

Metal-Free Multicomponent Synthesis of (α -Aminoalkyl)phosphonates Using 2,4,6-Trichloro-1,3,5-triazine¹⁾

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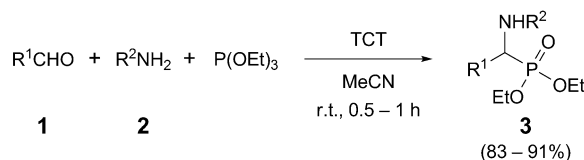
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(α -Aminoalkyl)phosphonates have efficiently been synthesized by multicomponent reaction of aldehydes, amines, and triethyl phosphite in the presence of 2,4,6-trichloro-1,3,5-triazine at room temperature. The products are formed in high yields (83–91%) within 0.5–1 h.

Introduction. – (α -Aminoalkyl)phosphonic acid and their derivatives possess various valuable medicinal properties including anticancer, anti-HIV, and antibacterial activities [1]. They are also applied as enzyme inhibitors and peptide mimics [2]. Additionally, they are useful as pesticides [3]. Thus, the synthesis of these compounds is an important goal for the organic chemists, and some methods have been developed for their preparation [4]. However, application of costly and toxic metal-based reagents, high temperature, long reaction time, or operational complexity are the drawbacks in many of these methods. Here, we report a simple synthesis of (α -aminoalkyl)phosphonates under metal-free conditions.

Results and Discussion. – In continuation of our work [5] on the development of useful synthetic methodologies, we have observed that the multicomponent reaction of aldehydes **1**, amines **2**, and triethyl phosphite ((EtO)₃P) in the presence of 2,4,6-trichloro-1,3,5-triazine (TCT) yielded the (α -aminoalkyl)phosphonates **3** at room temperature (*Scheme 1*).

Scheme 1



A series of (α -aminoalkyl)phosphonates was efficiently prepared from various aldehydes and amines following the above method (*Table*). Both aromatic and aliphatic aldehydes were applied to prepare these compounds. The aromatic aldehydes

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<i>Entry</i>	R ¹	R ²	Time [min]	Yield ^{b)} [%]	Product
1	Ph	4-Me-C ₆ H ₄	35	90	3a
2	Ph	4-HO-C ₆ H ₄	60	86	3b
3	Ph	4-Br-C ₆ H ₄	40	87	3c
4	4-Me-C ₆ H ₄	4-MeOOC-C ₆ H ₄	50	87	3d
5	4-HO-C ₆ H ₄	4-MeOOC-C ₆ H ₄	60	91	3e
6	4-EtO-C ₆ H ₄	Ph	30	88	3f
7	4- ⁱ Pr-C ₆ H ₄	Ph	35	90	3g
8	2,4-(Cl) ₂ -C ₆ H ₃	Ph	45	86	3h
9	4-Cl,3-F-C ₆ H ₃	4-Me-C ₆ H ₄	40	91	3i
10	2-NO ₂ -C ₆ H ₄	Ph	40	89	3j
11	4-NO ₂ -C ₆ H ₄	Ph	45	89	3k
12	Pr	Ph	60	84	3l
13	Pentyl	Ph	60	83	3m

R^1CHO
1

$+ \text{R}^2\text{NH}_2$
2

$\xrightarrow{\text{TCT}, [\text{H}^+]}$

$\left[\begin{array}{c} \text{N}=\text{R}^2 \\ | \\ \text{R}^1-\text{C}=\text{H} \end{array} \right]$

$\xrightarrow[\text{H}_2\text{O}]{\text{P(OEt)}_3, \text{TCT}, [\text{H}^+]}$

$\text{R}^1-\text{CH}(\text{NHR}^2)-\text{P}(=\text{O})(\text{OEt})_2$
3

(EtO)₃P using TCT at room temperature. The mild reaction conditions, excellent yields, rapid conversion, and application of a metal-free safe reagent are the notable advantages of this method.

Experimental Part

General. Column chromatography (CC): silica gel (SiO₂; BDH 100–200 mesh). Thin layer chromatography (TLC): silica gel GF254 (Merck) plates. IR Spectra: Perkin Elmer RX1 FT-IR spectrophotometer. ¹H- and ¹³C-NMR spectra: Varian Gemini 200 MHz spectrometer; CDCl₃ as solvent; at 200 MHz and 50 MHz, resp. ESI-MS: LC-MSD Trap-SL spectrometer. Elemental analyses: Elemental Vario EL instrument. Characterization data are provided only for novel compounds.

(α -Aminoalkyl)phosphonates. A mixture of an amine (1.2 mmol) and an aldehyde (1.0 mmol) in MeCN (5 ml) was stirred for a few min at r.t., and P(OEt)₃ (1.5 mmol) and TCT (10 mol-%) were added. The mixture was stirred for the appropriate time and the progress of the reaction was monitored by TLC. After completion of the reaction (determined by TLC), the solvent was evaporated, and H₂O (10 ml) was added. The mixture was extracted with AcOEt (3 $\times$ 10 ml), and the extract was dried (anh. Na₂SO₄) and concentrated. The residue was purified by CC (SiO₂; AcOEt in hexane) to afford a pure (α -aminoalkyl)phosphonate.

Diethyl [(4-Methylphenyl)amino](phenyl)methyl]phosphonate (3a). IR (KBr): 3292, 1622, 1504, 1243. ¹H-NMR: 7.31–7.26 (m, 2 H); 7.10–7.01 (m, 4 H); 6.61 (t, *J* = 8.0, 1 H); 6.51 (d, *J* = 8.0, 2 H); 4.75–4.66 (m, 2 H); 4.15–4.02 (m, 2 H); 3.91–3.89 (m, 1 H); 3.62–3.60 (m, 1 H); 2.31 (s, 3 H); 1.28 (t, *J* = 7.0, 3 H); 1.12 (t, *J* = 7.0, 3 H). ¹³C-NMR: 144.8; 137.2 (d, *J* = 10.0); 129.2; 127.9; 126.8; 126.0; 114.2; 63.0 (d, *J* = 6.0); 55.2 (d, *J* = 152.0); 23.7; 16.0 (d, *J* = 10.5). ESI-MS: 351 ([*M* + NH₄]⁺). Anal. calc. for C₁₈H₂₄NO₃P (333.36): C 64.85, H 7.26, N 4.20; found: C 65.34, H 7.20, N 4.27.

Methyl 4-[(Diethoxyphosphoryl)(4-methylphenyl)methyl]amino]benzoate (3d). IR (KBr): 3310, 1707, 1606, 1523, 1437, 1275. ¹H-NMR: 7.80 (d, *J* = 8.0, 2 H); 7.32 (d, *J* = 8.0, 2 H); 7.13 (d, *J* = 8.0, 2 H); 6.60 (d, *J* = 8.0, 2 H); 5.50 (t, *J* = 10.0, 1 H); 4.79 (dd, *J* = 24.0, 10.0, 1 H); 4.15–4.06 (m, 2 H); 3.92–3.88 (m, 1 H); 3.81 (s, 3 H); 3.63–3.61 (m, 1 H); 2.02 (s, 3 H); 1.10 (t, *J* = 7.0, 3 H); 0.88 (t, *J* = 7.0, 3 H). ¹³C-NMR: 166.2; 151.0; 135.9; 133.4 (d, *J* = 10.0); 129.2; 128.1; 126.8; 118.2; 113.8; 63.1 (d, *J* = 6.0); 55.9 (d, *J* = 152.0); 50.5; 24.2; 16.2 (d, *J* = 10.5). ESI-MS: 392 ([*M* + H]⁺). HR-ESI-MS: 392.1630 ([*M* + H]⁺, C₂₀H₂₇NO₅P⁺; calc. 392.1626).

Methyl 4-[(Diethoxyphosphoryl)(4-hydroxyphenyl)methyl]amino]benzoate (3e). IR (KBr): 3423, 1632, 1495, 1378, 1212. ¹H-NMR: 7.80 (d, *J* = 8.0, 2 H); 7.32 (d, *J* = 8.0, 2 H); 7.15 (d, *J* = 8.0, 2 H); 6.60 (d, *J* = 8.0, 2 H); 5.50 (t, *J* = 10.0, 1 H); 4.79 (dd, *J* = 24.0, 10.0, 1 H); 4.20–4.09 (m, 2 H); 3.92–3.90 (m, 1 H); 3.82 (s, 3 H); 3.63–3.61 (m, 1 H); 2.02 (s, 3 H); 1.11 (t, *J* = 7.0, 3 H); 0.87 (t, *J* = 7.0, 3 H). ¹³C-NMR: 166.8; 158.9; 150.4; 137.8 (d, *J* = 10.0); 130.8; 129.2; 120.1; 118.0; 114.4; 113.1; 110.9; 62.7 (d, *J* = 6.5); 55.0 (d, *J* = 153.0); 51.9; 16.2 (d, *J* = 10.5). ESI-MS: 394 ([*M* + H]⁺). HR-ESI-MS: 416.1236 ([*M* + Na]⁺, C₁₉H₂₄NNaO₆P⁺; calc. 416.1238).

Diethyl [(4-Ethoxyphenyl)(phenylamino)methyl]phosphonate (3f). IR (KBr): 3289, 1615, 1529, 1349, 1238. ¹H-NMR: 7.51–7.46 (m, 3 H); 7.34 (d, *J* = 8.0, 2 H); 7.20 (t, *J* = 8.0, 1 H); 6.88–6.79 (m, 3 H); 5.70 (t, *J* = 10.0, 1 H); 4.69 (dd, *J* = 24.0, 10.0, 1 H); 4.20–4.09 (m, 2 H); 3.98 (q, *J* = 7.0, 2 H); 3.91–3.89 (m, 1 H); 3.60–3.58 (m, 1 H); 1.41 (t, *J* = 7.0, 3 H); 1.31 (t, *J* = 7.0, 3 H); 1.11 (t, *J* = 7.0, 3 H). ¹³C-NMR: 159.1; 149.2; 147.2 (d, *J* = 10.0); 130.0; 129.5; 126.2; 120.0; 115.3; 113.3; 108.0; 64.0 (d, *J* = 6.5); 63.4; 63.2 (d, *J* = 6.5); 55.0 (d, *J* = 155.0); 16.1 (d, *J* = 6.0); 16.0 (d, *J* = 6.0); 14.7. ESI-MS: 363 (*M*⁺). Anal. calc. for C₁₉H₂₆NO₄P (363.16): C 62.80, H 7.21, N 3.85; found: C 62.89, H 7.12, N 3.92.

Diethyl [(2-Nitrophenyl)(phenylamino)methyl]phosphonate (3j). IR (KBr): 3303, 1601, 1499, 1277, 1232. ¹H-NMR: 7.09–6.98 (m, 4 H); 6.81–6.55 (m, 5 H); 5.18 (dd, *J* = 24.0, 10.0, 1 H); 4.74 (t, *J* = 10.0, 1 H); 4.21–4.10 (m, 2 H); 3.92–3.88 (m, 1 H); 3.62–3.60 (m, 1 H); 1.32 (t, *J* = 7.0, 3 H); 1.15 (t, *J* = 7.0, 3 H). ¹³C-NMR: 154.1; 151.9; 146.1 (d, *J* = 14.0); 129.5; 125.8; 118.3; 114.0; 113.2; 111.5; 63.6 (d, *J* = 6.5); 63.2 (d, *J* = 6.5); 48.1 (d, *J* = 155.0); 16.5 (d, *J* = 6.5); 16.1 (d, *J* = 6.5). ESI-MS: 365 ([*M* + H]⁺), 387 ([*M* + Na]⁺). Anal. calc. for C₁₇H₂₁N₂O₅P (364.12): C 56.04, H 5.81, N 7.69; found: C 56.16, H 5.72, N 7.64.

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