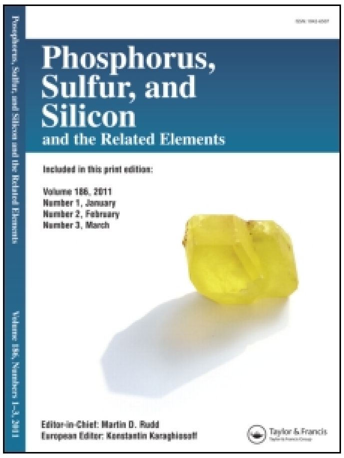

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One-Pot, Three-Component Synthesis of α-Aminophosphonates Catalyzed by Acyclic Acidic Ionic Liquids

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ONE-POT, THREE-COMPONENT SYNTHESIS OF α-AMINOPHOSPHONATES CATALYZED BY ACYCLIC ACIDIC IONIC LIQUIDS

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Some acyclic acidic ionic liquids were prepared and used as the catalysts for the one-pot, three-component synthesis of α-aminophosphonates from aldehydes, amines, and trimethylphosphite at room temperature in water. The products could simply be separated from the system of catalyst/water, and the catalysts could be reused at least six times without noticeably decreasing the catalytic activity.

Keywords α-Aminophosphonates; aqueous media; homogeneous catalysis; ionic liquids

INTRODUCTION

α-Aminophosphonates are pharmacologically important compounds that exhibit broad biological activities. These compounds have emerged as peptide mimics,[1] enzyme inhibitors,[2] antibiotics,[3] and catalytic antibodies.[4] Though substantial progress has been made to develop efficient methods for the preparation of these compounds, they suffer from harsh conditions, long reaction times, and frequently low yields, and the search for a milder and more efficient procedure and efficient catalysts for the synthesis of α-aminophosphonates continues to attract the attention of researchers.

Recently, nucleophilic addition of phosphite to imines has emerged as an important alternative to hydrophosphonylation of imines for the synthesis of α-aminophosphonates under the assistance of microwave or ultrasound irradiation,[5] and catalyzed by Lewis acids,[6] Brønsted acids,[7] solid acid,[8] and organocatalysts,[9] and the search for new water-tolerant, readily available, and green catalysts is still being actively pursued.

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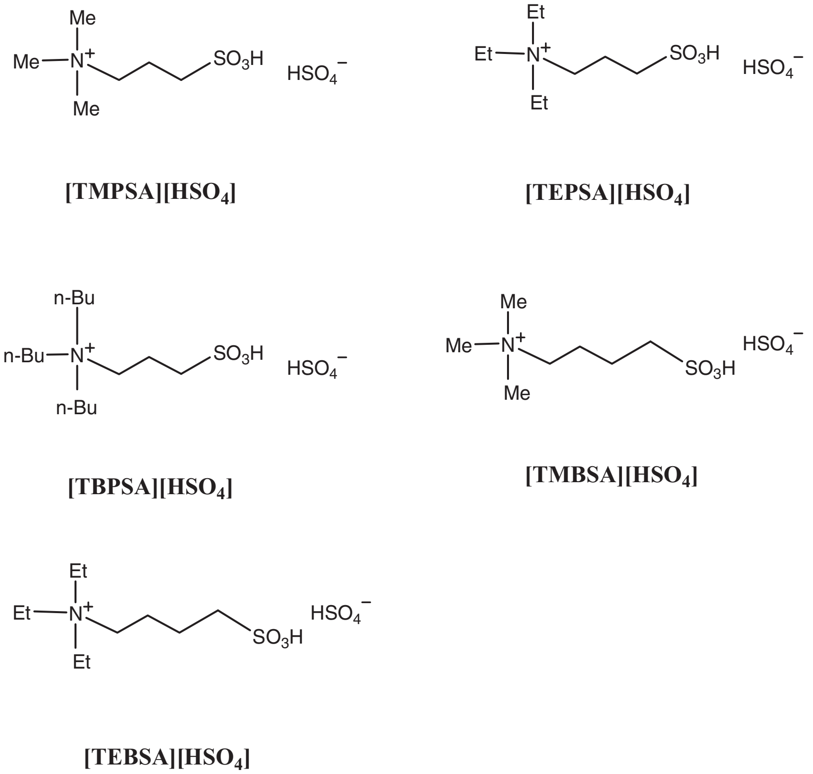
Currently, ionic liquids attract much interest as environmentally benign catalysts or excellent alternatives to organic solvents, due to their favorable properties such as negligible volatility and high thermal stability. Brønsted acidic or basic functionalized ionic liquids (TSILs) are designed to replace traditional acid or base catalysts in organic synthetic procedures. In view of both the advantages and disadvantages of homogeneous and heterogeneous catalytic reactions, the use of TSILs as reaction medium/catalytic system may offer a convenient solution to both the solvent emission and catalytic recycling problem. Yadav et al. used [bmim]BF_4/[bmim]PF_6 to synthesize α-aminophosphonates.[10] Very recently, Akbari and Heydari reported a sulfonic acid functionalized ionic liquid as a recyclable catalyst for the synthesis of α-aminophosphonates,[11] and Sadaphal et al. used functionalized ionic liquid [bnmim][HSO_4] to synthesize these compounds.[12] However, TSILs with imidazole as the cation are relatively expensive, which hinders their industrial applications. Furthermore, typical ionic liquids consist of halogen-containing anions (such as $[PF_6]^-$, $[BF_4]^-$, $[CF_3SO_3]^-$, or $[(CF_3SO_2)_2N]^-$), which in some regard limit their "greenness."[13] Therefore, it is necessary to synthesize novel, efficient, inexpensive, and halogen-free TSILs. In continuation of our work in studying ionic liquid–catalyzed multicomponent reactions (MCRs) in aqueous media,[14] we synthesized some SO_3H-functional Brønsted-acidic TSILs that bear an alkane sulfonic acid group in an acyclic tri-alkanyl-ammonium cation (Scheme 1), and their uses as novel catalysts for the one-pot, three-component synthesis of α-aminophosphonates (Scheme 2) were also explored.



[TMPSA][HSO_4]

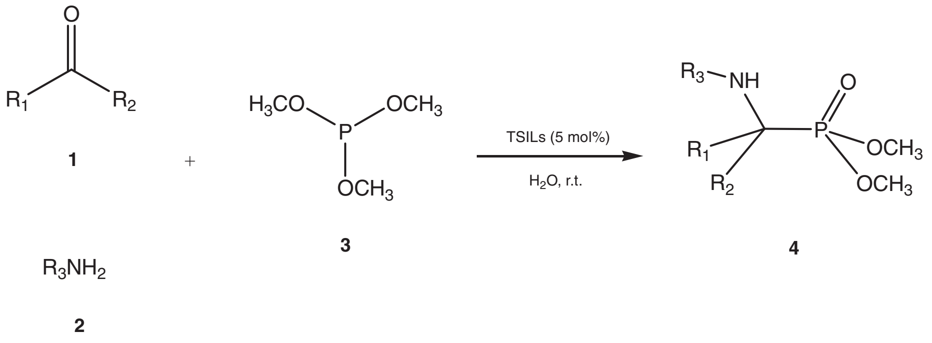
[TEPSA][HSO_4]

[TBPSA][HSO_4]

[TMBSA][HSO_4]

[TEBSA][HSO_4]

Scheme 1 TSIL a: [TMPSA][HSO_4]; **TSIL b**: [TEPSA][HSO_4]; **TSIL c**: [TBPSA][HSO_4]; **TSIL d**: [TMBSA][HSO_4]; **TSIL e**: [TEBSA][HSO_4].



Scheme 2

RESULTS AND DISCUSSION

The preparation of the catalyst TSILs were made up of a two-step atom economic reaction, and the fresh, new catalysts are somewhat viscous colorless or pale yellow liquids at room temperature. All produced catalysts are entirely miscible with water and are soluble or partly soluble in organic solvents. Indeed, all TSILs could act as water-tolerant catalysts.

In the initial catalytic activity experiments, benzaldehyde, aniline, and trimethylphosphite were employed as the model reactants at room temperature in TSILs for a length of time to compare the catalytic performance of the TSILs (Table I).

It was shown that no desirable product could be detected when a mixture of benzaldehyde, aniline, and trimethylphosphite was heated at r.t. for 60 min in the absence of TSILs (Table I, entry 1), which indicates that the catalysts were absolutely necessary for this three-component reaction. All the TSILs proved to be very active. It is clear that the yield was increased with adding TSILs, and the optimal amount of the TSILs was 0.5 mmol (Table I, entries 4, 7–10), amounting to 5 mol% of reactant **1**. A higher amount of the catalysts did not improve the yield. Additionally, ionic liquids containing the shorter

Table I Effect of different catalysts on the synthesis of α-aminophosphonates

Entry	Catalyst (mmol)	Isolated yield (%)
1	0	0
2	TSILs a (0.1)	61
3	TSILs a (0.3)	86
4	TSILs a (0.4)	90
5	TSILs a (0.5)	95
6	TSILs a (0.6)	95
7	TSILs a (0.7)	95
8	TSILs a (0.8)	95
9	TSILs a (0.9)	95
10	TSILs b (0.5)	95
11	TSILs c (0.5)	94
12	TSILs d (0.5)	95
13	TSILs e (0.5)	93

Reaction conditions: 10 mmol benzaldehyde, 10 mmol aniline, 12 mmol trimethyl phosphite, H_2O 5 mL, r.t., 10 min.

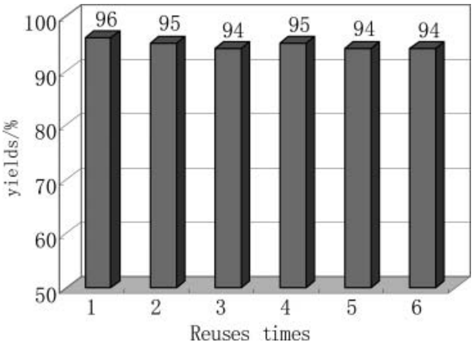


Figure 1 Recycle performance of the catalyst.

length of alkyl chain are relatively cheaper. Further, the better immiscibility of the resulting α-aminophosphonates with the ionic liquid containing shorter length of alkyl chain should facilitate the separation in workup procedure. Hence, [TMPSA][HSO_4] should be the best catalyst for this procedure among these acyclic TSILs, and the optimized reaction conditions are presented in Table I (entry 4). As a clean and cheap solvent, it is important to carry out this reaction in water for environmental and economic reasons.

The recycling performance of [TMPSA][HSO_4] was also investigated using the above same model reaction. After completion of the reaction, the products were isolated from the catalytic system by filtration; the catalyst was reused in the next run after the extraction with CH_2Cl_2. As shown in Figure 1, the catalyst can be reused at least six times without appreciable decrease in yield and reaction rate. Compared with the traditional solvents and catalysts, the easy recycling performance is also an attractive property of the TSILs for environmental protection and economic reasons.

Table II Synthesis of α-aminophosphonates catalyzed by [TMPSA][HSO_4]

Entry	R_1	R_2	R_3	Time (min)	Yield (%)[a]	Reference
1	$4\text{-}CH_3OC_6H_4$	H	C_6H_5	10	95	[6f]
2	$2,5\text{-}(CH_3O)_2C_6H_3$	H	C_6H_5	30	88	[6h]
3	$3,4,5\text{-}(CH_3O)_3C_6H_2$	H	C_6H_5	30	86	[6f]
4	$4\text{-}CH_3C_6H_4$	H	C_6H_5	10	90	[9b]
5	C_6H_5	H	C_6H_5	10	95	[6f]
6	$4\text{-}ClC_6H_4$	H	C_6H_5	10	95	[6f]
7	$2,6\text{-}Cl_2C_6H_3$	H	C_6H_5	60	85	[6h]
8	$4\text{-}NO_2C_6H_4$	H	C_6H_5	15	91	[5a]
9	2-Thiazolyl	H	C_6H_5	60	85	[6h]
10	2-Furyl	H	C_6H_5	60	85	[6f]
11	$4\text{-}CH_3OC_6H_4$	H	$3\text{-}NO_2C_6H_4$	15	90	[6f]
12	$4\text{-}CH_3C_6H_4$	H	$4\text{-}FC_6H_4$	15	90	[9b]
13	C_6H_5	H	$C_6H_5CH_2$	15	90	[6f]
14	$4\text{-}CH_3OC_6H_4$	H	2-Pyridyl	90	82	[6f]
15	$4\text{-}CH_3OC_6H_4$	CH_3	C_6H_5	60	90	[6f]

Reaction conditions: 10 mmol benzaldehyde, 10 mmol aniline, 12 mmol trimethyl phosphite, 0.5 mol [TMPSA][HSO_4], H_2O 5 mL, r.t.

[a] Isolated yield.

Then, this condensation reaction with various aldehydes/ketone, amines, and trimethylphosphites in the presence of [TMPSA][HSO_4] as the catalyst was explored under the optimized reaction conditions described above, and the results are presented in Table II.

It can easily be seen that this one-pot, three-component condensation completed within 10–90 min, and the products were isolated in good yields by filtration. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents could afford good yields of α-aminophosphonates (Table II, entries 1–8). In the case of anilines, it is noteworthy that both the weak electron-donating and electron-withdrawing substituents (Table II, entries 11, 12) were advantageous to this reaction. In addition, besides the aromatic aldehydes, aromatic ketones could also be employed to give good yield (Table II, entries 15).

CONCLUSION

In summary, an efficient procedure for the synthesis of α-aminophosphonates via a one-pot, three-component reaction catalyzed by acyclic ionic liquids was developed. The methodology gives the advantages of short reaction time, free of organic solvent, recyclability of catalysts, and easy workup in isolation of the products in good yield with high purity.

EXPERIMENTAL

Materials and Methods

Melting points were determined by using an X_6-Data microscope apparatus. The IR spectra were run on a Bruker Vectter 22 spectrometer and are expressed in cm^{-1} (KBr). ^1H NMR spectra were recorded on a Bruker DRX300 (300 MHz) spectrometer. Elemental analyses were recorded on a Perkin Elmer C spectrometer. Mass spectra were obtained with an automated Finnigan TSQ Quantum Ultra AM (Thermal) LC-MS spectrometer. All chemicals (AR grade) were commercially available and used without further purification.

Synthesis of SO_3H-Functional, Halogen-Free Acidic Ionic Liquids (TSILs)

All of the acyclic SO_3H-functionalized, halogen-free acidic ionic liquids used were synthesized according to our previous methods.[12] The TSILs were analyzed by ^1H NMR, ^{13}C NMR, and MS spectroscopes, and the spectral data agreed with their structures (Scheme 1).

N,N,N-Trimethyl-N-propanesulfonic acid ammonium hydrogen sulfate [TMPSA][HSO_4]. ^1H NMR (300 Mz, D_2O): $\delta = 3.22$ (t, $J = 7.2$Hz, 2H, $-N-CH_2-$), 2.90 (s, 9H, $-CH_3$), 2.73 (t, $J = 7.8$Hz, 2H, $-CH_2-SO_3$), 1.98–2.00 (m, 2H, $-CH_2-$). ^{13}C NMR (D_2O,): $\delta = 65.0$, 52.5, 47.9, 18.9. Anal. Calcd. For $C_6H_{17}NO_7S_2$: C,25.80; H,6.13; N,5.01; Found: C,25.53; H,6.14; N,4.96.

N,N,N-Triethyl-N-propanesulfonic acid ammonium hydrogen sulfate [TEPSA][HSO_4]. ^1H NMR (300 Mz, D_2O): $\delta = 3.22$–3.05 (m, 8H, (6H+2H), $-N-CH_2-CH_3$, $-N-CH_2-C_2H_4-$), 2.85 (t, $J = 7.2$Hz 2H, $-CH_2-SO_3$), 1.96–1.98 (m, 2H, $-CH_2-$), 1.12 (m, 9H, $-CH_3$). ^{13}C NMR (75.5Mz, D_2O): $\delta = 56.0$, 53.0, 48.3, 18.93, 8.0. Anal. Calcd. For $C_9H_{23}NO_7S_2$: C,33.63; H,7.21; N,4.36; Found: C,33.45; H,7.24; N,4.21.

N,N,N-Tributyl-N-propanesulfonic acid ammonium hydrogen sulfate [TBPSA][HSO$_4$]. ^{1}H NMR (500 Mz, D_2O): $\delta = 3.28$(t, 2H, $J = 4.0$ Hz, $-N-CH_2-$), 3.13 (t, 6H, $J = 8.5$ Hz, $-N-CH_2-$), 2.85 (t, 2H, $J = 7.0$Hz, $-CH_2-SO_3$), 2.03 (m, 2H, $CH_2-CH_2-CH_2$), 1.56 (m, 6H, $-CH_2-CH_2CH_3$), 1.25–1.28 (m, 6H, $-CH_2-CH_3$), 0.84 (t, 9H, $J = 7.5$Hz, $-CH_3$). ^{13}CNMR (300Mz, D_2O): $\delta = 58.5$, 50.7, 48.4, 24.0, 20.4, 19.2, 14.5. Anal. Calcd. For $C_{15}H_{35}NO_7S_2$: C,44.42; H,8.70; N,3.45; Found: C,44.27; H,8.71; N,3.28.

N,N,N-Trimethyl-N-butanesulfonic acid ammonium hydrogen sulfate [TMBSA][HSO$_4$]. ^{1}H NMR (300 Mz, D_2O): $\delta = 3.24$ (t, $J = 8.4$ Hz, 2H, $-N-CH_2-$), 2.99 (s, 9H, $-CH_3$), 2.85 (t, $J = 7.5$ Hz, 2H, $-CH_2-SO_3$), 1.82 (m, 2H, $-CH_2-$), 1.69–1.71 (m, 2H, $-CH_2-$). ^{13}C NMR (D_2O,): $\delta = 66.2$, 53.2, 50.3, 21.5, 19.9. Anal. Calcd. For $C_7H_{19}NO_7S_2$: C, 28.66; H, 6.53; N, 4.77; Found: C, 28.40; H, 6.51; N, 4.92.

N,N,N-Triethyl-N-butanesulfonic acid ammonium hydrogen sulfate [TEBSA][HSO$_4$]. ^{1}H NMR (300 Mz, D_2O): $\delta = 3.15$ (q, $J = 7.2$ Hz, 6H, $-N-CH_2-CH_3$), 3.07 (t, $J = 8.4$ Hz, 2H, $-N-CH_2-C_3H_6SO_3$), 2.82 (t, $J = 7.2$ Hz, 2H, $-CH_2-SO_3$), 1.67–1.69 (m, 4H, $-C_2H_4-CH_2SO_3$), 1.10–1.12 (m, 9H, $-CH_3$). ^{13}C NMR (D_2O,): $\delta = 56.2$, 52.9, 50.3, 21.5, 20.2, 6.9. Anal. Calcd. For $C_{10}H_{25}NO_7S_2$: C, 35.78; H, 7.51; N, 4.18; Found: C, 35.82; H, 7.53; N, 4.36.

General Procedure for the Synthesis of α-Aminophosphonates

In a typical experiment, to a round-bottomed flask charged with aldehyde (10 mmol) and aniline (10 mmol) in water (5 mL), TSILs (0.5 mmol) were added under stirring. The mixture was stirred at room temperature for 5 min, and then trimethyl phosphite (12 mmol) was added. Upon completion (monitored by TLC), the products were separated by filtration and dried under vacuum. The TSILs could be separated from the reaction mixture by extraction with water. The products were identified by ^{1}H NMR and physical data (mp) and compared with authentic characterized samples as given in Table II.

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