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An efficient synthesis of α-aminophosphonates from aldehydes, amines and phosphite in ionic liquids

Issa Yavari[a] and Rahimeh Hajinasiri[b*]

[a]*Chemistry Department, Tarbiat Modares University, Tehran, Iran*

[b]*Chemistry Department, Islamic Azad University, Ghaemshahr, Mazandaran, Iran*

Abstract: Ionic liquids such as 1, 3-dialkylimidazolium bromides make excellent catalysts and solvents for synthesis of α-aminophosphonates from aldehydes, amines and phosphites. The ionic liquid is successfully regenerated and reused.

Keywords: α-Aminophosphonates; Ionic liquid; Phosphites.

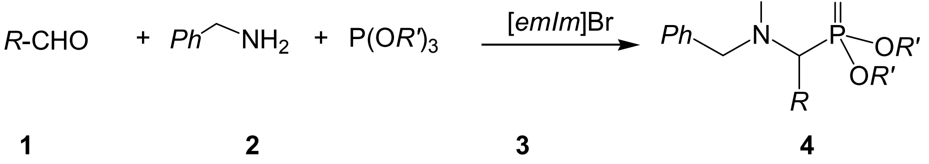
Introduction

Ionic liquids (ILs) have gained tremendous attention in the last 15 years [1–3]. They are, among other uses, solvents and are frequently fitted with attributes like "modern", "green", "designable", "non-volatile", "non-coordinating" etc., although it is increasingly recognized that none of these labels should be used lightly. Nonetheless, many chemical reactions have been attempted and successfully performed in IL media and oftentimes these systems show interesting and peculiar features. Yet, considerable work in IL chemistry is still based on trial-and-error rather than fundamental understanding and rational design. To rationalize the differences between ILs and molecular solvents, it is important to understand their properties [1–6].

α-Aminophosphonic acids are probably the most important substitutes for the corresponding amino acids in biological systems [7-10]. A large volume of research on their synthesis and biological activities has been reported during the last 20 years. A number of potent antibiotics, enzyme inhibitors, and pharmacological agents are *α*-aminophosphonic acids as well as their derivatives, notably peptides [11-14]. We wish to report that ILs make excellent catalysts and solvents for synthesis of *α*-aminophosphonates from aldehydes, amines and phosphites.

Results and Discussion

The reaction of aldehydes **1**, amines **2**, and phosphites **3** proceeds smoothly in [emim][Br] ionic liquid as a solvent at rt to produce *α*-aminophosphonates **4,** with 60-80% yields (Scheme 1, Table 1). The results indicated that ionic liquid exhibited excellent catalytic activities.



Scheme 1

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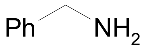
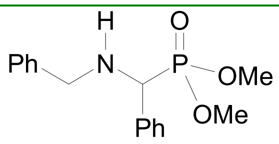
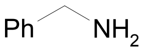
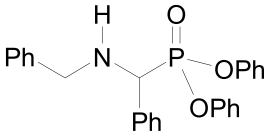
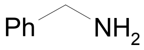
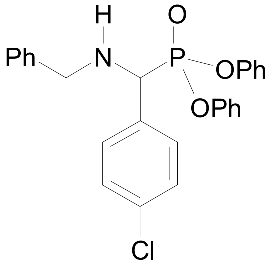
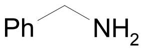
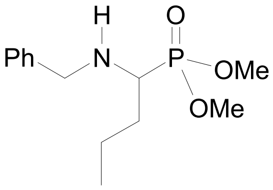
*Corresponding author. Fax: (+98) 123 2211647; E-Mail: *Rhmhajinsiri@yahoo.com*

Table1: Some of *α*-aminophosphonates prepared from aldehydes, amines and phosphite in [emim][Br] ionic liquid as a solvent

Entry	Aldehyde	Amine	Phosphate	Product	Yield(%)	
1	Ph-CHO		$P(OMe)_3$		76	**4a**
2	Ph-CHO		$P(OPh)_3$		70	**4b**
3	$4\text{-}ClC_6H_4\text{-}CHO$		$P(OPh)_3$		66	**4c**
4	*n*-Pr-CHO		$P(OMe)_3$		70	**4d**

The products were characterized based on their IR, ^1H NMR, and ^{13}C NMR. The mass spectra of compounds **4a-4d** displayed molecular ion peaks at appropriate *m/z* values. The ^1H NMR spectrum of **4a** exhibited characteristic doublets ($^3J_{PH}$ =10.5) for methoxy groups at δ 3.45 and 3.72, AB system for NCH_2 at δ 3.5 ($^2J_{HH}$ =13.5) and δ 3.8 ($^2J_{HH}$ = 13.4), and doublet for CH at δ 4.06 ($^3J_{PH}$ = 20.7) along with multiplets for the phenyl groups. The proton-decoupled ^{13}C NMR spectra of **4a** showed eleven distinct resonances in agreement with the proposed structure. The spectral data of **4b-4d** are similar to those of **4a**, except for the aryl and alkyl moieties, which exhibit characteristic signals in appropriate regions of the spectra.

In conclusion, IL [emim][Br] is proved to be useful and novel reaction media for synthesis of *α*-aminophosphonates from simple starting materials, avoiding the use of highly polar organic solvents. The use of imidazolium ILs significantly enhanced the rate of formation of *α*-aminophosphonates at room temperature. The present procedure has the advantage that the reaction is carried out in ionic liquid media as a green solvent, and the starting material can be used without any activation or modification. The procedure described here provides an acceptable one-pot method for the preparation of *α*-aminophosphonates.

Experimental

Compounds **1**, **2**, **3** and ionic liquids were obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^1H NMR and ^{13}C NMR spectra: Bruker DRX-300 AVANCE instrument; in $CDCl_3$ at 300 and 75 MHz, respectively; *δ* in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

General Procedure for the Preparation of Compounds **4a-4d**

To a stirred solution of **1** (2 mmol) and **2** (2 mmol) in 1 mL of IL [emim]Br was added 2 mmol of **3** at rt. After completion of the reaction (0.5-1 h), as indicated by TLC (*Et*OAc/*n*-hexane, 2:1), the products were extracted with *Et*$_2$O (3 × 10 cm^3). The solvent was evaporated under reduced pressure to leave the crude product, which was purified by column chromatography on silica gel and eluted with a mixture of *n*-hexane:*Et*O*Ac* (3:1) to afford pure α-aminophosphonates **4**. The IL was recovered by addition of water (5 mL), then collected and dried under vacuum. These reactions were performed without any protective atmosphere of inert gas.

Selected spectroscopic data:

Dimethyl [(benzylamino) (phenyl) methyl] phosphonate (4a, $C_{16}H_{20}NO_3P$):

Yellow oil; yield: 0.44 g (76%). IR (KBr): $\bar{\nu}$ = 1246 (P=O), 2953 (CH) cm^{-1}. EI-MS: 305 (2, M$^+$), 290 (5), 274 (35), 214 (38), 199 (38), 196 (80), 91 (100), 31 (86) 15 (70). ^{1}H NMR: δ = 2.98 (bs, NH), 3.48 (d, $^{3}J_{\text{P-H}}$ = 10.5, O*Me*), 3.53 (d, ^{2}J= 13.5, NCH$_2$), 3.73 ($^{3}J_{\text{P-H}}$ =10.5, O*Me*), 3.8 (^{2}J =13.4, NCH$_2$), 4.06 ($^{1}J_{\text{P-H}}$ =20.7, CH), 7.3 -7.5 (m,10 CH). ^{13}C NMR: δ = 51.1 (d, $^{3}J_{\text{C-P}}$= 17.4, NCH$_2$), 52.8 (d, $^{2}J_{\text{C-P}}$= 6.8, O*Me*), 53.3 (d, $^{2}J_{\text{C-P}}$= 6.8, O*Me*), 59.4 (d, $^{1}J_{\text{C-P}}$= 152.0, CH), 127.3 (CH), 128.0 (d, $^{5}J_{\text{C-P}}$= 2.9, CH), 128.6 (4CH), 128.7 (2CH), 129.1 (d, $^{3}J_{\text{C-P}}$= 6.2, 2CH), 136.8 (d, $^{2}J_{\text{C-P}}$= 2.9, C), 140.3 (C). ^{31}P NMR: 27.06 [P(O)(O*Me*)$_2$].

Diphenyl [(benzylamino) (phenyl) methyl] phosphonate (4b, $C_{26}H_{24}NO_3P$):

White solid; m.p.: 136°C, yield: 0.60 g (70%). IR (KBr): $\bar{\nu}$ = 1262 (P=O), 2949 (CH) cm^{-1}. EI-MS: 429 (2, M$^+$), 324 (25), 234 (98), 196 (98), 106 (70), 93 (95), 91 (100). ^{1}H NMR: δ = 2.91 (bs, NH), 3.65 (d, ^{2}J= 13.4, NCH$_2$), 3.93 (d, ^{2}J= 13.4, NCH$_2$), 4.36 ($^{1}J_{\text{P-H}}$ =21.2, CH), 7.3 – 7.5 (m, 15 CH). ^{13}C NMR: δ = 51.1 (d, $^{3}J_{\text{C-P}}$= 17.0, NCH$_2$), 59.4 (d, $^{1}J_{\text{C-P}}$= 152.0, CH), 120.8 (d, $^{3}J_{\text{C-P}}$= 4.0, CH), 121.1 (d, $^{3}J_{\text{C-P}}$= 4.25, 2CH), 125.2 (CH), 125.3 (CH), 127.4 (CH), 128.4 (d, $^{5}J_{\text{C-P}}$= 3.1, CH), 128.6 (2CH), 128.8 (2CH), 128.8 (2CH), 128.9 (d, $^{4}J_{\text{C-P}}$= 2.4, 2CH), 129.5 (d, $^{3}J_{\text{C-P}}$= 6.8, 2CH), 129.8 (2CH), 129.9 (2CH), 136.9 ($^{2}J_{\text{C-P}}$= 2.9, C), 140 (C), 151.2 (d, $^{3}J_{\text{C-P}}$= 9.6, C$_{ipso}$), 151.6 (d, $^{3}J_{\text{C-P}}$= 9.6, C$_{ipso}$).^{31}P NMR: 17.73 [P(O)(O*Ph*)$_2$].

Diphenyl [(benzylamino) (4- chlorophenyl) methyl]phosphonate (4c, $C_{26}H_{24}NO_3P$):

Yellow oil; yield: 0.51 g (66%). IR (KBr): $\bar{\nu}$ = 1262 (P=O), 2949 (CH) cm^{-1}. EI-MS: 464 (2, M$^+$), 434 (35), 359 (35), 234 (100), 231 (68), 106 (85), 93 (85), 91 (100), 35 (65). ^{1}H NMR: δ = 2.91 (bs, NH), 3.66 (d, ^{2}J= 13.4, NCH$_2$), 3.92 (d, ^{2}J= 13.5, NCH$_2$), 4.49 ($^{1}J_{\text{P-H}}$ =21.3, CH), 6.99-7.66 (m, 14 CH). ^{13}C NMR: δ = 51.2 (d, $^{3}J_{\text{C-P}}$= 16.7, NCH$_2$), 59.0 (d, $^{1}J_{\text{C-P}}$= 167.0, CH), 120.7 (d, $^{3}J_{\text{C-P}}$ = 4.4, 2CH), 121.0 (d, $^{3}J_{\text{C-P}}$= 4.2, 2CH), 125.3 (CH), 125.4 (CH), 127.4 (CH), 128.7 (2CH), 128.8 (2CH), 128.9 (d, $^{4}J_{\text{C-P}}$= 2.4, 2CH), 130.0 (d, $^{3}J_{\text{C-P}}$= 6.2, 2CH), 131.1 (2CH), 131.2 (2CH), 134.9 (C), 135.0 ($^{2}J_{\text{C-P}}$= 2.9, C), 151.0 (d, $^{3}J_{\text{C-P}}$= 10.7, C$_{ipso}$), 151.2 (d, $^{3}J_{\text{C-P}}$= 10.7, C$_{ipso}$).^{31}P NMR: 17.0 [P(O)(O*Ph*)$_2$].

Dimethyl [1-(benzylamino) butyl] phosphonate (4d, $C_{13}H_{22}NO_3P$):

Yellow oil; yield: 0.38g (70%). IR (KBr): $\bar{\nu}$ = 1246 (P=O), 2953 (CH) cm^{-1}. EI-MS: 271 (2, M$^+$), 215 (25), 165 (35), 162 (68), 106 (70), 109 (86), 91 (100), 57(90).^{1}H NMR: δ =0.86 (t, ^{3}J= 7.3, *Me*), 1.29-1.67 (m, 2CH$_2$), 1.39-1.51 (m, 2CH$_2$), 3.5 (m,CH), 2.88 (bs, NH), 3.74 (d, $^{3}J_{\text{P-H}}$ = 10.4, O*Me*), 3.75 (d, $^{3}J_{\text{P-H}}$ = 10.4, O*Me*), 3.90 (d, $^{2}J_{\text{H-H}}$ = 14.2, NCH$_2$), 4.00 (d, $^{2}J_{\text{H-H}}$ = 13.3, NCH$_2$), 7.22 – 7.4 (m, 5 CH). ^{13}C NMR: δ = 13.7 (*Me*), 19.4 (d, $^{3}J_{\text{C-P}}$= 11.0, CH$_2$), 32.3 (d, $^{2}J_{\text{C-P}}$ = 1.9, CH$_2$), 51.1 (d, $^{3}J_{\text{C-P}}$ = 15.0, NCH$_2$), 51.9 (d, $^{2}J_{\text{C-P}}$= 5.12, O*Me*), 52.2 (d, $^{2}J_{\text{C-P}}$ = 6.9, O*Me*), 53.5 (d, $^{1}J_{\text{C-P}}$ = 148.0, CH), 127.1 (CH), 128.5 (2CH), 128.7 (2CH), 141.2 (C). ^{31}P NMR: 26.90 [P(O)(O*Me*)$_2$].

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