summarized in Table 1. Variety of functional groups present in the aryl aldehydes and aniline such as halogen, methoxy, hydroxyl, cyano, and nitro groups were tolerated (see Table 1). It was found that most of the reactions proceeded smoothly to afford the corresponding  $\alpha$ -aminophosphonates in good to excellent yields (75–97%). These reactions proceeded very cleanly under mild conditions at room temperature, and no side reactions were observed.

To show the merit of the present work in comparison with results reported in the literature, we compared results of the reaction of benzaldehyde, aniline and trimethyl phosphite in the presence of  $[\text{Et}_3\text{NH}][\text{HSO}_4]$  with some of the other catalysts used for the similar reaction (Table 2). Similarly, a comparative study of five reported ionic liquids is presented in Table 2 (entries 7–11). As Table 2 indicates,  $[\text{Et}_3\text{NH}][\text{HSO}_4]$  is superior to the previously reported catalysts in term of simplicity, low cost, ease of preparation and separation of the catalytic system.



Scheme 1 – Synthesis of  $\alpha$ -aminophosphonates.

Table 1

Synthesis of  $\alpha$ -aminophosphonates in the presence of  $[\text{Et}_3\text{NH}][\text{HSO}_4]$

Entry	Aldehyde	Amine	product	Time/min	Yield/%	Ref. <sup>a</sup>
1	$\text{C}_6\text{H}_5\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4a</b>	15	96	11
2	4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4b</b>	15	95	19
3	4- $\text{ClC}_6\text{H}_4\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4c</b>	10	95	11
4	4- $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4d</b>	10	92	24
5	4- $\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4e</b>	15	97	19
6	4- $\text{CNC}_6\text{H}_4\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4f</b>	30	93	30
7	4- $\text{OHC}_6\text{H}_4\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4g</b>	15	89	30
8	2,4- $\text{Cl}_2\text{C}_6\text{H}_3\text{CHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4h</b>	25	91	12
9	$\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$	$\text{C}_6\text{H}_5\text{NH}_2$	<b>4i</b>	60	95	30
10	4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$	4- $\text{ClC}_6\text{H}_4\text{NH}_2$	<b>4j</b>	10	86	13
11	4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$	4- $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$	<b>4k</b>	10	80	30

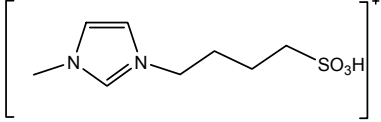
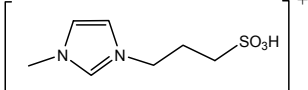
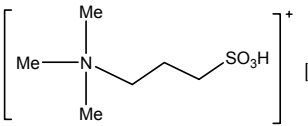
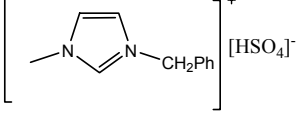
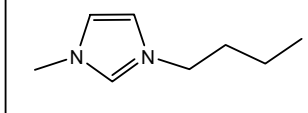
Table 1 (continued)

12	C <sub>6</sub> H <sub>5</sub> CHO	4-ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<b>4l</b>	60	93	30
13	C <sub>6</sub> H <sub>5</sub> CHO	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<b>4m</b>	60	95	30
14	C <sub>6</sub> H <sub>5</sub> CHO	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>4n</b>	15	96	15
15	4-ClC <sub>6</sub> H <sub>4</sub> CHO	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>	<b>4o</b>	30	91	30
16	4-OHC <sub>6</sub> H <sub>4</sub> CHO	4-ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<b>4p</b>	10	87	30

<sup>a</sup> All products are known compounds and their structures were verified by comparison of their physical and spectral data with these appreciate references.

Table 2

Comparison of efficiency of various catalysts in the reaction of benzaldehyde, aniline and trimethyl phosphite<sup>a</sup>

Entry	Catalyst	Reaction conditions	time	Yield/%	Ref.
1	H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub> (0.5 mol%)	CH <sub>2</sub> Cl <sub>2</sub> , r.t.	25 min	94	11
2	Silica sulfuric acid (10 mol%)	Acetonitrile, r.t.	5 h	87	12
3	graphene oxide (3mg)	Methanol, r.t.	3 h	88	13
4	Cu(OTf) <sub>2</sub> (1 mol %)	Acetonitrile, 25°C	5 h	84	15
5	Cd(ClO <sub>4</sub> ) <sub>2</sub> ·xH <sub>2</sub> O (5 mol%)	40 °C, solvent-free	45 min	92	17
6	LiClO <sub>4</sub> 2equiv.	under argon, r.t.	45 min	92	19
7	 [CF <sub>3</sub> SO <sub>3</sub> ] <sup>-</sup>	10 mol% catalyst, H <sub>2</sub> O, r.t.	10 min	98	22
8	 [HSO <sub>4</sub> ] <sup>-</sup>	100 mol %, catalyst, H <sub>2</sub> O, r.t.	30 min	92	23
9	 [HSO <sub>4</sub> ] <sup>-</sup>	50 mol% catalyst, H <sub>2</sub> O, r.t.	10	95	24
10	 [HSO <sub>4</sub> ] <sup>-</sup>	50 mol% catalyst, r.t.	10 min	96	25
11	 [AlCl <sub>4</sub> ] <sup>-</sup>	10 mol% catalyst, EtOH, Ultrasonic irradiation,	5 min	91	26
12	[Et <sub>3</sub> NH][HSO <sub>4</sub> ]	50 mol% catalyst, r.t.	15 min	96	This work

<sup>a</sup> triethyl phosphite has been utilized in entries 2,8,10

## EXPERIMENTAL

All reagents were commercially available and used without further purification. Melting points were measured by an electrothermal type 9100 melting point apparatus. The infrared (IR) spectra were recorded on a Bruker Tensor 27 FTIR spectrophotometer as KBr disks. NMR spectra were determined on a Bruker AC 400 MHz spectrometer as CDCl<sub>3</sub> solutions.

Triethylammonium hydrogen sulfate [Et<sub>3</sub>NH][HSO<sub>4</sub>] has been easily prepared from the reaction of triethyl amine and sulfuric acid according to reported method.<sup>27</sup>

## General Procedure for the Synthesis of $\alpha$ -Aminophosphonates

The mixture of the aldehyde (1 mmol), amine (1 mmol), trimethyl phosphite (1 mmol), and [Et<sub>3</sub>NH][HSO<sub>4</sub>] (0.1 g) as acidic IL catalyst was stirred under ambient and solvent-free conditions for the appropriate time as indicated in Table 1. After completion of the reaction, 5 mL of water was added to the mixture. The IL was dissolved in water and filtered for separation of the crude product. The separated product was washed twice with water. The solid product was purified by recrystallization procedure in ethanol. All the desired products

were characterized by comparison of their physical data with those of known compounds.

**Compound 4a** (Table 1, Entry 1): white solid, mp 87-89 °C; IR (KBr): 3305, 3105, 2956, 1602, 1521, 1946, 1454, 1240, 1063, 1032 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.51 (d, J = 10.5 Hz, 3H, OCH<sub>3</sub>), 3.81 (d, J = 10.6 Hz, 3H, OCH<sub>3</sub>), 4.82 (d, J = 24 Hz, 1H, CHP), 6.64 (d, J = 8.0 Hz, 2H, ArH), 6.74 (t, J = 7.2 Hz, 1H, ArH), 7.10 (t, J = 7.7 Hz, 2H, ArH), 7.30 (t, J = 7.5 Hz, 1H, ArH), 7.39 (t, J = 7.4 Hz, 2H, ArH), 7.50 (d, J = 7.3 Hz, 2H, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 54.1 (d, J = 7.0 Hz, OCH<sub>3</sub>), 54.2 (d, J = 6.8 Hz, OCH<sub>3</sub>), 56.2 (d, J = 150 Hz, CH), 114.3 (CH), 119.0 (CH), 128.2 (d, J = 5.8 Hz, CH), 128.4 (d, J = 3.1 Hz, CH), 129.1 (CH), 131.2 (CH), 136.0 (C), 146.6 (d, J = 14.5 Hz, C).

## CONCLUSION

In conclusion, we describe here the one-pot three-component reaction of aldehydes, amines, and trimethyl phosphite to synthesize α-aminophosphonates in simple ammonium ionic liquid. This ionic liquid is air and water stable, and easy to prepare from cheap amine and acid. In addition, it is relatively cheap compared with the imidazolium ionic liquids. Hence this ionic liquid is used as solvents and catalysts for the reaction, eliminating the need for a volatile organic solvent and additional catalyst. The conversion and yield obtained with this method are significantly increased in comparison with those reported in traditional organic solvents to date. In particular, this ionic liquid is very easy to be separated from the reaction mixture.

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