One-pot synthesis of α-aminophosphonates on silica under solvent-free conditions from aromatic aldehydes

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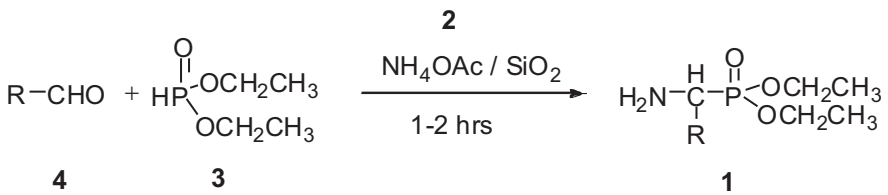
α-Aminophosphonates were synthesised under solvent-free conditions on an acidic silica gel support using aromatic aldehydes, diethyl phosphite and anhydrous ammonium acetate as starting materials in moderate yields

Keywords: α-aminophosphonates, synthesis, solvent-free, silica gel

The chemistry of α-aminophosphonic acids as phosphonic analogues of naturally occurring α-amino acids has always attracted considerable interest because of their potential biological properties as antibiotics, enzyme inhibitors, and pharmacological agents as well as their utility as synthetic intermediates.[1–5] A number of synthetic methods for the synthesis of α-alkylamino phosphonates have been developed over the past 20 years.[6] Most syntheses of α-alkylamino phosphonates involved the nucleophilic addition of an alkylamine to a carbonyl compound followed by the addition of a dialkyl or diaryl phosphite to the resulting imine in either one-step or multi-step operation using Lewis acids[7,8] such as $SnCl_2$, $SnCl_4$, BF_3 Et_2O, $ZnCl_2$, $MgBr_2$, $InCl_3$, $ZrCl_4$, $AlCl_3$, $Mg(ClO_4)_2$, $TaCl_5$ and (bromodimethyl)sulfonium bromide[9] as catalysts. However, in contrast to the widely studied α-alkylamino phosphonates, relatively few papers have reported the direct synthesis of α-amino phosphonates by the use of ammonia. A typical procedure is a Strecker-type reaction which involves the treatment of an aldehyde with ammonia and dialkyl phosphite[10,11]. This method, is neither high-yielding nor suitable for large scale production since the reaction is performed in a sealed vessel at 100 °C. An alternative reaction[12] of an aldehyde, benzyl carbamate and triphenyl phosphite gives a fully-protected α-amino phosphonic acid derivative and requires an additional deprotection step(H_2–Pd/C, or HBr–AcOH) to provide α-amino phosphonic acid. In addition, Kaboudin and coworker[13,14] recently reported on the synthesis of α-amino phosphonates by reaction of aldehyes and diethyl phosphite with ammonium formate on an acidic alumina support under microwave assistance, with ammonia solution to give diethyl *N*-(alkylmethylene)-1-aminomethylposponate intermediate followed by hydrolysis with *p*-toluenesulfonic acid and neutralisation of the sulfonate salt to provide the target compounds. Yoshioka and coworkers[15] have also described a method for the preparation of α-amino phosphonic acid from aldehydes and diethyl phosphite with ammonium acetate in a large amount of ethanol solvent for long time 44–60 hours. Consequently, there still remains a need to develop a more efficient method, particularly in view of the disadvantages associated with some of the reported procedures such as the requirement of solvent, long time, costly, multi-step and moisture sensitive catalysts and special apparatus.

Surface-mediated solid-phase reaction are of growing interest because of their ease of set up and work-up, mild reaction conditions, rate of reaction, the absence of solvent and their low cost in comparison with their homogeneous counterparts. Here we report a convenient and efficient method which overcomes the drawbacks of the previous reactions, for synthesis of α-amino phosphonates under solvent-free conditions on an acidic silica gel support (Scheme 1).

As shown in Table 1, the reaction of a mixture of aromatic aldehydes with diethyl phosphite under solvent-free conditions, in the presence of an acidic silica gel support, afforded the desired products in moderate yields(**1a–i**). It was found that the reactivity of aromatic aldehydes with electron-donating groups is better than that of aromatic aldehydes with electron-attacting groups such as *p*-N, N-dimethylbenzaldehyde. This is possibly because aromatic aldehydes with electron-attacting groups easily reacted first with diethyl phosphite



Scheme 1

Table 1 Synthesis of α-amino phosphonates(**1a–i**) under solvent-free reaction conditions on acidic silica gel supported

Product **1**	R	T/°C	Time/h	Yields/%
a	C_6H_5	60	2	76
b	*p*-Cl C_6H_4	50	2	67
c	2-Cl, 4-Cl C_6H_3	60	1.5	50
d	*m*-NO_2 C_6H_4	60	2	40
e	*p*-OH C_6H_4	60	2	70
f	*m*-OCH_3, p-OHC_6H_3	50	2	73
g	*p*-OCH_3 C_6H_4	50	2	65
h	*p*-$N(CH_3)_2$ C_6H_4	50	1.5	83
i	furfuryl	60	1.5	66

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instead of ammonia to give α-hydroxy phosphonates instead of an imine followed by the addition of a diethyl phosphite to form target products.

In summary, a facile and straightforward synthesis of α-amino phosphonates under solvent-free reaction conditions is described on an acidic silica gel support using anhydrous ammonium acetate, aromatic aldehydes and diethyl phosphite as starting materials in moderate yields. This method is a simple operation, and it has relatively fast reaction rates and short reaction times. These make the method an attractive and useful contribution to present syntheses.

Experimental

All melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were measured on a Bruker 400 NMR instrument in $CDCl_3$ and chemical shifts are expressed as δ units, TMS was used as an internal standard for ^1H NMR, ^{13}C NMR. IR spectra were determined as liquid films on Avatar360FT-IR spectrophotometer.

Elemental analysis was carried out with a Yanaco CHNcorder MT-3 Analyser. All aldehydes were redistilled before being used.

General method

To the mixture of anhydrous ammonium acetate **2** (0.037 mol) and chromatography silica gel (2 g) was added aromatic aldehydes **4** (0.025 mol), then diethyl phosphite **3** (0.025 mol) was added with vigorous stirring. After the completion of the addition, the reaction mixture is smoothly heated at 50–60 °C for 1–2 h. and then allowed to cool to room temperature. The resulting reaction mixture is extracted with dichloromethane(2 × 25 ml). Evaporation of the solvent gave the crude product. The product was purified by column chromatography on silica gel using a mixture of ethylacetate and hexane as eluent (10 : 90) to give oil liquid compounds **1**.

(1a): Oil,^1H NMR ($CDCl_3$) 2.74 (br, 2H, NH_2); 4.22 (d, 1H, $^2J_{PH}$ = 17.2, CH); 1.27–1.13 (m, 6H, $2CH_3$); 4.04–3.82 (m, 4H, $2CH_2$); 7.48–7.27 (m, 5H, Ar); ^{13}C NMR($CDCl_3$) 16.11, 16.32, 62.7, 62.9, 49.5, 128.3, 136.7, 126.7; IR(Film, cm^{-1}) 1241 (P = O), 1028 (P–O–Et), 3383 (NH_2); Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.46; N, 5.76. Found: C, 54.37; H, 7.61; N, 5.42%.

(1b): Oil, ^1H NMR ($CDCl_3$) 1.97(br, 2H, NH_2); 4.24 (d, 1H, $^2J_{PH}$ = 17.2, CH); 1.28 (t, 3H, ^3J = 7.2, CH_3); 1.21 (t, 3H, ^3J = 7.2, CH_3); 4.09–3.89 (m, 4H, $2CH_2$); 7.41–7.28(m, 4H, Ar); ^{13}C NMR($CDCl_3$) 16.21, 16.32, 62.4, 62.6, 49.5, 128.5, 134.7, 130.7; IR(film, cm^{-1}) 1240 (P = O), 1026 (P–O–Et), 3376 (–NH_2); Anal. Calcd for $C_{11}H_{17}ClNO_3P$: C, 47.58; H, 6.17; N, 5.04. Found: C, 47.36; H, 6.21; N, 5.10%.

(1c): Oil, ^1H NMR ($CDCl_3$) 1.98 (br, 2H, NH_2); 4.77 (d, 1H, $^2J_{PH}$ = 18.4, CH); 1.34–1.15 (m, 6H, $2CH_3$); 4.18–3.87 (m, 4H, $2CH_2$); 7.63–7.29 (m, 3H, Ar); ^{13}C NMR($CDCl_3$) 16.52, 16.41, 60.7, 61.5, 44.5, 140.5, 129.7, 126.2, 133.2, 130.1, 133.1; IR(Film, cm^{-1}) 1241 (P = O), 1031 (P–O–Et), 3384 (–NH_2); Anal. Calcd for $C_{11}H_{16}Cl_2NO_3P$: C, 42.33; H, 5.17; N, 4.49. Found: C, 42.36; H, 5.31; N, 4.70%.

(1d): Oil, ^1H NMR ($CDCl_3$) 2.25 (br, 2H, NH_2); 4.44 (d, 1H, $^2J_{PH}$ = 18.0, CH); 1.28–1.25 (m, 6H, $2CH_3$); 4.11–4.07 (m, 4H, $2CH_2$); 8.37–7.52 (m, 4H, Ar); ^{13}C NMR($CDCl_3$) 16.51, 16.31, 62.7, 61.5, 48.5, 147.3, 137.0, 134.3, 123.3, 129.6, 121.9; IR(Film, cm^{-1}) 1244 (P = O), 1027 (P–O–Et), 3277 (–NH_2), 1531, 1362 (–NO_2); Anal. Calcd for $C_{11}H_{17}N_2O_5P$: C, 45.84; H, 5.94; N, 9.72. Found: C, 45.66; H, 5.61; N, 9.70%.

(1e): Oil, ^1H NMR ($CDCl_3$) 2.09(br, 2H, NH_2); 4.18(d, 1H, $^2J_{PH}$ = 16.0, CH); 1.29 (t, 3H, ^3J = 7.2, CH_3); 1.19(t, 3H, ^3J = 7.2, CH_3); 4.11–3.83 (m, 4H, $2CH_2$); 7.20–6.66 (m, 4H, Ar); ^{13}C NMR($CDCl_3$) 16.21, 16.31, 62.7, 62.0, 49.5, 128.3, 115.2, 154.3; IR(Film, cm^{-1}) 1216 (P = O), 1027 (P–O–Et), 3193(br,–OH, –NH_2); Anal. Calcd for $C_{11}H_{18}NO_4P$: C, 50.96; H, 7.00; N, 5.40. Found: C, 51.21; H, 6.91; N, 5.20%.

(1f): Oil, ^1H NMR ($CDCl_3$) 2.08(br, 2H, NH_2); 4.18(d, 1H, $^2J_{PH}$ = 16.0, CH); 3.85 (s, 3H, –OCH_3); 1.29(t, 3H, ^3J = 7.2, CH_3); 1.19 (t, 3H, ^3J = 7.2, CH_3); 4.08–3.96 (m, 4H, $2CH_2$); 7.02–6.83 (m, 3H, Ar); ^{13}C NMR($CDCl_3$) 15.81, 15.41, 59.7, 58.3, 50.6, 56.9, 129.7, 120.6, 112.3, 115.7, 146.9, 148.5; IR(Film, cm^{-1}) 1218 (P = O), 1027 (P–O–Et), 3184(–OH, –NH_2); Anal. Calcd for $C_{12}H_{20}NO_5P$: C, 49.83; H, 6.97; N, 4.84. Found: C, 49.56; H, 6.81; N, 4.71%.

(1g): Oil, ^1H NMR ($CDCl_3$) 2.00 (br, 2H, NH_2); 4.20 (d, 1H, $^2J_{PH}$ = 16.4, CH); 3.79 (s, 3H, –OCH_3); 1.28 (t, 3H, ^3J = 7.2, CH_3); 1.18 (t, 3H, ^3J = 7.2, CH_3); 4.08–3.87 (m, 4H, $2CH_2$); 7.38–6.87 (m, 4H, Ar); ^{13}C NMR($CDCl_3$) 16.21, 16.31, 62.7, 62.0, 49.7, 55.8, 128.4, 158.6, 127.2, 114.3; IR(Film, cm^{-1}) 1249 (P = O), 1023 (P–O–Et), 3458 (–NH_2); Anal. Calcd for $C_{12}H_{20}NO_4P$: C, 52.74; H, 7.38; N, 5.13. Found: C, 52.76; H, 7.21; N, 5.21%.

(1h): Oil, ^1H NMR ($CDCl_3$) 2.01(br, 2H, NH_2); 4.15 (d, 1H, $^2J_{PH}$ = 16.0, CH); 2.93 (s, 6H, –$N(CH_3)_2$); 1.30–1.12 (m, 6H, $2CH_3$); 4.11–3.95 (m, 4H, $2CH_2$); 7.31–6.63 (m, 4H, Ar); ^{13}C NMR($CDCl_3$) 14.8, 14.0, 58.3, 59.1, 49.8, 40.4, 125.5 154.4, 112.2, 127.0; IR(Film, cm^{-1}) 1240 (P = O), 1027 (P–O–Et), 3457 (–NH_2); Anal. Calcd for $C_{13}H_{23}N_2O_3P$: C, 54.54; H, 8.10; N, 9.78. Found: C, 54.46; H, 8.21; N, 9.51%.

(1i): Oil, ^1H NMR ($CDCl_3$) 2.03 (br, 2H, NH_2); 4.29 (d, 1H, $^2J_{PH}$ = 18.4, CH); 7.39 (d, 1H, ^3J = 1.6, furfuryl); 6.37 (d, 2H, ^3J = 3.2, furfuryl); 1.32(t, 3H, ^3J = 6.8, CH_3); 1.25 (t, 3H, ^3J = 6.8, CH_3); 4.15–3.99(m, 4H, $2CH_2$); ^{13}C NMR($CDCl_3$) 16.3, 16.0, 60.3, 60.1, 50.9, 110.6, 106.4, 141.6, 152.2; IR(Film, cm^{-1}) 1240 (P = O), 1024 (P–O–Et), 3379 (–NH_2); Anal. Calcd for $C_9H_{16}NO_4P$: C, 46.35; H, 6.92; N, 6.01. Found: C, 46.46; H, 6.92; N, 6.11%.

Received 17 June 2008; accepted 31 July 2008
Paper 08/5332 doi: 10.3184/030823408X349998
Published online: 8 October 2008

References

1 P.P. Giannous and P.A. Bartlett, *J. Med. Chem.,* 1987, **30**, 1603.
2 R. Engel, *Chem. Rev.,* 1977, **77**, 349.
3 J. Hiratake and J. Oda, *Biosci. Biotechnol. Biochem*., 1997, **61**, 211.
4 K.A. Schug and W. Lindner, *Chem. Rev.,* 2005, **105**, 64.
5 K. Moonen, I. Laureyn and C.V. Stevens, *Chem. Rev.*, 2004, **104**, 6177.
6 V.P. Kukhar and H.R. Hudson, *Aminophosphonic and aminophosphinic acids*, John Wiley & Sons, Chichester, 2000.
7 S. Bhagat and A.K. Chakraboorti, *J. Org. Chem.,* 2007, **72**, 3158.
8 S. Chandrasekhar, S.J. Prakash, V. Jagadeshwar and C. Narsihmulu, *Tetrahedron Lett.,* 2001, **42**, 5561.
9 S. Kudrimoti and V.R. Bommena, *Tetrahedron Lett.,* 2005, **46**, 1209.
10 M.E. Chalmers and G.M. Kosolapoff, *J. Am. Chem. Soc.,* 1953, **75**, 5278.
11 H. Takahashi, M. Yoshioka, N. Imai, K. Onimura and S. Kobayashi, *Synthesis*, 1994, 763.
12 J. Olcksyszyn, L. Subotkowska and P. Mastalerz, *Synthesis,* 1979, 985.
13 B. Kaboudin and R. Nazari *Tetrahedron Lett.,* 2001, **42**, 8211.
14 B. Kaboudin and K. Moradi, *Tetrahedron Lett.,* 2005, **46**, 2989.
15 H. Takahashi, M. Yoshioka, N. Imai, K. Onimura and S. Kobayashi *Synthesis,* 1994, 763.