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

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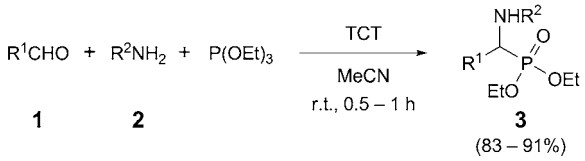
(α-Aminoalkyl)phosphonates have efficiently been synthesized by multicomponent reaction of aldehydes, amines, and triethyl phosphite in the presence of 2,4,6-trichloro-1,3,5-triazine at room temperature. The products are formed in high yields (83–91%) within 0.5–1 h.

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



1 **2** **3** (83–91%)

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

[1]) Part 220 in the series, 'Studies on Novel Synthetic Methodologies'.

Table. *Synthesis of α-Amino Phosphonates Using Trichloro Triazine* (TCT)[a])

Entry	R^1	R^2	Time [min]	Yield[b]) [%]	Product
1	Ph	4-Me–C_6H_4	35	90	**3a**
2	Ph	4-HO–C_6H_4	60	86	**3b**
3	Ph	4-Br–C_6H_4	40	87	**3c**
4	4-Me–C_6H_4	4-MeOOC–C_6H_4	50	87	**3d**
5	4-HO–C_6H_4	4-MeOOC–C_6H_4	60	91	**3e**
6	4-EtO–C_6H_4	Ph	30	88	**3f**
7	4-^{i}Pr–C_6H_4	Ph	35	90	**3g**
8	2,4-$(Cl)_2$–C_6H_3	Ph	45	86	**3h**
9	4-Cl,3-F–C_6H_3	4-Me–C_6H_4	40	91	**3i**
10	2-NO_2–C_6H_4	Ph	40	89	**3j**
11	4-NO_2–C_6H_4	Ph	45	89	**3k**
12	Pr	Ph	60	84	**3l**
13	Pentyl	Ph	60	83	**3m**

[a]) The structures of the products were deduced from their spectral (IR, ^{1}H- and ^{13}C-NMR, and MS) and analytical data. [b]) Yields of isolated pure products after column chromatography.

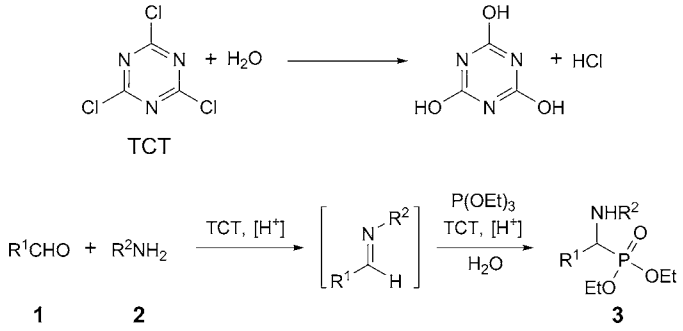
and the anilines used for this conversion contained electron-donating as well as electron-withdrawing groups. Various functional groups such as halogen, OH, NO_2, and ester remained unchanged. The conversion was complete within 0.5–1 h, and the products were formed in high yields (83–91%). The structures of the products were established from their spectral (IR, ^{1}H- and ^{13}C-NMR, and MS) and analytical data.

TCT is an inexpensive solid material. It reacts with the H_2O generated by the reaction of aldehydes and amines (during the formation of imines) or with incipient moisture to release HCl [6]. This acid subsequently activates the =C=N– bond of the imines to produce (α-aminoalkyl)phosphonates (*Scheme 2*).

TCT is easy to handle and is safe to use compared to the direct application of protic acid. Expensive and toxic metal-based reagents have also been avoided.

Conclusions. – We have developed a simple and efficient method for the synthesis of (α-aminoalkyl)phosphonates **3** by a one-pot reaction of aldehydes, amines, and

Scheme 2



$(EtO)_3P$ 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 (SiO_2; *BDH* 100–200 mesh). Thin layer chromatography (TLC): silica gel *GF254* (*Merck*) plates. IR Spectra: *Perkin Elmer RX1* FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: *Varian Gemini 200* MHz spectrometer; $CDCl_3$ as solvent; at 200 MHz and 50 MHz, resp. ESI-MS: *LC-MSD Trap-SL* spectrometer. Elemental analyses: *Elementar 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 H_2O (10 ml) was added. The mixture was extracted with AcOEt (3×10 ml), and the extract was dried (anh. Na_2SO_4) and concentrated. The residue was purified by CC (SiO_2; AcOEt in hexane) to afford a pure (α-aminoalkyl)phosphonate.

Diethyl {[(4-Methylphenyl)amino](phenyl)methyl}phosphonate (**3a**). IR (KBr): 3292, 1622, 1504, 1243. ^{1}H-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). ^{13}C-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 ($[M+NH_4]^+$). Anal. calc. for $C_{18}H_{24}NO_3P$ (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. ^{1}H-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). ^{13}C-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 ($[M+H]^+$, $C_{20}H_{27}NO_5P^+$; calc. 392.1626).

Methyl 4-{[(Diethoxyphosphoryl)(4-hydroxyphenyl)methyl]amino}benzoate (**3e**). IR (KBr): 3423, 1632, 1495, 1378, 1212. ^{1}H-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). ^{13}C-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 ($[M+Na]^+$, $C_{19}H_{24}NNaO_6P^+$; calc. 416.1238).

Diethyl [(4-Ethoxyphenyl)(phenylamino)methyl]phosphonate (**3f**). IR (KBr): 3289, 1615, 1529, 1349, 1238. ^{1}H-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). ^{13}C-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 $C_{19}H_{26}NO_4P$ (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. ^{1}H-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). ^{13}C-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 $C_{17}H_{21}N_2O_5P$ (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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