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Synthesis of tertiary α-amino phosphonate by one-pot three-component coupling mediated by LPDE

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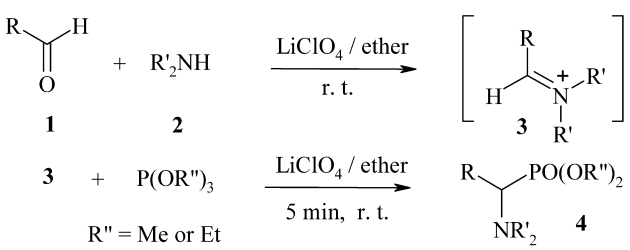
Abstract—A very mild, efficient and simple method for the synthesis of tertiary α-amino phosphonates is reported by reaction of an aldehyde, a secondary amine and trialkylphosphite in ethereal solution of lithium perchlorate, LPDE, at ambient temperature with high yields.

α-Amino phosphonates are an important class of compounds in pharmaceutical chemistry. The potential of α-amino phosphonates as peptide mimics,[1] enzyme inhibitors,[2] antibiotics and pharmacological agents[3] has been proved. Thus a variety of synthetic approaches are desirable to synthesize of α-amino phosphonate. Among the available methods, the nucleophilic addition of phosphite to imines is the most convenient and is usually activated by an alkali metal alkoxide or by a Lewis acid.[4]

A direct one-pot synthesis of tertiary α-amino phosphonates has been reported via the reaction of an aldehyde with an amine and dialkyl phosphite.[5–8] Recently, we have reported a one-pot three-component, general method for the aminoalkylation of aldehyde with different nucleophiles.[9] In this paper we describe a mild, convenient and simple procedure for a three-component reaction of an aldehyde, a secondary amine and trialkylphosphite for the preparation of tertiary α-amino phosphonates. One-pot reaction mild working condition and absence of tedious procedure for the preparation of the iminium salt in separate step is the advantage of this method compare to those reported before.[4c] In addition to this, in most cases, almost pure products are obtained by a simple work up procedure. Reaction of aldehyde **1**, a secondary amine **2** in concentrated ethereal solution of lithium perchlorate, leads to the iminium ion **3** as an intermediate. The intermediate **3** can be detected by NMR spectroscopy in solution.[10] Thus, by the addition of benzaldehyde and amine to the 5 M ethereal solution of $LiClO_4$, the benzaldehyde proton signal disappeared, and at the same time a signal at 8.6 ppm appeared, which indicated the formation of iminium ion **3**. The mixture of **1** and **2** in diethyl ether, in the absence of lithium perchlorate, did not produce the iminium ion **3** (no signal at 8.6 ppm). Upon addition of trialkylphosphite, tertiary α-amino phosphonates **4** was prepared in good yields after few minutes at room temperature, Scheme 1.

To show the generality of this method, a wide range of aldehydes were subjected to this procedure and converted to the corresponding tertiary α-amino phosphonates with high yields. Both aromatic and aliphatic aldehydes reacted with secondary amines such as pyrrolidine, morpholine,[11] diethylamine (trimethylsilyl)dimethyamine and piperidine. The results are shown in Table 1.

In conclusion, we have developed a general and efficient method for one-pot synthesis of tertiary α-amino phosphonates in concentrated LPDE solution. The notable advantages of this procedure are (a) general applicability to a wide range of aldehydes and amines, (b) operational simplicity with using relatively cheap $LiClO_4$, in comparison with many other Lewis acids used for these transformations and preparation of iminium salt in separate step, (c) simple procedure with easy work up and high yields of the product.



Scheme 1.

Keywords: tertiary α-amino phosphonate; trialkylphosphite; lithium perchlorate.

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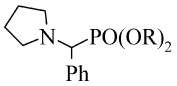
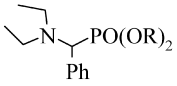
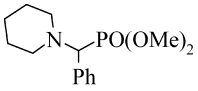
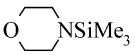
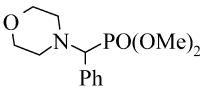
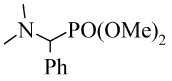
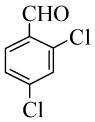
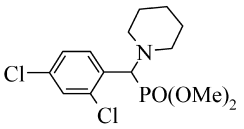
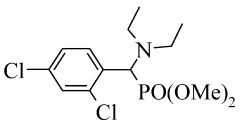
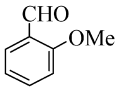
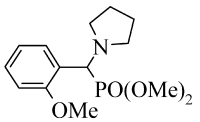
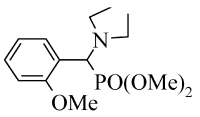
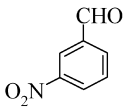
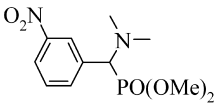
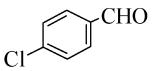
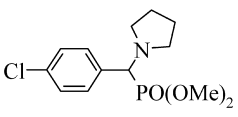
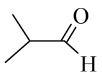
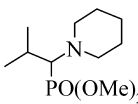
Table 1. Synthesis of tertiary α-amino phosphonates from aldehyde mediated by LPDE

Aldehydes	Amines	Product	References	Yield[a] (%)
PhCHO			**4a**,[8] R=Me	98
			**4b**,[8] R=Et **4c**,[8] R=Me	96 90
			**4d**,[8] R=Et **4e**[4c]	92 95
			**4f**[12]	95
	Me_2NsiMe_3		**4g**[4c]	95
			**4h**[16]	98
			**4i**[12]	95
			**4j**[12]	96
			**4k**[16]	93
	Me_2NSiMe_3		**4m**[14]	95
			**4n**[15]	95
			**4o**[8]	84

[a] Isolated yields.

1. Experimental

1.1. General

$LiClO_4$ (Fluka) was dried at 160°C for 24 h. Ether was dried over Na/benzophenone under argon. IR spectra were taken on a Mattson 1000 Unicam FTIR. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 500 instruments. All reactions were performed under argon. Chemicals were purchased from Merck and Fluka.

1.2. General procedure for the preparation of tertiary α-amino phosphonates 4

The aldehyde (2 mmol) and 3 ml of 5 M solution of $LiClO_4$ in diethyl ether were placed in a 50 ml flask under argon and

stirred for 2 min. Then a secondary amine (4 mmol) was added via a syringe. After 10 min, trialkylphosphite (3 mmol) was added and the mixture was stirred at room temperature for 5 min. Water (15 mL) and dichloromethane (15 ml) were added. The organic phase was separated, and dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. In some cases (ca. **4a**, **4b**, **4h** and **4j**) almost pure product was obtained. All compounds were known and characterized by comparison of their IR and NMR (^1H and ^{13}C) spectra with those reported in the literature or with an authentic sample.

1.2.1. α-Pyrrolidino phosphonates 4a.[8] Yield 98%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.66 (m, 4H), 2.55 (m, 4H), 3.34 (d, J=10.4 Hz, 3H), 3.75 (d, J=10.5 Hz, 3H), 3.72 (d, J=16.0 Hz, 1H), 7.22–7.24 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.1 (CH_2), 52.8 (d, J=9.1 Hz, CH_3), 53.9 (d, J=6.6 Hz, CH_3), 55.8 (CH_2), 56.8 (d, J=148.1 Hz, CH), 127.7 (CH), 129.3 (CH), 130.4 (CH), 133.1 (d, J=2.2 Hz, C); IR ν_{max} (CH_2Cl_2), 2940, 2850, 1470, 1230, 1042, 770 cm^{-1}.

1.2.2. α-(*N*,*N*-Diethylamino) phosphonates 4c.[8] Yield 90%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.94(t, J=7.2 Hz, 6H), 2.22 (m, 2H), 2.89 (m, 2H), 3.37 (d, J=10.5 Hz, 3H), 3.77 (d, J=10.4 Hz, 3H), 4.00 (d, J=24.9 Hz, 1H), 7.16–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.5 (CH_3), 45.1 (d, J=8.25 Hz, CH_2), 52.8 (d, J=6.8 Hz, CH_3), 54.5 (d, J=7.2 Hz, CH_3), 61.9 (d, J=163.3 Hz, CH), 128.2 (CH), 128.4 (CH), 130.7 (d, J=8.8 Hz, CH), 133.2 (d, J=4.7 Hz, C); IR ν_{max} (KBr), 2973, 2840, 1494, 1452, 1247, 1033, 829, 569 cm^{-1}.

1.2.3. α-Piperidino phosphonates 4e.[4c] Yield 95%; white solid; mp, 69–70°C; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.34 (t, J=6.2 Hz, 2H), 1.56–1.64 (m, 4H), 2.41 (m, 2H), 2.78 (m, 2H), 3.54 (d, J=8.6 Hz, 3H), 3.92 (d, J=8.7 Hz, 3H), 4.01 (d, J=22.8 Hz, 1H), 7.20–7.61 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.3 (CH_2), 26.2 (CH_2), 51.3 (CH_2), 53.8 (d, J=6.8 Hz, CH_3), 54.9 (d, J=7.8 Hz, CH_3), 61.9 (d, J=160.3 Hz, CH), 128.6 (CH), 128.9 (CH), 131.7 (d, J=8.8 Hz, CH), 134.2 (d, J=4.7 Hz, C); IR ν_{max} (CH_2Cl_2), 2933, 2852, 1450, 1248, 1034, 557 cm^{-1}.

1.2.4. α-Morpholino phosphonates 4f.[12] Yield 95%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.58 (t, J=6.3 Hz, 2H), 2.79 (t, J=6.1 Hz, 2H), 3.51 (m, 3H), 3.67–3.74 (m, 4H), 3.81–3.88 (m, 4H), 7.19–7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 24.3 (CH_2), 26.5 (CH_2), 52.3 (CH_2), 52.8 (CH_2), 54.8 (d, J=6.8 Hz, CH_3), 54.9 (d, J=7.8 Hz, CH_3), 63.9 (d, J=161.3 Hz, CH), 128.1 (CH), 128.8 (CH), 131.2 (d, J=5.6 Hz, CH), 134.8 (d, J=3.4 Hz, C); IR ν_{max} (CH_2Cl_2), 2925, 2850, 1230, 1020, 760 cm^{-1}.

1.2.5. α-(*N*,*N*-Dimethylamino) phosphonates 4g.[4c] Yield 95%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.13 (s, 6H), 3.20 (d, J=10.5 Hz, 3H), 3.59 (d, J=10.7 Hz, 3H), 3.61 (d, J=20.8 Hz, 1H), 7.12–7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 43.8 (d, J=9.3 Hz), 53.2 (m, CH_3), 68.1 (d, J=160.4 Hz, CH), 128.4 (CH), 130.6 (CH), 130.7 (CH), 132.2 (C); IR ν_{max} (CH_2Cl_2) 2937, 2860, 1480, 1213, 1029 cm^{-1}.

1.2.6. α-(*N*,*N*-Diethylamino) phosphonates 4i.[12] Yield 95%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.98 (t, J=7.2 Hz, 6H), 2.38 (m, 2H), 2.89 (m, 2H), 3.44 (d, J=10.6 Hz, 3H), 3.84 (d, J=10.6 Hz, 3H), 4.74 (d, J=24.7 Hz, 1H), 7.18 (m, 1H), 7.35 (m, 1H), 7.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.5 (CH_3), 48.1 (CH_2), 52.8 (d, J=7.2 Hz, CH_3), 54.6 (d, J=9.1 Hz, CH_3), 58.8 (d, J=152.1 Hz, CH), 126.1 (CH), 128.3 (CH), 131.3 (C), 132.8 (CH), 134.6 (C), 137.8 (C); IR ν_{max} (KBr) 2880, 1499, 1240, 760 cm^{-1}.

1.2.7. α-Pyrrolidino phosphonates 4j.[13] Yield 96%; yellow solid; mp, 93–94°C; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.68 (m, 4H), 2.64 (m, 4H), 3.46 (d, J=10.4 Hz, 3H), 3.75 (d, J=10.5 Hz, 3H), 3.85 (s, 3H), 4.65 (d, J=18.0 Hz, 1H), 6.89–6.98 (m, 2H), 7.26–7.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.5 (CH_2), 52.6 (d, J=9.1 Hz, CH_3), 53.4 (d, J=6.6 Hz, CH_3), 55.9 (CH_3), 56.1 (CH_2), 56.8 (d, J=145.1 Hz, CH), 111.0 (CH), 120.7 (d, J=2.25 Hz, CH), 122.9 (CH), 129.3 (d, J=2.1 Hz, CH), 131.5 (d, J=4.1 Hz, CH), 157.8 (d, J=9.2 Hz, CH); IR ν_{max} (KBr) 2953, 2839, 1598, 1491, 1463, 1246, 1028, 760 cm^{-1}.

1.2.8. α-(*N*,*N*-Dimethylamino) phosphonates 4m.[14] Yield 95%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.22 (s, 6H), 3.34 (d, J=9.8 Hz, 3H), 3.68 (d, J=9.7 Hz, 3H), 3.70 (d, J=18.9 Hz, 1H), 7.49 (m, 1H), 7.87 (m, 1H), 8.12 (m, 1H), 8.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 43.9 (d, J=8.9 Hz, CH_3), 52.8 (m, CH_3), 69.7 (d, J=161.4 Hz, CH), 123.1 (C), 129.2 (CH), 134.3 (C), 136.8 (CH), 139.1 (CH), 148.5 (C); IR ν_{max} (KBr) 2948, 2880, 1598, 1495, 1350, 1090, 960 cm^{-1}.

1.2.9. α-Pyrrolidino phosphonates 4n.[15] Yield 95%; oil; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.67 (m, 4H), 2.66 (m, 4H), 3.41 (d, J=9.4 Hz, 3H), 3.77 (d, J=10.1 Hz, 3H), 3.86 (d, J=18.0 Hz, 1H), 7.23–7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.5 (CH_2), 52.6 (d, J=9.1 Hz, CH_3), 53.4 (d, J=6.6 Hz, CH_3), 56.1 (CH_2), 57.8 (d, J=148.1 Hz, CH), 128.7 (d, J=2.25 Hz, CH), 130.4 (C), 131.1 (d, J=4.2 Hz, CH), 132.7 (C); IR ν_{max} (KBr) 2950, 2860, 1480, 1246, 1082, 986, 888 cm^{-1}.

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