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Efficient Synthesis of α-Aminophosphonates via One-Pot Reactions of Aldehydes, Amines, and Phosphates in Ionic Liquid

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ABSTRACT: *Ionic liquids such as 1,3-dialkylimidazolium bromides make excellent solvents for synthesis of α-aminophosphonates from aldehydes, amines, and phosphites. The ionic liquids are successfully regenerated and reused.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:625–629, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20724

INTRODUCTION

Ionic liquids (ILs) have gained great attention in recent years [1–3]. ILs have a high polarity and low vapor pressure. These characteristics combined with immiscibility with most of the less polar organic solvents led to their use as a solvent or cosolvent in catalysis. ILs have shown great assurance as an alternative to conventional solvents [3]. ILs have the unique properties of high thermal stability, low vapor pressure, immiscibility with a number of organic solvents, nonflammability, and recyclability [4–6].

α-Aminophosphonic acids are probably the most important substitutes for corresponding amino acids in biological systems [7–10]. The importance of this area is highlighted by an increasing number of studies dedicated to the topic, and a large volume of research on their synthesis and biological activities has been reported in recent years. A number of potent antibiotics, enzyme inhibitors, and pharmacological agents are α-aminophosphonic acids as well as their derivatives, particularly peptides [11–13]. Aminophosphonic acids are also found as constituent of natural products. Several methods are available for the preparation of α-aminophosphonic acids [14–24]. Here, we describe an efficient method for the synthesis of α-aminophosphonates through the reaction of aldehydes **1**, amines **2**, and phosphites **3** in ethyl methyl imidazolium bromide.

RESULTS AND DISCUSSION

The reaction of aldehydes **1**, amines **2**, and phosphites **3** proceeds smoothly with ethyl methyl imidazolium bromide as a solvent at room temperature to produce α-aminophosphonates **4** in good yields (Fig. 1, Table 1).

For optimizing the reaction conditions, a sample reaction between benzaldehyde, benzyl amine, and triphenylphosphite was carried out with different ILs as solvents (Fig. 2, Table 2). The results indicated that IL ethyl methyl imidazolium

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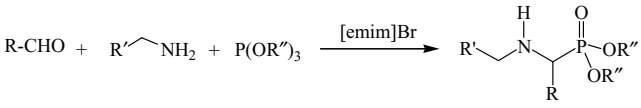


FIGURE 1 Synthesis of α-aminophosphonate derivatives.

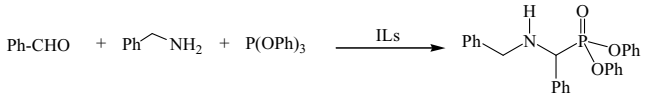


FIGURE 2 The reaction of benzaldehyde, benzyl amine, and triphenylphosphite.

bromide is an excellent solvent for these reactions (see Table 2).

The products were characterized on the basis of their IR, ^{1}H NMR, and ^{13}C NMR studies. The mass spectra of compounds **4a–4i** displayed molecular ion peaks at appropriate *m*/*z* values.

In conclusion, ILs are proved to be useful and novel reaction media for the synthesis of α-aminophosphonates from simple starting materials, avoiding the use of highly polar organic solvents. The effects of the type of IL used on the activity and selectivity were investigated. The IL [emim][Br] was found to be the most effective. The use of imidazolium ILs at room temperature

TABLE 1 α-Aminophosphonate Derivatives

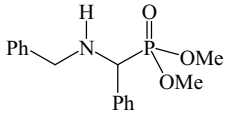
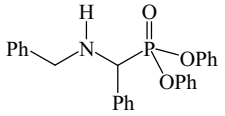
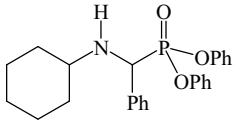
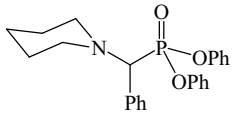
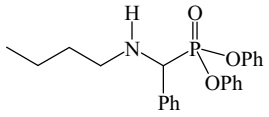
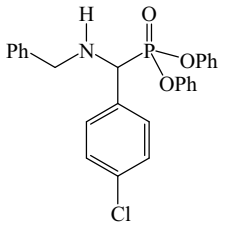
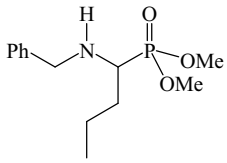
Entry	*Aldehyde*	*Amine*	*Phosphite*	*Product*		*Yield (%)*
1	Ph-CHO	Ph NH$_2$	P(OMe)$_3$		**4a**	76
2	Ph-CHO	Ph NH$_2$	P(OPh)$_3$		**4b**	70
3	Ph-CHO	NH$_2$	P(OPh)$_3$		**4c**	75
4	Ph-CHO	NH	P(OPh)$_3$		**4d**	68
5	Ph-CHO	NH$_2$	P(OPh)$_3$		**4e**	65
6	4-ClC$_6$H$_4$-CHO	Ph NH$_2$	P(OPh)$_3$		**4f**	66
7	n-Pr-CHO	Ph NH$_2$	P(OMe)$_3$		**4g**	70

TABLE 2 Optimization of the Reaction with Different ILs

Entry	*Ionic Liquids*	*Yield (%)*
1	[C-mim]HSO_4	40
2	[C-7mim]H_2PO_4	41
3	[bmim]Cl	55
4	[bmim]Br	54
5	[emim]Br	68
6	[bmim]CF_3SO_3	38

significantly enhanced the rate of formation of α-aminophosphonates. Advantages of our work are as follows: (1) The reactions were performed with IL media as the green solvent. (2) The starting material can be used without any activation or modification. (3) This method is convenient for the synthesis of dialkyl and diaryl esters.

EXPERIMENTAL

All chemicals and ionic liquids were obtained from Fluka (Switzerland) and were used without further purification. We used the following for the measurement of mp, Electrothermal-9100 apparatus (Labequip, Markham, Ontario, Canada); IR spectra, Shimadzu IR-460 spectrometer; ^{1}H 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, and 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 **4**

To a magnetically stirred solution of **1** (2 mmol) and **2** (2 mmol) in 1 mL of IL [emim][Br], **3** (2 mmol) was added at room temperature. After completion of the reaction (0.5–1 h), as indicated by TLC (EtOAc/*n*-hexane, 2:1), the products were extracted with Et_2O (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:EtOAc (3:1) to afford pure title compounds. The IL was recovered by addition of water (5 cm^3), and collected and dried under vacuum.

*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: $\delta = 2.98$ (bs, NH), 3.48 (d, $^3J_{P\text{-}H} = 10.5$, OMe), 3.53 (d, $^2J_{HH} = 13.5$, NCH_2), 3.73 ($^3J_{HP} = 10.5$, OMe), 3.80 ($^2J_{HH} = 13.5$, NCH_2), 4.06 ($^1J_{HP} = 20.7$, CH), 7.3–7.5 (m, 10CH). ^{13}C NMR: $\delta = 51.1$ (d, $^3J_{C\text{-}P} = 17.4$, NCH_2), 52.8 (d, $^2J_{CP} = 6.8$, OMe), 53.3 (d, $^2J_{CP} = 6.8$, OMe), 59.4 (d, $^1J_{CP} = 152.0$, CH), 127.3 (CH), 128.0 (d, $^5J_{CP} = 2.9$, CH), 128.7 (4CH), 128.8 (d, $^4J_{CP} = 2.3$, 2CH), 129.1 (d, $^3J_{CP} = 6.2$, 2CH), 136.8 (C), 140.3 (C). ^{31}P NMR: 27.06 [P(O)$(OMe)_2$].

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

White solid; mp: 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: $\delta = 2.91$ (bs, NH), 3.65 (d, $^2J_{HH} = 13.4$, NCH_2), 3.93 (d, $^2J_{HH} = 13.4$, NCH_2), 4.36 ($^2J_{HP} = 21.2$, CH), 7.3–7.5 (m, 20CH). ^{13}C NMR: $\delta = 51.1$ (d, $^3J_{CP} = 17.0$, NCH_2), 59.4 (d, $^1J_{CP} = 152.0$, CH), 120.8 (d, $^3J_{CP} = 4.0$, CH), 121.1 (d, $^3J_{CP} = 4.3$, 2CH), 125.2 (CH), 125.3 (CH), 127.4 (CH), 128.4 (d, $^5J_{CP} = 3.1$, CH), 128.7 (4CH), 128.5 (d, $^5J_{CP} = 2.4$, CH), 128.8 (d, $^4J_{CP} = 3.1$, 2CH), 129.5 (d, $^3J_{CP} = 6.9$, 2CH), 129.9 (4CH), 136.9 (C), 140 (C), 151.2 (d, $^3J_{C\text{-}P} = 9.6$, C), 151.6 (d, $^3J_{CP} = 9.6$, C).^{31}P NMR: 17.73 [P(O)$(OPh)_2$].

*Diphenyl[(cyclohexylamino)(phenyl)methyl] phosphonate (***4c***, $C_{25}H_{28}NO_3P$)*

Yellow oil; yield: 0.63 g (75%). IR (KBr): $\bar{\nu} = 1738$ (C=O), 1246 (P=O), 2953 (CH) cm^{-1}. EI-MS: 421 (2, M$^+$), 338 (25), 324 (35), 234 (100), 187 (85), (77), 93 (90), 91 (95), 83 (55). ^{1}H NMR: $\delta = 1.12$–1.18 (m, $3CH_2$), 1.65–1.67 (m, CH_2), 1.73–1.78 (m, CH_2), 2.46–2.48 (m, CH), 2.94 (bs, NH), 4.67 (d, $^2J_{HP} = 23.0$, CH), 6.94–7.46 (m, 15CH). ^{13}C NMR: $\delta = 24.6$ (CH_2), 24.9 (CH_2), 26.3 (CH_2), 32.1 (CH_2), 34.4 (CH_2), 54.0 (d, $^3J_{CP} = 16.9$, CH), 57.7 (d, $^1J_{CP} = 156.5$, CH), 120.8 (d, $^3J_{CP} = 4.2$, 2CH), 121.1 (d, $^3J_{CP} = 4.1$, 2CH), 125.1 (CH), 125.2 (CH), 128.3 (d, $^5J_{CP} = 3.2$, CH), 128.7 (d, $^4J_{CP} = 2.3$, 2CH), 129.3 (d, $^3J_{CP} = 6.7$, 2CH), 129.8 (4CH), 136.9 (C), 151.1 (d, $^3J_{CP} = 9.6$, C), 151.6 (d, $^3J_{CP} = 9.6$, C).^{31}P NMR: 15.50 [P(O)$(OPh)_2$].

*Diphenyl[phenyl(pipperidino)methyl] phosphonate (**4d**, $C_{24}H_{26}NO_3P$)*

White solid, mp: 127°C; yield: 0.55 g (68%). IR (KBr): $\bar{\nu} = 1246$ (P=O), 2953 (CH) cm^{-1}. EI-MS: 407 (2, M^+), 333 (25), 234 (100), 173 (65), 93 (75), 91 (95), 74 (66). ^{1}H NMR: δ = 1.42–1.49 (m, $3CH_2$), 2.80–2.91 (m, $2NCH_2$), 2.94 (bs, NH), 4.48 (d, $^2J_{HP} = 25.4$, CH), 6.94–7.62 (m, 15CH). ^{13}C NMR: $\delta = 24.2$ (CH_2), 26.4 ($2CH_2$), 52.3 (d, $^3J_{CP} = 9.6$, $2NCH_2$), 68.1 (d, $^1J_{CP} = 165.4$, CH), 121 (d, $^3J_{CP} = 3.9$, 2CH), 121.2 (d, $^3J_{CP} = 4.2$, 2CH), 125.1 (CH), 125.2 (CH), 128.2 (d, $^5J_{CP} = 3.0$, CH), 128.6 (d, $^4J_{CP} = 2.4$, 2CH), 128.8 (d, $^3J_{CP} = 7.0$, 2CH), 129.8 (4CH), 136.9 (C)), 150.8 (d, $^3J_{CP} = 9.6$, C), 152.3 (d, $^3J_{CP} = 9.6$, C). ^{31}P NMR: 16.50 [P(O)$(OPh)_2$].

*Diphenyl[(butyllamino)(phenyl)methyl] phosphonate (**4e**, $C_{23}H_{26}NO_3P$)*

Yellow oil; yield: 0.51 g (65%). IR (KBr): $\bar{\nu} = 1246$ (P=O), 2953 (CH) cm^{-1}. EI-MS: 395 (2, M^+), 324 (25), 234 (100), 162 (78), 93 (88), 91 (100), 71 (86), 57 (80). ^{1}H NMR: $\delta = 0.87$ (t, $^3J_{HH} = 7.3$, Me), 1.27–1.37 (m, CH_2), 1.39–1.51 (m, CH_2), 2.52–2.70 (m, NCH_2), 2.88 (bs, NH), 4.50 (d, $^1J_{HP} = 21.1$, CH), 6.95–7.41 (m, 15CH). ^{13}C NMR: δ = 13.7 (Me), 20.4 (CH_2), 32.0 (CH_2), 47.7 (d, $^3J_{CP} = 17.1$, NCH_2), 60.9 (d, $^1J_{CP} = 156.7$, CH), 120.8 (d, $^3J_{CP} = 4.1$, 2CH), 121.2 (d, $^3J_{CP} = 4.2$, 2CH), 125.2 (CH), 125.3 (CH), 128.4 (d, $^5J_{CP} = 3.0$, CH), 128.7 (d, $^4J_{CP} = 2.4$, 2CH), 129.3 (d, $^3J_{CP} = 6.7$, 2CH), 129.8 (4CH), 136.3 (C), 151.2 (d, $^3J_{CP} = 9.6$, C), 151.5 (d, $^3J_{CP} = 9.6$, C). ^{31}P NMR: 16.80 [P(O)$(OPh)_2$].

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

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, $^2J_{HH} = 13.4$, NCH_2), 3.92 (d, $^2J_{HH} = 13.5$, NCH_2), 4.49 ($^2J_{HP} = 21.3$, CH), 6.99–7.66 (m, 19 CH). ^{13}C NMR: $\delta = 51.2$ (d, $^3J_{CP} = 16.7$, NCH_2), 59.0 (d, $^1J_{CP} = 167.0$, CH), 120.7 (d, $^3J_{CP} = 4.4$, 2CH), 121.0 (d, $^3J_{CP} = 4.2$, 2CH), 125.3 (CH), 125.4 (CH), 127.4 (CH), 128.8 (4CH), 128.9 (d, $^4J_{CP} = 2.4$, 2CH), 130.0 (d, $^3J_{CP} = 6.2$, 2CH), 131.1 (4CH), 134.9 (C), 135.0 (C), 151.0 (d, $^3J_{CP} = 10.7$), 151.2 (d, $^3J_{CP} = 10.7$, C).^{31}P NMR: 17.0 [P(O)$(OPh)_2$].

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

Yellow oil; yield: 0.38 g (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: $\delta = 0.86$ (t, $^3J = 7.3$, Me), 1.29–1.67 (m, CH_2), 1.39–1.51 (m, CH_2), 3.5 (m, CH), 2.88 (bs, NH), 3.74 (d, $^3J_{HP} = 10.4$, OMe), 3.75 (d, $^3J_{HP} = 10.4$, OMe), 3.90 (d, $^2J_{HH} = 14.2$, NCH_2), 4.00 (d, $^2J_{HH} = 13.3$, NCH_2), 7.22–7.4 (m, 5CH). ^{13}C NMR: $\delta = 13.7$ (Me), 19.4 (d, $^3J_{CP} = 11.0$, CH_2), 32.3 (d, $^2J_{CP} = 1.9$, CH_2), 51.1 (d, $^3J_{CP} = 15.0$, NCH_2), 51.9 (d, $^2J_{CP} = 5.12$, OMe), 52.2 (d, $^2J_{CP} = 6.9$, OMe), 53.5 (d, $^1J_{CP} = 148.0$, CH), 127.1 (CH), 128.6 (4CH), 141.2 (C). ^{31}P NMR: 26.90 [P(O)$(OMe)_2$].

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