

1-Benzyl-3-Methyl Imidazolium Hydrogen Sulphate [bnmim][HSO₄] Promoted Synthesis of α -Aminophosphonates

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We have demonstrated a one-pot three component coupling of an aldehydes, an amines, and triethyl phosphite using 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim][HSO₄] as an efficient catalyst. All the reactions proceed under solvent-free conditions at room temperature. This methodology afforded the corresponding α -aminophosphonates in shorter reaction times with excellent yields.

Key Words: 1-Benzyl-3-methyl imidazolium hydrogen sulphate [bnmim][HSO₄], α -Aminophosphonates, Aldehydes/ketone, Amines, Triethyl phosphite

Introduction

Ionic liquid has been turned to be a kind of promising alternative medium for various chemical processes due to their unique properties such as good solvating capability, non-inflammability, negligible vapor pressure, easy of recyclability, high thermal stability.¹ It is referred as 'designer solvent' as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Several organic reactions have been reported in ionic liquids.² In particular, ionic liquids based on imidazolium ion has been extensively employed for various organic transformations includes Diels-Alder,^{3a} Wittig,^{3b} Suzuki cross-coupling,^{3c} Hantzsch condensation.^{3d} Moreover, ionic liquids with the acidic counter ions is also found to be an efficient medium in synthetic chemistry.⁴

Organophosphorus compounds are an important class of organic compounds due to their potent pesticidal, insecticidal activities and having wide range of applications.⁵ α -Aminophosphonates have received considerable attention in medicinal chemistry since they are considered as structural analogues of the corresponding α -amino acids and their utilities as enzyme inhibitors, antibiotics, pharmacological agents, peptidomimetics, hapten design in antibody generation and many other applications are well documented.⁶

One-pot syntheses of α -aminophosphonates have been carried out in organic solvents using In(OTf)₃/MgSO₄,^{7a} GaI₃,^{7b} BiCl₃,^{7c} Cu(OTf)₂,^{7d} SbCl₅/Al₂O₃,^{7e} α -Aminophosphonates also been synthesized in solvent-free conditions in the presence of LiClO₄/Et₂O,^{8a,b} TFA,^{8c} LiClO₄,^{8d} metal triflate,^{8e} Na₂CaP₂O₇,^{8f} Mg(ClO₄)₂,^{8g} ZrOCl₂·8H₂O or ZrO(ClO₄)₂·6H₂O,^{8h} TsCl.⁸ⁱ Ionic liquid were also used as a medium for such three component syntheses of α -aminophosphonates.⁹ However, some of the reported procedures are associated with the disadvantages like use of solvent, additional reagent, long reaction time, costly and moisture sensitive catalyst.

Solvent-free reaction condition has been demonstrated to be an efficient technique for various organic reactions. It often lead to a remarkable decrease in reaction times, increased

yields, easier workup, enhancement of regio and stereo selectivity offers additional convenience in the organic synthesis.¹⁰

Hence the search continues for a better catalyst in the synthesis of α -aminophosphonates in terms of operational simplicity and ecological viability. Herein first time we report the use of highly water soluble acidic ionic liquid 1-benzyl-3-methyl imidazolium hydrogen sulphate for the synthesis of α -aminophosphonates that meets the demand for greener catalyst.

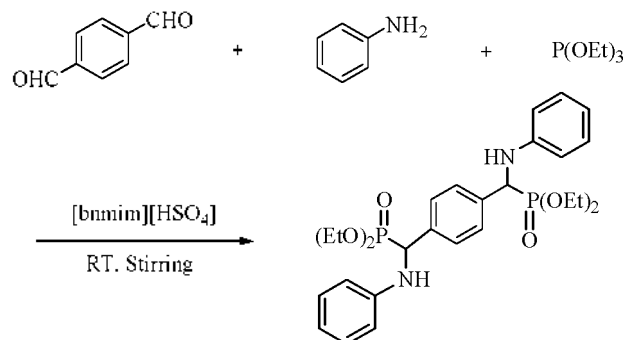
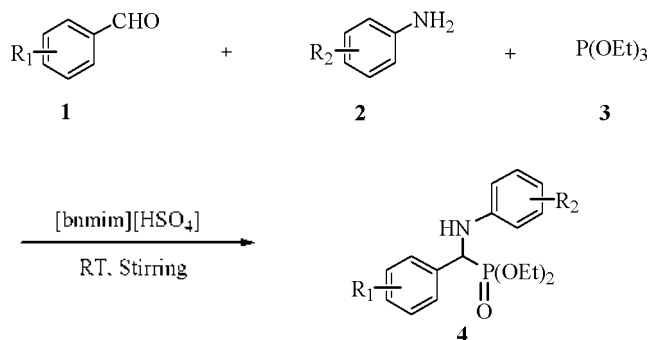
Experimental

Melting point was recorded in open capillary in liquid paraffin bath. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. ¹H NMR spectra were recorded on Mercury Plus Varian in DMSO-*d*₆ at 400 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique, showing (m+1) peak as a base peak. The elemental analysis was carried out on Flash EA-1112, 50/60 Hz, 1400-VA CHNS analyzer. The progress of the reactions was monitored by TLC.

General Procedure. A mixture of aldehyde (1 mmol), amine (1 mmol, 2 mmol in case of terephthalaldehyde), triethyl phosphite (1.2 mmol, 2.4 mmol in case of terephthalaldehyde) and [bnmim][HSO₄] (50 mol%) was stirred magnetically at room temperature for appropriate time (Table 3). After the completion of reaction as monitored by TLC: 20 mL ice cold water was added to the reaction mixture and product was extracted by chloroform (2 × 25 mL). The organic layer washed by brine (2 × 20 mL) and dried over anhydrous sodium sulphate. The solvent was distilled out on Rota-evaporator under reduced pressure to afford the solid or viscous products. The solid products were recrystallized from ethanol to get pure α -aminophosphonates.

Results and Discussion

As a part of our research devoted to the phosphorus chemistry¹¹ and interest in the development of novel synthetic methodologies¹² herein, we wish to report [bnmim][HSO₄]

**Table 1.** Screening of ionic liquids^a

Entry	Ionic liquids	Time (min)	Yield ^b (%)
1	[heemim][HSO ₄]	10	81
2	[hmim][HSO ₄]	10	85
3	[bnmim][HSO ₄]	10	96

^aReaction Conditions: Benzaldehyde (1 mmol), aniline (1 mmol), triethyl phosphite (1.2 mmol), ionic liquid (50 mol%), solvent-free at rt. ^bIsolated yields.

Table 2. Effect of concentration catalyst^a

Entry	[bnmim][HSO ₄] (mol%)	Time (min)	Yield ^b (%)
1	10	30	40
2	20	30	52
3	30	30	64
4	40	20	80
5	50	10	96
6	60	10	96
7	80	10	96
8	100	10	96

^aReaction Conditions: Benzaldehyde (1 mmol), aniline (1 mmol), triethyl phosphite (1.2 mmol), solvent-free at rt. ^bIsolated yields.

catalyzed one-pot three component synthesis of α -aminophosphonates by the coupling of an aldehyde/ketone, an amine and triethyl phosphite under solvent-free conditions (Scheme 1). During the course of our efforts towards the synthesis of α -aminophosphonates, we have considered the reaction of benzaldehyde, aniline and triethyl phosphite under solvent-free conditions at room temperature as the standard model reaction. In order to evaluate the effect of acidic ionic liquid, we have screened different acidic ionic liquids for the model reaction such as [heemim][HSO₄], [hmim][HSO₄] and [bnmim][HSO₄] (Table 1). The best result was obtained by using [bnmim][HSO₄] catalyst forms the desired product in 96% yield within 10 min (Table 1, Entry 3).

To determine the appropriate concentration of catalyst we investigated the model reaction at different concentrations of [bnmim][HSO₄] (Table 2). It was found that 50 mol% of [bnmim][HSO₄] is sufficient for better result (Table 2, Entry 5).

We also examine the [bnmim][HSO₄] catalyzed synthesis of bis- α -aminophosphonates by the reaction of terephthalaldehyde with aniline (2 mole) and triethyl phosphite (2.4 mole). The desired product is obtained in 90% yield in 20 min and characterized by the spectroscopic analysis.¹³

Table 3. [bnmim][HSO₄] catalyzed synthesis of α -aminophosphonates^a

Entry	Compound	Aldehyde/Ketone	Aniline	Time (min)	Yield ^b (%)
1	4a			10	96
2	4b			10	94
3	4c			20	90
4	4d			15	83
5	4e			15	87
6	4f			15	91
7	4g			25	88
8	4h			20	94
9	4j			35	83
10	4k			35	81
11	4l			180	30

^aReaction Conditions: Aldehyde/Ketone (1 mmol), amine (1 mmol), triethyl phosphite (1.2 mmol), [bnmim][HSO₄] (50 mol%), solvent-free at rt. ^bIsolated yields.

Table 4. Comparison of ionic liquids used for the synthesis of α -aminophosphonate

Entry	Ionic Liquid	Catalyst	Condition	Time	Yield (%) ^a	Reference
1	[bmim]PF ₆ (Solvent)	-	RT	8 h	82	9a
2	[bmim]BF ₄ (Solvent)	-	RT	5 h	90	9a
3	[bmim]OTf (Solvent)	Yb(OTf) ₃	MW/850W	2 min	55	9b
4	[bmim]SbF ₆ (Solvent)	Yb(OTf) ₃	MW/850W	2 min	72	9b
5	[bmim]PF ₆ (Solvent)	Yb(OTf) ₃	MW/850W	2 min	86	9b
6	[bmim]BF ₄ (Solvent)	Yb(OTf) ₃	MW/850W	2 min	99	9b
7	[bnmim][HSO ₄] (50 mol%)	-	RT	10 min	96	Present work

^aIsolated yields.

With these optimized reaction conditions: various aldehydes/ketone, an amines and triethyl phosphite were subjected for one-pot reaction catalyzed by [bnmim][HSO₄]. The reactions are clean and the products are obtained in excellent yield even for the reaction with enolized ketone *i.e.* cyclohexanone (Table 3, Entry 11). The reactions with heteroaryl aldehydes give their respective α -aminophosphonates in 35 min (Table 3, Entry 9, 10).

In order to show the merit of [bnmim][HSO₄] in comparison with the other ionic liquids used for the similar reaction: we are tabulated some of the results in Table 4. As it is evidence from the results, [bnmim][HSO₄] found to be effective ionic liquid for the synthesis of α -aminophosphonates.

Conclusion

In conclusion, [bnmim][HSO₄] allows efficient one-pot synthesis of a variety of α -aminophosphonates. The remarkable advantages offered by this method are solvent-free reaction conditions, short reaction times, easy workup procedures, high yields *etc.* We believe that this method is useful addition to the present methodology for the syntheses of α -aminophosphonates.

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- M.P. 165-167 °C; IR (KBr, cm⁻¹): 3304 (-NH), 1239 (-P=O), 1040 (-O-P-C). ¹H NMR (400 MHz, DMSO-d₆, δ): 0.90-1.30 (t, 12H), 3.40-4.20 (m, 8H), 4.8 (m, 4H, [2-NH, 2-CH]), 6.40-6.60 (dd, 4H), 6.60-6.80 (m, 2H), 7.0-7.10 (m, 4H), 7.40 (m, 4H); Elemental analysis C₂₃H₃₈N₂O₆P₂; Calcd: C: 59.99; H: 6.83; N: 5.00; Found: C: 59.95; H: 6.82; N: 4.94. MS: m/z 561 (M+1).