One-pot synthesis of α–amino phosphonates in chloroaluminate-based ionic liquid

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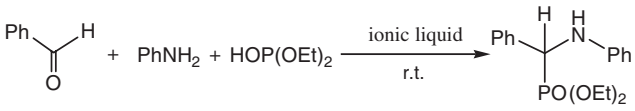
In chloroaluminate-based ionic liquid [bmim]Cl–$AlCl_3$, *N*=0.67, the one-pot coupling reaction of carbonyl compounds, amines and diethyl phosphite gave the corresponding α–amino phosphonates in good to excellent yields. The method is appropriate to both primary and secondary amines. The effect of the ionic liquids with different compositions is also investigated.

Keywords: ionic liquids, catalysis, α–amino phosphonates, synthesis

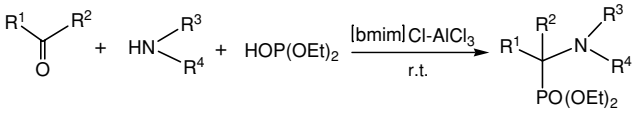
In synthetic organic chemistry, one of the most attractive developments in recent years has been the organic reaction in ionic liquids.[1] Ionic liquids not only provide an environmentally friendly media for many reactions, but also catalyse some processes. The diversity of the solutes solvated by ionic liquids is vast, ranging from organic to organometallic to inorganic substrates. Their properties, such as negligible vapour pressure and recyclability make them useful alternatives to conventional molecular organic solvents in some reactions.[2] Chloroaluminate-based ionic liquids have aroused our interest owing to their Lewis acidity, which can be varied over a range, and their intrinsic ability to solvate substances.[3] These properties offer the advantage of homogeneous Lewis acid catalysis and prompted us to investigate their application in organic synthesis.

As important structural analogues of the corresponding α–amino acids, α–amino phosphonates have received an increasing amount of attention. They have been widely used in biochemical and pharmaceutical chemistry, for example, as enzyme inhibitors,[4] antibiotics and pharmacological agents.[5] Thus, it is important to search for a convenient and useful method for the synthesis of this type of compounds. One of the most attractive approaches for the preparation of α–amino phosphonates is by a three-component coupling reaction. Under the catalysis of Lewis acid, the reaction of carbonyl compound, amine and diethyl phosphite produces the corresponding α–amino phosphonates. Traditional Lewis acids such as $SnCl_2$, $SnCl_4$, BF_3–Et_2O,[6] as well as $ZnCl_2$ and $MgBr_2$[7] have been used to catalyse this reaction, $La(OTf)_3$, $TaCl_5$–SiO_2 and $InCl_3$ were found to be effective for this procedure.[8-10] Recently, $LiClO_4$ and SmI_2 have also been employed to promote this reaction.[11,12] However, there are some drawbacks to these procedures. For example, some Lewis acids are moisture sensitive and require special care in handling and storage, and some need a long reaction time and more catalyst has to be used. Moreover, metal triflates are highly expensive. So the development of new methods with greater efficiency, convenient procedures capable of delivering better yields is of great interest. Here, we report a facile synthesis of α–amino phosphonates in chloroaluminate-based ionic liquids.

The ionic liquids [bmim]Cl–$AlCl_3$ were prepared from $AlCl_3$ and 1-butyl-3-methylimidazolium chloride [bmim]Cl.[13] The Lewis acidity of such ionic liquids is a function of the apparent mole fraction of $AlCl_3$, *N*, present in the liquid. It can be varied over a wide range by manipulating the relative amounts of organic base and $AlCl_3$. $AlCl_3$ mole fractions less than 0.5 afford basic, *N* =0.5 gives neutral, and those greater than 0.5 afford acidic ionic liquids. The Lewis acidic species in such liquids is $[Al_2Cl_7]^-$, and its concentration in the liquid is the function of the mole fraction of $AlCl_3$. This was confirmed by Salunkhe by ^{27}Al NMR spectral studies.[3] In an attempt to analyse the effect of Lewis acidity on this reaction, we investigated the reaction in several ionic liquids of different compositions. The reaction of benzaldehyde, aniline and diethyl phosphite was selected as representative to optimise the reaction conditions (Scheme 1).



Scheme 1



1 **2** **3**

Scheme 2

The model reaction proceeded at ambient temperature and was monitored by TLC. In the basic ionic liquid [bmim]Cl (*N*=0), it gave only trace products. In neutral ionic liquid [bmim]Cl–$AlCl_3$, *N*=0.5, a moderate yield was given. But in acidic ionic liquid [bmim]Cl–$AlCl_3$, *N*=0.67, the reaction took place smoothly and a very high yield was obtained. So a powerful catalysis of this chloroaluminate-based ionic liquid to the reaction was evident. For the reactants aldehyde, amine, diethyl phosphite and ionic liquid, an appropriate mole ratio was 1.0 : 1.0 : 1.2 : 1.0. The results of this model reaction in a series of ionic liquids are listed in Table 1.

Encouraged by these results, we studied the reaction using various carbonyl compounds (aldehydes and ketones, **1**), amines (primary and secondary, **2**) and diethyl phosphite in ionic liquid [bmim]Cl–$AlCl_3$ (*N*=0.67) under the similar conditions (Scheme 2),[14] and the corresponding α–amino phosphonates (**3**) were generated from this one-pot reaction with good to excellent yields.

The results are summarised in Table 2. It is clear that both aldehydes and ketones could undergo the reaction with high yields although the reaction of ketones proceeded slower than

Table 1 The reaction in several ionicliquids of different compositions[a]

Entry	Ionic liquid	*N*	Yield[b]/%
1	[bmim]Cl		Trace
2	[bmim]Cl–$AlCl_3$	0.33	35
3	[bmim]Cl–$AlCl_3$	0.50	72
4	[bmim]Cl–$AlCl_3$	0.67	95

[a]All reactions were run in aldehyde–aniline-diethyl phosphite–ionic liquid = 1.0:1.0:1.2:1.0 (mole ratio) at room temperature. [b]Isolated yields.

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Table 2 The reaction of carbonyl compounds, amines and diethyl phosphite in ionic liquid[a]

Entry	R^1	R^2	R^3	R^4	Product	Time/h	Yield[b]/%
1	Ph	H	Ph	H	**3a**[8a]	2.0	95
2	Ph	H	$PhCH_2$	H	**3b**[8a]	2.0	90
3	2-furyl	H	Ph	H	**3c**[8a]	2.5	88
4	2-furyl	H	*p*-$MeOC_6H_4$	H	**3d**[14]	2.5	85
5	Ph	H	*p*-$MeOC_6H_4$	H	**3e**[14]	2.5	86
6	PhCH=CH	H	Ph	H	**3f**[8a]	3.5	80
7	*p*-BrC_6H_4	H	Ph	H	**3g**[11a]	2.0	95
8	*o*-$O_2NC_6H_4$	H	Ph	H	**3h**[16]	2.0	94
9	Ph	CH_3	Ph	H	**3i**[12]	4.0	82
10	$-(CH_2)_5-$		Ph	H	**3j**[15]	4.0	85
11	Ph	H	$-(CH_2)_5-$		**3k**[11b]	3.0	90
12	Ph	H	Et	Et	**3l**[11b]	3.0	85
13	*o*-$O_2NC_6H_4$	H	$-(CH_2)_5-$		**3m**[11a]	2.5	92

[a]All reactions were run in aldehyde–aniline–diethyl phosphite–ionic liquid = 1.0:1.0:1.2:1.0 (mole ratio) at room temperature.
[b]Isolated yields. The structures of the products are confirmed by IR, ^{1}H NMR, ^{31}P NMR spectra and elemental analysis.

that of aldehydes (Entries 9 and 10). It was also found that the reaction of imine generated from the corresponding carbonyl compound and primary amine with diethyl phosphite gave the same results as this one pot reaction. Another obvious characteristic of this reaction is that the reaction of carbonyl compounds, secondary amines and diethyl phosphite gave the corresponding tertiary α–amino phosphonates in good yields, although imines did not form using this procedure.

In summary, we have developed a new and efficient procedure for the synthesis of α–amino phosphonates in ionic liquid [bmim]Cl–$AlCl_3$. We have shown that [bmim]Cl–$AlCl_3$ has a powerful catalytic activity in this type of reaction. The method offers several advantages such as mild reaction conditions, short reaction time, high yield of products, and simple experimental operation, which leads to a useful and attractive process for the preparation of this type of compound. Further applications of ionic liquids in organic synthesis are being explored in our laboratory.

Experimental

All manipulations were conducted under an atmosphere of dry N_2. ^{1}H NMR and ^{31}P NMR spectra were obtained on a Bruker-300 spectrometer using TMS as an internal reference. IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Elemental analyses were determined on a Carlo Erba EA1110 analyser.

Typical procedure.
Ionic liquids were prepared from $AlCl_3$ and 1-butyl-3-methylimidazolium chloride [bmim]Cl according to ref. 13. To this liquid (1.0 mmol) was added carbonyl compound (1.0 mmol), amine (1.0 mmol) followed by diethyl phosphite (1.2 mmol). The resulting mixture was stirred at room temperature, then quenched with water and extracted with ether for three times. The combined solution was then washed with water, dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel with hexane/ethyl acetate (2:1) as eluent to yield the products.

3a: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.10 (t, *J*=6.9 Hz, 3H), 1.30 (t, *J*=6.9 Hz, 3H), 3.64–4.14 (m, 4H), 4.75 (d, *J*=24.0 Hz, 1H), 6.58–6.75 (m, 3H), 7.07–7.50 (m, 7H); ^{31}P NMR: δ 24.0; IR (CCl_4): 3325, 2954, 1437, 1358, 1245, 1033 cm^{-1}; Calcd for $C_{17}H_{22}NO_3P$: C, 63.94; H, 6.94; N, 4.39. Found: C, 63.80; H, 6.85; N, 4.43.

3c: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.22 (t, *J*=6.9 Hz, 3H), 1.30 (t, *J*=6.9 Hz, 3H), 3.28 (br, 1H), 3.88–4.23 (m, 4H), 4.92 (d, *J*=23.7 Hz, 1H), 6.35–6.42 (m, 2H), 6.69–6.81 (m, 3H), 7.15–7.40 (m, 3H); ^{31}P NMR: δ 24.0; IR (CCl_4): 3292, 2983, 1602, 1499, 1319, 1255, 1151, 1029 cm^{-1}; Calcd for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53. Found: C, 58.75; H, 6.70; N, 4.42.

3e: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.13 (t, *J*=6.9 Hz, 3H) , 1.30 (t, *J*=6.9 Hz, 3H), 3.70–4.17 (m, 4H), 3.72 (s, 3H), 4.70 (d, *J*=24.0 Hz, 1H), 6.56 (d, *J*=9.0 Hz, 2H), 6.71 (d, *J*=9.0 Hz, 2H), 7.27–7.37 (m, 3H), 7.46–7.49 (m, 2H); ^{31}P NMR: δ 24.0; IR (CCl_4): 3328, 2945, 1440, 1362, 1240, 1038 cm^{-1}; Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01. Found: C, 63.82; H, 6.86; N, 4.09.

3g: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.18 (t, *J*=7.2 Hz, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 3.79–3.84 (m, 1H), 3.97–4.05 (m, 2H), 4.12 (t, *J*=7.2Hz, 2H), 4.72 (d, *J*=24.3 Hz, 1H), 6.57 (d, *J*=7.8 Hz, 2H), 6.71–6.76 (m, 1H), 7.10–7.15 (m, 2H), 7.35–7.38 (m, 2H), 7.48 (d, *J*=8.4 Hz, 2H); ^{31}P NMR: δ 24.0; IR (CCl_4): 3326, 2962, 1445, 1362, 1233, 1028 cm^{-1}; Calcd for $C_{17}H_{21}BrNO_3P$: C, 51.27; H, 5.32; N, 3.52. Found: C, 51.43; H, 5.22; N, 3.60.

3i: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.21–1.30 (m, 6H), 2.00 (d, *J*=16.5 Hz, 3H), 3.81–4.06 (m, 4H), 4.76 (br, 1H), 6.41 (d, *J*=7.5 Hz, 2H), 6.70–6.72 (m, 1H), 7.01–7.06 (m, 2H), 7.31–7.38 (m, 3H), 7.61–7.65 (m, 2H); ^{31}P NMR: δ 24.3; IR (CCl_4): 3296, 2980, 1610, 1506, 1322, 1257, 1095, 1016 cm^{-1}; Calcd for $C_{18}H_{24}NO_3P$: C, 64.85; H, 7.26; N, 4.20. Found: C, 64.77; H, 7.20; N, 4.22.

3j: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.23–1.31 (m, 6H), 1.55–1.87 (m, 8H), 2.18–2.20 (m, 2H), 3.30 (br, 1H), 3.99–4.11 (m, 4H), 6.82 (t, *J*=7.2Hz, 1H), 7.05 (d, *J*=7.8 Hz, 2H), 7.16–7.21 (m, 2H); ^{31}P NMR: δ 24.3; IR (CCl_4): 3312, 2938, 1602, 1500, 1322, 1220, 1093, 1017 cm^{-1}; Calcd for $C_{16}H_{26}NO_3P$: C, 61.72; H, 8.42; N, 4.50. Found: C, 61.48; H, 8.55; N, 4.43.

3l: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.04–1.09 (m, 9H), 1.35 (t, *J*=7.2 Hz, 3H), 2.33 (q, *J*=6.6 Hz, 2H), 3.00 (q, *J*=6.6 Hz, 2H), 3.76–3.96 (m, 2H), 4.17 (d, *J*=23.7 Hz, 1H), 4.28 (q, *J*=7.2 Hz, 2H), 7.32–7.37 (m, 3H), 7.49 (d, *J*=6.6 Hz, 2H); ^{31}P NMR: δ 24.0; IR (CCl_4): 3012, 2938, 1603, 1492, 1322, 1237, 1094, 1015 cm^{-1}; Calcd for $C_{15}H_{26}NO_3P$: C, 60.19; H, 8.75; N, 4.68. Found: C, 60.08; H, 8.69; N, 4.72.

3m: ^{1}H NMR (300MHz, $CDCl_3$): δ=1.11 (t, *J*=6.9Hz, 3H), 1.35 (t, *J*=6.9Hz, 3H), 1.57–1.64 (m, 6H), 2.36–2.40 (m, 2H), 2.78–2.82 (m, 2H), 3.77–4.01 (m, 3H), 4.23–4.32 (m, 2H), 7.42–7.47 (m, 1H), 7.55–7.60 (m, 1H), 7.75 (d, *J*=7.8Hz, 1H), 8.02 (d, *J*=8.1Hz, 1H); ^{31}P NMR: δ 24.0; IR (CCl_4): 3028, 2990, 1605, 1498, 1312, 1235, 1094, 1010 cm^{-1}; Calcd for $C_{16}H_{25}N_2O_5P$: C, 53.93; H, 7.07; N, 7.86. Found: C, 53.87; H, 7.10; N, 7.82.

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