

## Research Article

# [BPy]HSO<sub>4</sub> as an Efficient and Recyclable Catalyst for One-Pot Synthesis of $\alpha$ -Aminophosphonates under Solvent-Free Conditions

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[BPy]HSO<sub>4</sub> was prepared and used as an efficient and recyclable catalyst for the one-pot three-component synthesis of  $\alpha$ -aminophosphonates at room temperature under solvent-free conditions with good-to-excellent yields. The workup procedure is very simple, and the catalyst can be reused at least four times without any loss in catalytic activity.

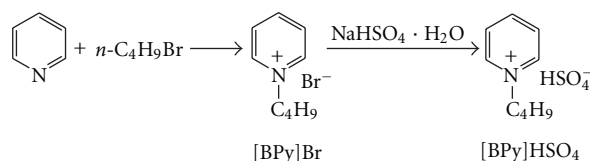
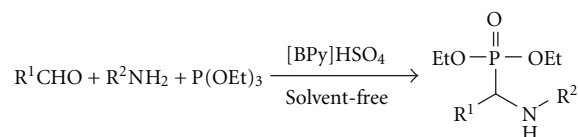
## 1. Introduction

$\alpha$ -Aminophosphonates are an important class of compounds because they are considered to be used as phosphorous analogs of the corresponding  $\alpha$ -amino acids. Their diverse applications include as enzyme inhibitors [1], HIV protease [2], antibiotics [3], herbicides, fungicides, insecticides [4], as well as antithrombotic agents [5]. Various methods have been developed for the synthesis of  $\alpha$ -aminophosphonates [6]. Recently, the synthesis of  $\alpha$ -aminophosphonates by the one-pot three-component condensation of aldehydes, amines, and diethylphosphite or triethylphosphite has been explored in the presence of a variety of catalysts such as Cd(ClO<sub>4</sub>)<sub>2</sub>·xH<sub>2</sub>O [7], KH<sub>2</sub>PO<sub>4</sub> [8], choline chloride·2ZnCl<sub>2</sub> [9], H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> [10], Zn(OAc)<sub>2</sub>·2H<sub>2</sub>O [11], [Cu(3,4-tmtppa)](MeSO<sub>4</sub>)<sub>4</sub> [12], sulfamic acid [13], HClO<sub>4</sub>·SiO<sub>2</sub> [14], NbCl<sub>5</sub> [15], ytterbium perfluorooctanoate [16], nano-CeO<sub>2</sub> [17], alum [18], Al(OTf)<sub>3</sub> [19], thiamine hydrochloride (VB1) [20], CeCl<sub>3</sub>·7H<sub>2</sub>O [21], xanthan sulfuric acid [22], and silica sulfuric acid [23, 24]. However, some of these methods suffer from one or more drawbacks such as use of toxic catalysts which are usually nonrecoverable and organic solvents, tedious workup procedures, and the requirement of heating conditions. Thus, the development of simple, efficient, and environmentally friendly methods

under mild conditions using recyclable catalysts for the synthesis of  $\alpha$ -aminophosphonates is of current interest. Acidic ionic liquids have emerged as promising acid catalysts in replacement of conventional homogeneous and heterogeneous acidic catalysts because they are flexible, nonvolatile, noncorrosive, of low toxicity, immiscible with many organic solvents, and reusable [25]. Ionic liquids' ([bnmim][HSO<sub>4</sub>] [26], [psmim][HSO<sub>4</sub>] [27]) catalyzed synthesis of  $\alpha$ -aminophosphonates has also been reported. Solvent-free organic reactions make procedures simpler and prevent solvent wastes, hazards, and toxicity [28]. We report herein the acidic ionic liquid [BPy]HSO<sub>4</sub> catalyzed one-pot synthesis of  $\alpha$ -aminophosphonates at room temperature under solvent-free conditions.

## 2. Results and Discussion

We herein report, a simplified and benign procedure for the preparation of the ionic liquid [BPy]HSO<sub>4</sub> using sodium bisulphate (Scheme 1), in place of sulphuric acid [29]. The significant advantages of using sodium bisulphate in place of sulphuric acid in the preparation of [BPy]HSO<sub>4</sub> over the previous method is to avoid the release of corrosive hydrogen bromide and reduction in processing time from 48 h to

SCHEME 1: Synthesis of [BPy]HSO<sub>4</sub>.SCHEME 2: Synthesis of  $\alpha$ -aminophosphonates catalyzed by [BPy]HSO<sub>4</sub>.TABLE 1: Effects of the amount of [BPy]HSO<sub>4</sub> on the synthesis of  $\alpha$ -aminophosphonate<sup>a</sup>.

Entry	Catalyst (mol%)	Time (min)	Yield <sup>b</sup> (%)
1	0	30	0
2	5	20	85
3	10	20	93
4	20	20	95
5	30	10	94
6	40	10	92

<sup>a</sup>Reaction of benzaldehyde (10 mmol), aniline (10 mmol), and triethyl phosphite (12 mmol) in the presence of [BPy]HSO<sub>4</sub> at room temperature under solvent-free conditions. <sup>b</sup>Isolated yield.

1 h. The acidic nature of [BPy]HSO<sub>4</sub> has been exploited in the preparation of 1,5-benzodiazepine derivatives by the reaction of *o*-phenylenediamine with chalcones [29]. We now report a clean and efficient method for the one-pot three-component synthesis of  $\alpha$ -aminophosphonates using [BPy]HSO<sub>4</sub> as recyclable catalyst at room temperature under solvent-free conditions (Scheme 2).

In the initial experiments, in order to evaluate the catalytic efficiency of [BPy]HSO<sub>4</sub> in this three-component reaction, the reaction of benzaldehyde with aniline and triethyl phosphite was selected as model. The experimental procedure is very simple. A mixture of benzaldehyde, aniline, triethyl phosphite, and [BPy]HSO<sub>4</sub> was stirred at room temperature. After completion of the reaction, the product was purified by crystallization with ethanol. To optimize the amount of a catalyst under solvent-free conditions, we examined the effects of catalyst loading on the synthesis of  $\alpha$ -aminophosphonate. The results are summarized in Table 1. It is important to note that the synthesis of  $\alpha$ -aminophosphonate could not be achieved in the absence of catalyst (Table 1, entry 1) [8]. The optimum catalyst loading



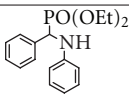
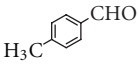

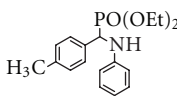
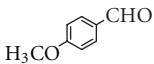

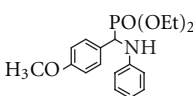
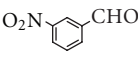

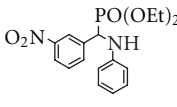

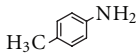
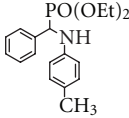

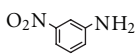
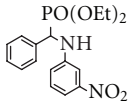

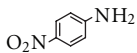
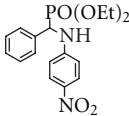

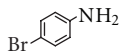
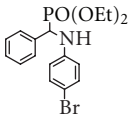

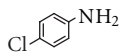
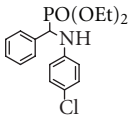
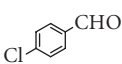
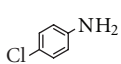
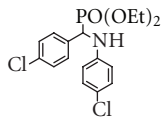
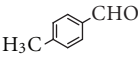
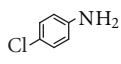
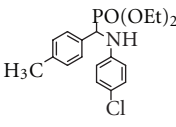
for [BPy]HSO<sub>4</sub> was found to be about 30 mol %. When the amount of the catalyst decreased to 20 mol% from 30 mol% relative to the substrates, the yield was not reduced but longer time was required to complete the reaction (Table 1, entries 4 and 5). However, the use of 40 mol% of the catalyst showed almost the same yield and the same time was required (Table 1, entry 6).

After optimizing the conditions, we examined the scope of the reaction by condensing several substituted aromatic aldehydes with amines and triethyl phosphite using 30 mol% of [BPy]HSO<sub>4</sub> as catalyst under solvent-free conditions at room temperature. The examples studied covered electron-rich and electron-deficient aromatic aldehydes with aniline derivatives containing electron-donating and electron-withdrawing groups. As shown in Table 2, the presence of electron-donating groups on the aldehyde produced the corresponding  $\alpha$ -aminophosphonates in good yields and the reaction was sluggish (Table 2, entries 2, 3, and 11). The presence of electron-donating groups on the aldehyde resulted in increased electron density on the nitrogen atom of the imine. This makes the iminium ion a bad electrophilic center which is subsequently attacked by the nucleophilic phosphite species to give the  $\alpha$ -aminophosphonates. The steric hindrance of the aromatic ring had some influence on the rate and yield of the reaction.

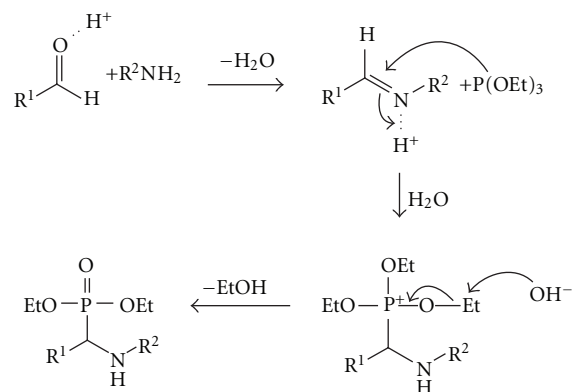
A proposed mechanism for the synthesis of  $\alpha$ -aminophosphonates catalyzed by [BPy]HSO<sub>4</sub> is shown in Scheme 3. The mechanism of this reaction is believed to involve formation of an activated imine by the acidic ionic liquid so that addition of the phosphite is facilitated to give a phosphonium intermediate, which then undergoes reaction with the water generated during formation of the imine to give the  $\alpha$ -aminophosphonate and ethanol [17].

From both an environmental and an economic standpoint, it is highly desirable that the catalyst can be recovered and reused. The reusability of the [BPy]HSO<sub>4</sub> catalyst

TABLE 2: [BPy]HSO<sub>4</sub> catalyzed synthesis of  $\alpha$ -aminophosphonates under solvent-free conditions.

Entry	R <sup>1</sup> CHO	R <sup>2</sup> NH <sub>2</sub>	Product	Mp (°C)	Time (min)	Yield <sup>a</sup> (%)
1				89–91 (90–91 [22])	10	94
2				64–66 (64–65 [22])	4 h	89
3				100–102 (102–103 [22])	20 h	89
4				98–100 (96–97 [22])	1 h	89
5				118–120 (116–118 [22])	10	89
6				117–118 (118 [21])	20	69
7				145–147 (143–145 [22])	1 h	67
8				122–124 (122 [21])	30	77
9				118–120 (119 [21])	20	80
10				106–108 (106–107 [10])	2 h	70
11				86–88 (86–87 [10])	6 h	70

<sup>a</sup> Isolated yield.



SCHEME 3: Proposed mechanism for the synthesis of  $\alpha$ -aminophosphonates catalyzed by [BPy]HSO<sub>4</sub>.

TABLE 3: Recycling of the [BPy]HSO<sub>4</sub> catalyst.

Run	Time (min)	Yield (%)
1	10	94
2	10	93
3	10	94
4	10	95
5	10	95

was also examined. For this purpose, the same model reaction was again studied under optimized conditions. After completion of the reaction, the product was purified by crystallization with ethanol. The mother liquor containing the catalyst was rotary evaporated to remove solvent and the resulting catalyst was reused directly for the next run. As shown in Table 3, the recovered catalyst can be reused at least four additional times in subsequent reactions without any loss in catalytic activity, more than 90% yield of  $\alpha$ -aminophosphonate could be obtained in each recycle.

Finally, the efficiency of [BPy]HSO<sub>4</sub> was compared with that of other ionic liquids reported earlier in the synthesis of  $\alpha$ -aminophosphonates via condensation of aniline and benzaldehyde with triethyl phosphite. The data summarized in Table 4 clearly demonstrate that [BPy]HSO<sub>4</sub> is an effective ionic liquid for the synthesis of  $\alpha$ -aminophosphonates.

### 3. Conclusion

In summary, we have demonstrated that a readily available ionic liquid [BPy]HSO<sub>4</sub> can be used as a recyclable catalyst for the synthesis of  $\alpha$ -aminophosphonates by the one-pot reaction of an aldehyde, an amine, and triethyl phosphite at room temperature under solvent-free conditions. The operational simplicity together with the use of recyclable and environmentally benign catalyst are remarkable features of the procedure.

## 4. Experimental

All chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd. or Acros Organics. FT-IR spectra were obtained on a Nexus 470 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Bruker Avance III 400 with TMS as internal standard. Melting points were determined on a melting point apparatus and were uncorrected. Products obtained are all known compounds and were identified by comparing their physical and spectral data with the reported ones.

**4.1. Preparation of Ionic Liquid [BPy]HSO<sub>4</sub>.** n-Bromobutane (21.6 mL, 0.2 mol) was added to pyridine (16 mL, 0.2 mol) in a 100 mL three-neck round-bottom flask fitted with a reflux condenser. This mixture was stirred with a mechanical stirrer at 90°C for 12 h. Then NaHSO<sub>4</sub>·H<sub>2</sub>O (27.6 g, 0.2 mol) was added to three-neck round-bottom flask. The resulting mixture was stirred at 90°C for 1 h. The reaction mixture was cooled to room temperature and filtered, the filtrate was dried under vacuum to afford [BPy][HSO<sub>4</sub>] as viscous liquid in 86% yield. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)  $\delta$ : 0.89 (t, *J* = 7.2, 3H), 1.23–1.32 (m, 2H), 1.85–1.93 (m, 2H), 4.66 (t, *J* = 7.2, 2H), 6.07 (1H, br s, OH), 8.17 (t, *J* = 6.8, 2H), 8.62 (t, *J* = 7.6, 1H), 9.19 (d, *J* = 6.0, 2H).

**4.2. Typical Procedure for the Synthesis of  $\alpha$ -Aminophosphonates.** A mixture of aldehyde (10 mmol), amine (10 mmol), triethyl phosphite (12 mmol), and [BPy]HSO<sub>4</sub> (30 mol%) was stirred at room temperature for the appropriate time (Table 2). After completion of the reaction, as indicated by thin-layer chromatography, the reaction mixture was purified by crystallization with ethanol. The mother liquor containing the catalyst was rotary evaporated to remove solvent and the resulting catalyst was reused directly for the next run.

TABLE 4: Comparison of ionic liquids used for the synthesis of  $\alpha$ -aminophosphonate.

Entry	Ionic liquid	Condition	Time	Yield (%)	Reference
1	[bnmim][HSO <sub>4</sub> ] (50 mol%)	Room temperature	10 min	96	[26]
2	[BPy]HSO <sub>4</sub> (30 mol%)	Room temperature	10 min	94	present
3	[psmim][HSO <sub>4</sub> ] (10 mol%)	Room temperature	30 min	92	[27]
4	[BPy]HSO <sub>4</sub> (10 mol%)	Room temperature	20 min	93	present

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