A sulfonic acid functionalized ionic liquid as a homogeneous and recyclable catalyst for the one-pot synthesis of α-aminophosphonates

Jafar Akbari, Akbar Heydari *

Chemistry Department, Tarbiat Modares University, PO Box 14155-4838, Tehran, Iran

ABSTRACT

A sulfonic acid functionalized ionic liquid is used as a Brønsted acid catalyst for the one-pot, three-component synthesis of α-aminophosphonates from aldehydes and ketones at room temperature in water. This homogeneous catalytic procedure is simple and efficient and the catalyst can be reused at least six times without any noticeable decrease in catalytic activity.

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α-Aminophosphonates are important compounds from a biological point of view. It is known that they can act as peptide mimetics,[1] enzyme inhibitors,[2] and antibiotic and pharmacological agents,[3,4] and as herbicides, fungicides, insecticides[5] and plant growth regulators.[6] Substantial progress has been made towards the development of efficient methods for the preparation of these compounds.[7–9] Although many methods have been developed for hydrophosphonylation of imines, they suffer from drawbacks such as the use of expensive and hazardous phosphorus sources, high temperatures, multistep synthesis, stoichiometric amounts of catalyst and low product selectivities and yields. Recently, nucleophilic addition of phosphite to imines, catalyzed by an acid or a base, has emerged as an important alternative for the synthesis of α-aminophosphonates.[10–20] Typically, Lewis acids such as $SnCl_4$, $ZnCl_2$, $SnCl_2$, $BF_3 \cdot OEt_2$, $MgBr_2$ and $InCl_3$ have been used as catalysts[21,22] for this process. However, these reactions could not be carried out efficiently in a single step with carbonyl, amine and phosphite functionalities because amines and the water formed during imine formation can decompose or deactivate these Lewis acids.[23] In previous reports, we have shown that Brønsted acids such as heteropoly acid, guanidine hydrochloride and supported oxalic acid catalyzed the synthesis of α-aminophosphonates.[24–26] However, there is a need to develop one-pot syntheses of α-aminophosphonates using water-tolerant catalysts.

In recent years, ionic liquids have emerged as useful alternatives to conventional organic solvents due to their specific properties, such as wide liquid range, negligible vapor pressure, as well as their ease of recovery and reuse, which makes them viable alternatives to volatile organic solvents.[27,28] Combining the useful characteristics of solid acids and mineral acids, Brønsted-acidic task-specific ionic liquids (TSILs) have been synthesized to replace traditional mineral liquid acids, such as hydrochloric acid and sulfuric acid in chemical reactions.[29] Such acidic TSILs play dual roles as solvent and catalyst in organic reactions.[30–33] The use of Brønsted-acidic TSILs as catalysts is an area of ongoing activity and it is expected that these TSILs may further expand the application of ILs in chemistry.

In continuation of our interest in ionic liquid mediated organic reactions, we have explored the utility of a task-specific ionic liquid as a catalyst for the reaction between various aldehydes or ketones, amines and trimethyl phosphite to afford the corresponding α-aminophosphonates (Scheme 1). The synthesis of the ionic liquid was carried out using a method similar to that reported.[34] To the best of our knowledge, this is the first report of a functionalized ionic liquid catalyzed synthesis of α-aminophosphonates.
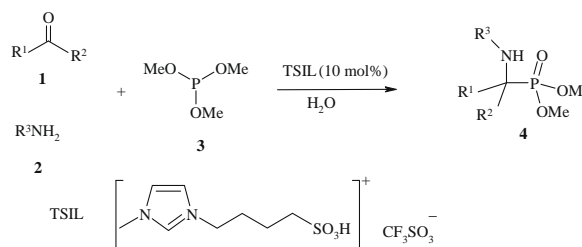
Scheme 1. Three-component reaction catalyzed by a TSIL.

* Corresponding author. Fax: +98 21 82883455.
E-mail address: akbar.heydari@gmx.de (A. Heydari).

The reaction of trimethyl phosphite with the imine generated in situ from benzaldehyde and aniline at room temperature in the presence of 5 mol % of the sulfonic acid functionalized ionic liquid afforded the corresponding α-aminophosphonate in 98% yield (Table 1, entry g). The reaction was complete in 10 min at room temperature and the product was isolated in high purity by filtration. In order to examine the scope of this process, several aliphatic and aromatic aldehydes were reacted under the optimized conditions and the results are shown in Table 1. Both aromatic and aliphatic aldehydes reacted with aniline to form the corresponding α-aminophosphonates. Importantly, aromatic aldehydes possessing either electron-donating or electron-withdrawing substituents reacted efficiently giving excellent yields of the expected α-aminophosphonates **4a,b,e,h,i**. Encouraged by these results, we next directed our studies towards a ketone and performed the reaction under similar conditions. Reaction of 4-methoxyacetophenone with aniline and trimethyl phosphite proceeded under mild conditions (room temperature, 1 h) to give the corresponding α-aminophosphonate **4l** in excellent yield and high purity (Table 1, entry l), despite the fact that the reactions of ketones and amines has been repeatedly reported as challenging.[35] It is important to note that when benzaldehyde, aniline and trimethyl phosphite were reacted in the absence of the ionic liquid, the reaction did not proceed. The effect of solvent was also examined. Reaction in the absence of water did not take place, but in the presence of water (1 mL) the product formed rapidly.

The mechanism of this reaction is believed to involve formation of an activated imine by the 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 α-aminophosphonate and methanol as shown in Scheme 2.[36]

The ionic liquid could be recycled after removing the products and water. The reaction of benzaldehyde, aniline and trimethyl phosphite gave the corresponding product in similar yields and purities over six cycles (Fig. 1). The ionic liquid retained its structure as confirmed by NMR spectroscopy.

In summary, we have demonstrated that a readily available, highly efficient, task-specific ionic liquid can be used as a recyclable catalyst for the synthesis of α-aminophosphonates from aldehydes and ketones in water.

General procedure for the one-pot, three-component synthesis of α-aminophosphonates: TSIL (0.018 g, 0.1 mmol) was added to a mixture of aldehyde/ketone (2 mmol) and amine or amine derivative (2.2 mmol) in water (1 mL) at room temperature. The mixture was stirred at room temperature for 10 min and then trimethyl
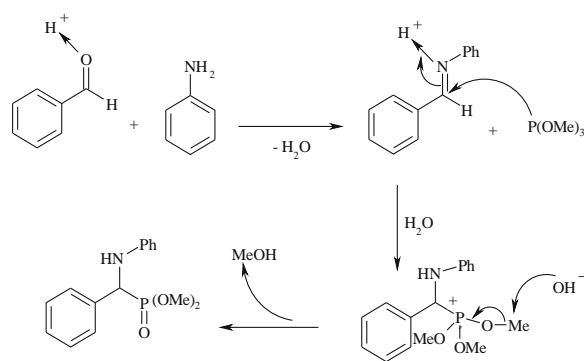
Scheme 2. Proposed mechanism for the three-component reaction.
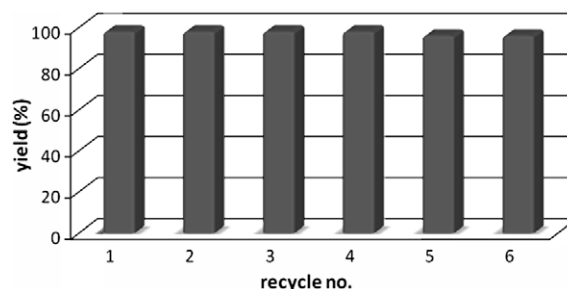

Figure 1. Recycling of the TSIL catalyst. All reactions run for 10 min at rt.

phosphite (3 mmol) was added. After completion of the reaction, as indicated by TLC, the ionic liquid was separated from the reaction mixture by extraction with water. The products were separated by filtration and vacuum dried. The products were identified by NMR spectroscopy. Spectral data for selected products: *Compound* **4a**: white solid, mp 60 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.51 (m, 1H), 3.79 (d, J = 11.8 Hz, 3H), 3.83 (d, J = 10.1 Hz, 3H), 5.20 (d, J = 24 Hz, 1H), 6.80–7.28 (m, 5H), 7.30 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 56.1 (d, $^2J_{P-C}$ = 7.0 Hz, OCH$_3$), 56.2 (d, $^2J_{P-C}$ = 6.8 Hz, OCH$_3$), 57.2 (d, $^1J_{P-C}$ = 150 Hz, CH), 114.3 (CH), 120.0 (CH), 128.2 (d, $^3J_{P-C}$ = 5.8 Hz, CH), 128.4 (d, $^3J_{P-C}$ = 3.1 Hz, CH), 130.1 (CH), 131.2 (C), 140.0 (C), 146.6 (d, $^2J_{P-C}$ = 14.5 Hz, C). *Compound* **4g**: white solid, mp 87 °C; ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.51 (d, J = 10.5 Hz, 3H), 3.81 (d, J = 10.6 Hz, 3H), 4.82 (d, J = 24 Hz, 1H), 4.84 (br s, 1H), 6.64 (d, J = 8.0 Hz, 2H), 6.74 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 54.1 (d, $^2J_{P-C}$ = 7.0 Hz, OCH$_3$), 54.2 ($^2J_{P-C}$ = 6.8 Hz, OCH$_3$), 56.2 (d, $^1J_{P-C}$ = 150 Hz, CH), 114.3 (CH), 119.0 (CH), 128.2 (d, $^3J_{P-C}$ = 5.8 Hz, CH), 128.4 (d, $^3J_{P-C}$ = 3.1 Hz, CH), 129.1 (CH), 131.2 (CH), 136.0 (C), 146.6 (d, $^2J_{P-C}$ = 14.5 Hz, C).

Acknowledgement

References and notes

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Table 1
Synthesis of α-aminophosphonates from aldehydes or a ketone, amines and trimethylphosphite

	R^1	R^2	R^3	Time (h)	Yield (%)
a	4-ClC$_6$H$_4$	H	Ph	15 min	96
b	4-O$_2$NC$_6$H$_4$	H	Ph	15 min	98
c	2-Furyl	H	Ph	1	95
d	4-Pyridyl	H	Ph	1	94
e	4-MeOC$_6$H$_4$	H	Ph	2	96
f	Benzyl	H	Ph	0.5	98
g	Phenyl	H	Ph	10 min	98
h	4-NCC$_6$H$_4$	H	Ph	0.5	96
i	4-MeC$_6$H$_4$	H	Ph	0.5	95
j	*i*-Propyl	H	Ph	1	97
k	Cinnamyl	H	Ph	1	94
l	4-MeOC$_6$H$_4$	Me	Ph	1	92
m	Phenyl	H	Benzyl	15 min	98
n	Phenyl	H	4-ClC$_6$H$_4$	2	95
o	Phenyl	H	4-MeC$_6$H$_4$	1	92
p	Phenyl	H	4-MeOC$_6$H$_4$	45 min	96

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