S_{0_3} H-Functionalized Ionic Liquids Catalyzed the Synthesis of α -Aminophosphonates in Aqueous Media

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ABSTRACT: SO_3H -functionalized halogen-free ionic liquids were prepared and used as efficient and recyclable catalysts for the synthesis of α aminophosphonates at room temperature via the one-pot three-component condensation reaction in aqueous media with good yields of 80-96%. The postprocessing was simple, and the catalysts could be reused at least six times without noticeably decreasing the catalytic activity. © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:546–550, 2010; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20644

INTRODUCTION

 α -Aminophosphonates have received considerable attention in medicinal chemistry for their broad biological activities such as peptide mimics, enzyme inhibitors, antibiotics, and catalytic antibodies[1].

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Some synthetic methods including one-pot synthesis of α -aminophosphonates have been explored in the presence of Lewis acids [2–6], Brønsted acids [7–8], solid acids [9–10], rare metal salts [11], or metal oxides [12] over recent decades.

One of the prime concerns of industry and academia is the search for replacements to the environmentally damaging solvents/catalysts used on a large scale, especially those that are volatile and difficult to handle. Ionic liquids have been turned to be a kind of promising alternative medium/catalysts for various chemical processes, of which functionalized ionic liquids (FILs) have been one of the most exciting topics. In view of both the advantages and disadvantages of homogeneous and heterogeneous catalytic system, the use of FILs as reaction media/catalytic system may be in terms of settlement to both the solvent emission and catalytic recycling problem in traditional chemical procedure. However, very few papers were concerned with the synthesis of α -aminophosphonates in the presence of ionic liquids. Yadav et al. used ionic liquids [bmim]BF₄/[bmim]PF₆ as novel reaction media for the synthesis of α -aminophosphonates [13]. Very recently, Akbari and Heydari used imidazoliumbased ionic liquid [bsmim][CF₃SO₃] and Sadaphal et al. used [bnmim][HSO₄] as the recyclable catalyst for the synthesis of α -aminophosphonates, respectively [14,15]. However, typical ionic liquids consist of halogen-containing anions (e.g., [PF₆]⁻, [BF₄]⁻,

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SCHEME 1 Structure of FILs.

 $[CF_3COO]^-$, $[CF_3SO_3]^-$, or $[(CF_3SO_2)_2N]^-$), which in some regard limits their "greenness" [16,17]. Thus, it is necessary to synthesize less expensive and halogen-free ionic liquids that can be used in simple procedures. In fact, the search for new, readily available, and green catalysts is still being actively pursued.

We are especially interested in preparation and developing the potential use of efficient, simple and readily available FIL catalysts, and some novel SO₃H-functional halogen-free acidic ionic liquids have been prepared and their catalytic activities for acid-catalyzed reactions have also been investigated previously [18,19]. In continuation of our work, we report here the preparation of SO₃H-functionalized halogen-free ionic liquids ([psmim][HSO₄], [psmim][H₂PO₄], [bsmim][HSO₄]), and [bsmim][H₂PO₄] (Scheme 1), and their uses as the novel catalysts in one-pot, three-component condensation in water have also been investigated (Scheme 2). To the best of our knowledge, such FILs used for the synthesis of α aminophosphonates have not been reported in the open literature.

FILs [psmim][HSO₄]: n = 1, A = HSO₄ [psmim][H₂PO₄]: n = 1, A = H₂PO₄ [bsmim][HSO₄]: n = 2, A = HSO₄ [bsmim][H₂PO₄]: n = 2, A = H₂PO₄

TABLE 1 Effect of the Different Catalysts on the Synthesis of α -Aminophosphonates^{*a*}

Entry	Catalyst (mmol)	Time (min)	Isolated Yield (%)
1	0	120	0
2	[psmim][HSO4] (0.5)	60	78
3	[psmim][HSO ₄] (1.0)	30	92
4	[psmim][HSO ₄] (1.5)	30	92
5	[psmim][HSO ₄] (2.0)	30	91
6	[psmim][H ₂ PO ₄] (0.5)	60	65
7	$[psmim][H_2PO_4](1.0)$	60	80
8	$[psmim][H_2PO_4]$ (1.5)	60	81
9	[bsmim][HSO ₄] (0.5)	60	53
10	[bsmim][HSO ₄] (1.0)	30	79
11	[bsmim][HSO ₄] (1.5)	30	79
12	$[psmim][H_2PO_4](0.5)$	60	50
13	$[psmim][H_2PO_4](1.0)$	60	82
14	[psmim][H ₂ PO ₄] (1.5)	60	82

 $^{a}10$ mmol benzaldehyde, 10 mmol aniline, 10 mmol triethyl phosphite, and 0.5 mL $H_{2}\text{O};$ r.t.

RESULTS AND DISCUSSION

To begin with catalytic activity experiments, benzaldehyde, aniline, and triethyl phosphite were employed as the model reactants at room temperature in FILs for a length of time to compare the catalytic performance (Table 1). It was shown that no desirable product could be detected when a mixture of benzaldehyde, aniline, and triethyl phosphite was stirred at room temperature for 120 min in the absence of FILs (entry 1), which indicated that the catalysts were absolutely necessary for this one-pot three-component reaction.

All the FILs were proved to be very active, and it is clear that the yield was increased with the increase in FILs and the optimal amount of FILs was 1.0 mmol (entry 3, 7, 10, and 13), leading to 79–92% yield of α -aminophosphonates in the presence of 10% mmol FILs. Higher amount of the catalysts could not improve the yield obviously. It is suggested that the increase in acidity of FILs should facilitate the reaction and may decrease the amount of catalyst[15]. In addition, ionic liquids containing the



SCHEME 2 Synthesis of α -aminophosphonates via one-pot three-component condensation reaction catalyzed by FILs.

Entry	Water (mL)	Isolated Yield (%)	
1	0	92	
2	0.5	92	
3	1.0	91	
4	2.0	90	
5	4.0	87	
6	6.0	85	
7	8.0	83	
8	10.0	81	

TABLE 2 Influence of the Amounts of Water on the Synthesis of α -Aminophosphonates^{*a*}

^a10 mmol benzaldehyde, 10 mmol aniline, 10 mmol triethyl phosphite, and 1 mmol [psmim][HSO₄]; r.t., 30 min.

shorter length of alkyl chain are relatively inexpensive. Furthermore, the better immiscibility of the resulted α -aminophosphonates with the FILs containing shorter length of alkyl chain should facilitate the separation in the workup procedure. Hence, [psmim][HSO₄] should be the best catalyst for this procedure among the four FILs and the optimized reaction conditions are presented in Table 1 (entry 3).

The chemical industry is under considerable pressure to replace many of the volatile organic compounds that are currently used as solvents in organic synthesis. For overcoming these problems, one approach is to use the water as the green medium, another approach is to develop new processes involving the solvent-free conditions. To our surprise, the reaction could be carried out either in aqueous media or under solvent-free condition, which is different from the literature [14]. As a clean and cheap solvent, it is important to carry out the reaction in water for the environmental and economic reasons, as well as the workup procedure. Then, effect of the amount of water on the reaction was explored and the results are listed in Table 2.

The recycling performance of the [psmim] [HSO₄] was also investigated using the abovementioned model reaction. After completion of the reaction, the products were isolated from the catalytic system by filtration; the catalyst contained in filtrate was reused in the next run after the extraction with CH_2Cl_2 . The catalyst can be reused at least six times without an appreciable decrease in yield and the reaction rate, more than 90% yield of α aminophosphonates could be obtained in each recycle. Compared with the traditional solvents and catalysts, the easy recycling performance is also an attractive property of the FILs for the environmental protection and economic reasons.

Then, this condensation reaction with various aldehydes, amines, and tri/diethyl phosphite in the presence of $[psmim][HSO_4]$ as the catalyst was explored under the optimized reaction conditions described above, and the results are presented in Table 3.

It can easily be seen that this one-pot, three-component condensation completed within 20–60 min, and the products were isolated in good yields by filtration. For aromatic aldehydes carrying either electron-donation or electronwithdrawing substituents could afford good yields

Entry	<i>R</i> ₁	R ₂	3	Time (min)	Yield ^b %
1	4-CH ₃ OC ₆ H ₄	C ₆ H ₅	P(OEt) ₃	60	90
2	4-CH ₃ OC ₆ H ₄	C _e H ₅	H(O)P(OEt) ₂	60	91
3	4-CH ₃ OC ₆ H ₄	4-ČH ₃ C ₆ H ₄	P(OEt) ₃	60	93
4	4-CH ₃ OC ₆ H ₄	$4 - NO_2 C_6 H_4$	H(O)P(OEt) ₂	60	95
5	$4-CH_3OC_6H_4$	4-FC ₆ H ₄	$H(O)P(OEt)_2$	60	82
6	4-CH ₃ OC ₆ H ₄	4-CIC ₆ H ₄	$H(O)P(OEt)_2$	60	81
7	4-CH ₃ OC ₆ H ₄	$4-BrC_{6}H_{4}$	H(O)P(OEt)	60	83
8	4-CH ₃ C ₆ H ₄	C ₆ H ₅	$H(O)P(OEt)_2$	60	80
9	C ₆ H ₅	C_6H_5	P(OEt) ₃	30	92
10	C_6H_5	C_6H_5	H(O)P(OEt) ₂	30	90
11	C_6H_5	3-NO ₂ C ₆ H ₄	P(OEt) ₃	60	89
12	C_6H_5	$4-NO_2C_6H_4$	P(OEt) ₃	60	89
13	2-CIC ₆ H ₄	C ₆ H ₅	P(OEt) ₃	20	96
14	$4-CIC_6H_4$	C_6H_5	P(OEt) ₃	20	96
15	4-HOC ₆ H ₄	C ₆ H ₅	P(OEt) ₃	30	93
16	$4-NO_2C_6H_4$	C_6H_5	P(OEt) ₃	30	93
17	butyl	C_6H_5	P(OEt) ₃	60	86
18	Cyclohexyl	C ₆ H ₅	P(OEt) ₃	60	80

TABLE 3 One-Pot Three-Component Condensation for *α*-Aminophosphonates^{*a*}

^a10 mmol benzaldehyde, 10 mmol aniline, 10 mmol tri/diethyl phosphite, 1 mmol [psmim][HSO₄], and 0.5 mL H₂O; r.t. ^bIsolated yields.

of α -aminophosphonates (entries 2, 13–16). In the case of anilines, it is noteworthy that both the electron-donating and electron-withdrawing substituents (entries 3–7) were advantageous to this reaction. In addition, both triethyl phosphite and diethyl phosphite could be employed to carry out the condensation.

CONCLUSION

In summary, some readily available SO₃Hfunctionalized halogen-free ionic liquids were prepared and behaved as the novel recyclable catalysts for one-pot synthesis of a variety of α aminophosphonates at room temperature in aqueous media; the procedure offers several advantages including short reaction time, good yields, and easy workup procedures; and this method is useful addition to the present methodology for α aminophosphonates.

EXPERIMENTAL

Melting points were determined by use of an X₆-Data microscope apparatus. The IR spectra were run on a Bruker Vectter 22 spectrometer and expressed in cm⁻¹ (KBr). ¹H NMR spectra were recorded on a Bruker DRX300 (300 MHz) spectrometer. ¹³C NMR spectra were recorded on a Bruker DRX300 (75 MHz) spectrometer. Mass spectra were obtained with an automated Fininigan TSQ Quantum Ultra AM (Thermal) LC-MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

Preparation of SO₃ H-Functionalized Halogen-Free Ionic Liquid

All used acyclic SO_3H -functionalized halogen-free acidic ionic liquids were synthesized according to our previous methods [20]. The FILs were analyzed by ¹H NMR, ¹³C NMR, and MS spectroscopic methods, and the spectral data agreed with their structures (Scheme 1).

The selected spectroscopic data for FILs are [psmim][HSO4] ¹H NMR (D₂O): δ (ppm): 8.47 (s, 1H, CH), 7.24 (d, *J* = 1.5 Hz, 1H, CH), 7.17 (d, *J* = 1.5 Hz, 1H, CH), 4.08 (t, *J* = 6.9 Hz, 2H, CH₂), 3.62 (s, 3H, CH₃), 2.64 (t, *J* = 7.5 Hz, 2H, CH₂), 2.03 (m, 2H, CH₂). ¹³C NMR (D₂O): δ (ppm): 136.53, 124.32, 122.57, 48.13, 47.66, 36.46, 25.48. MS *m*/*z*:. 302.0 (M⁺), 300.93 (100).

General Procedure for Synthesis of α-Aminophosphonates Catalyzed by FILs

In a typical experiment, to a round-bottomed flask charged with aldehyde (10 mmol) and aniline (10 mmol) in water of 0.5 mL, FIL (1.0 mmol) was added under stirring. The mixture was stirred at room temperature for 5 min, and then tri/diethyl phosphite (10 mmol) was added. On completion (monitored by TLC), the products were separated by filtration and dried under vacuum. The products were identified by ¹H NMR and physical data (mp) matches with the literature.

Selected Spectral Data for *a*-Aminophosphonates

Diethy(phenyl)-N-(phenyl)aminomethylphosphonate (entry 9): White solid, mp 89–90°C(lit. 90–91°C) [12], ¹H NMR, δ : 1.02 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.0Hz, 3H), 3.36 (s, 1H), 3.72–3.64 (m, 1H), 3.90–3.82 (m, 1H), 4.09–3.99 (m, 2H), 5.02 (d, J = 24.9 Hz, 1H), 6.52 (t, J = 7.1 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.99 (t, J = 7.75 Hz, 2H), 7.32–7.20 (m, 3H), 7.52 (d, J = 7.2 Hz, 2H).

Diethy(phenyl)-N-(phenyl)aminomethylphosphonate (entry 11): Yellow solid, mp 124–125°C (lit.124– 126°C) [12], ¹H NMR, δ : 1.04 (t, J = 7.0 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H), 3.37 (brs, 1H), 3.76–3.68 (m,1H), 3.93–3.85 (m, 1H), 4.09–4.02 (m, 2H), 5.23 (d, J = 24.3 Hz, 1H), 7.27–7.20 (m, 3H), 7.33 (t, J = 7.5 Hz, 3H), 7.54 (d, J = 7.1 Hz, 2H), 7.68 (d, J = 2.0 Hz, 1H).

Diethy(2-cholorophenyl)-N-(phenyl)aminomethylphosphonate (entry 13): White solid, mp 59–60°C (lit. 60°C) [12], ¹H NMR (300 MHz, DMSO- d_6), δ : 0.99 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H), 3.37 (d, J = 6.2 Hz, 1H), 3.67–3.64 (m, 1H), 3.86–3.83 (m, 1H), 4.13–4.07 (m, 2H), 5.20 (d, J = 25.0 Hz, 1H), 6.55(t, J = 7.0 Hz, 1H), 6.68 (d, J = 7.9 Hz. 2H), 7.03 (t, J = 7.1 Hz, 2H), 7.32–7.27 (m, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.69–7.66 (m, 1H).

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