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One-Pot Synthesis of Primary 1-Aminophosphonates: Coupling Reaction of Carbonyl Compounds, Hexamethyldisilazane, and Diethyl Phosphite Catalyzed by $Al(OTf)_3$

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ABSTRACT: *$Al(OTf)_3$ has been utilized as a new and efficient catalyst for the selective synthesis of primary 1-aminophosphonates by a one-pot coupling reaction of various types of aldehydes/ketones, hexamethyldisilazane, and diethyl phosphite under solvent-free conditions.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:109–115, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20517

INTRODUCTION

1-Aminophosphonates (Scheme 1), which are considered as phosphorus analogues of 1-amino acids, have received considerable attention owing to their biological and biochemical properties. They have been used as antibacterial agents [1], carriers of hydrophilic organic molecules across phospholipid membranes [2], enzyme inhibitors [3–5] (including human immunodeficiency virus protease) [6,7], as well as plant growth regulators [8]. The wide application of 1-aminophosphonates has provoked the search for simple and efficient procedures for the synthesis of such significant scaffolds in recent years. Several multistep approaches to the synthesis of primary 1-aminophosphonates are available: (a) addition of the P—H function to imines [9,10]; (b) Hofmann rearrangement of substituted phosphonoacetic esters [11]; (c) alkylation of nucleophilic precursors such as Schiff bases [12]; (d) conversion of the corresponding 1-hydroxyphosphonates to 1-aminophosphonates [13,14]; (e) reduction of 1-hydroxyiminophosphonates [15,16]; and (f) addition of the P—H function to nitriles [17]. In contrast to the widespread studies on the one-pot synthesis of secondary and tertiary 1-aminophosphonates [18–23], relatively few papers have reported on the one-pot synthesis of primary 1-aminophosphonates. The most typical procedure for the one-pot synthesis of primary 1-aminophosphonates is a Strecker-type reaction [24,25], which involves the treatment of an aldehyde with ammonia and diethyl phosphite. This method, however, is not high yielding and is unsuitable for large-scale production since the reaction is performed in a sealed vessel at 100°C. Recently, in this reaction, ammonia has been substituted by ammonium salts or hexamethyldisilazane (HMDS). These reactions are conducted by catalysts such as molecular sieves [25], $LiClO_4$ [26], tetra-*tert*-butyl-substituted phthalocyanine [27], and solid supports [28–32]. However, all the existing methods have displayed drawbacks, such as having long reaction times [25,27], being amenable only for aldehydes as carbonyl compounds [25,28–33], using foul-smelling trialkyl phosphite as the phosphorus nucleophile [26], requiring a promoter such as microwave treatment [28–31], giving low yields of the products [25,27], producing 1-hydroxyphosphonates or

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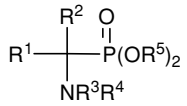


Primary 1–aminophosphonates: $R^3 = H$; $R^4 = H$
Secondary 1–aminophosphonates: R^3 = alkyl, aryl; $R^4 = H$
Tertiary 1–aminophosphonates: R^3 = alkyl, aryl; R^4 = alkyl, aryl

SCHEME 1

1-trimethylsilyloxyphosphonates as side products [33], and using large amounts of solid supports or catalysts that would eventually result in the generation of a large amount of toxic waste [26,28–31].

RESULTS AND DISCUSSIONS

As part of our efforts to introduce new methods for the synthesis of phosphonate derivatives [34–38], we have recently reported on different metal triflates [$M(OTf)_x$; M = Al, Mg, Ce, Li, Cu] as efficient catalysts for the successful one-pot synthesis of secondary diethyl 1-aminophosphonates under solvent-free conditions [38]. Thus, we envisioned that these types of catalysts could be effective for the one-pot synthesis of primary 1-aminophosphonates under solvent-free conditions.

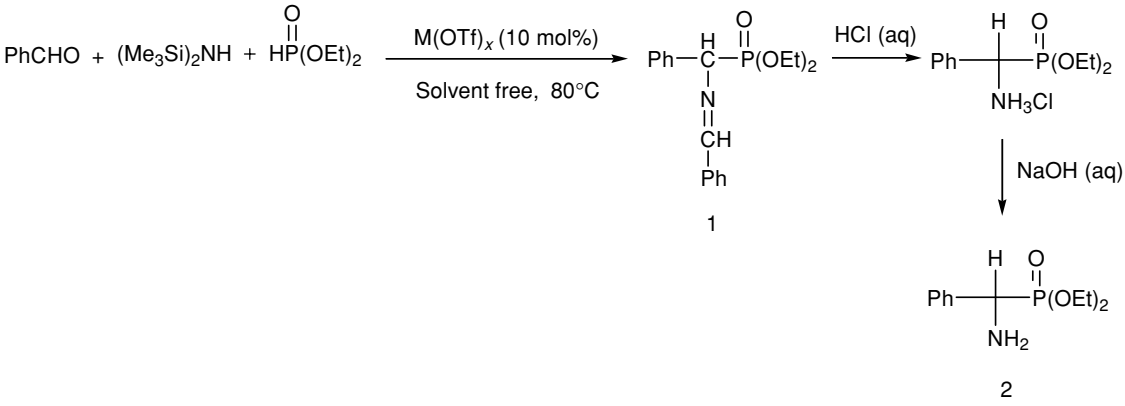
First, we examined the feasibility of the reaction between benzaldehyde, HMDS, and diethyl phosphite as a model in the presence of different metal triflates [$M(OTf)_x$; M = Al, Mg, Ce, Li, Cu, Zn] under solvent-free conditions (Table 1, Scheme 2). Among the metal triflates tested, $Al(OTf)_3$ turned out to be the most effective catalyst leading to *N*-(phenylmethylene)-1-aminophenylmethylphosphonate (**1**) (Scheme 2). The ^1H NMR spectrum of the reaction mixture exhibits a doublet at 8.40 ppm, which is indicative of the coupling for the HC—P (J_{HP} = 5 Hz) moiety in the imine (**1**) in 98% yield (based on ^1H NMR data) [(The structure of **1** was confirmed by spectral data of pure imine, isolated from the reaction mixture by plate chromatography and eluted with *n*-hexane:ethyl acetate (1:3; R_f = 0.65)]. Hydrolysis of **1** with HCl and neutralization of the resulting chloride salt gave 1-aminophenylmethylphosphonate (**2**) (Scheme 2) [R_f = 0.25 [*n*-hexane:ethyl acetate (1:3)]. Excellent selectivity for the synthesis of **1** was observed in the presence of $Al(OTf)_3$, $Mg(OTf)_2$, $Ce(OTf)_4$, LiOTf, and $Cu(OTf)_2$ with no formation of diethyl 1-(trimethylsilyloxy)-1-phenylmethylphosphonate and diethyl 1-hydroxyphenylmethylphosphonate. In the presence of $Zn(OTf)_2$, lower selectivity for **2** was observed owing to the formation of diethyl 1-(trimethylsilyloxy)-1-phenylmethylphosphonate in 43% yield as a side product (Table 1, Entry 6).

TABLE 1 One-Pot Synthesis of Primary 1-Aminophenylmethylphosphonate (**2**) in the Presence of $M(OTf)_x$ at 80°C Under Solvent-Free Conditions

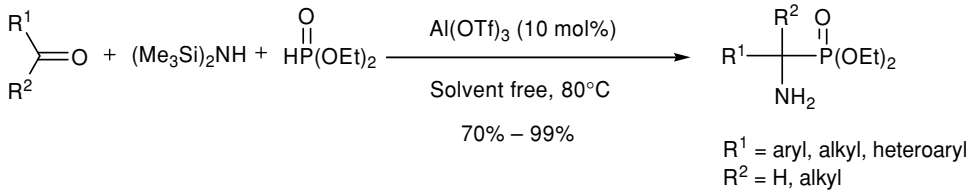
Entry	*$M(OTf)_x$*	*Time (h)*	*Yield[a,b] (%)*
1	$Al(OTf)_3$	0.5	96
2	$Ce(OTf)_4$	3	72
3	$Cu(OTf)_2$	2	83
4	LiOTf	5	80
5	$Mg(OTf)_2$	2	65
6	$Zn(OTf)_2$	3	52[c]

[a]Isolated yield based on half of aldehyde.
[b]Conditions: benzaldehyde (2 mmol), HMDS (1.2 mmol), and diethyl phosphite (1.2 mmol).
[c]Diethyl 1-(trimethylsilyloxy)-1-phenylmethylphosphonate was obtained in 43% yield as a side product.

To establish the generality of this method, various aldehydes and ketones were subjected to



SCHEME 2



SCHEME 3

one-pot reaction with HMDS and diethyl phosphite catalyzed by $Al(OTf)_3$ under solvent-free conditions (Scheme 3). The results are listed in Table 2.

As is indicated in Table 2, benzaldehydes substituted with different electron-donating and electron-withdrawing groups underwent smooth reactions with HMDS and diethyl phosphite (Entries 1–8) and the desired products were obtained in good to high yields. The catalyst was compatible with functional groups on the aromatic ring, such as Cl and O—Me groups. No competitive nucleophilic methyl ether cleavage was observed for the substrate having an aryl—O—Me group (Table 2, Entry 4) in spite of the good nucleophilic property of phosphites. Naphthalene-2-carbaldehyde, a polynuclear aromatic aldehyde, also reacted with diethyl phosphite to give the desired product (**10**) in high yield. This procedure worked well for the synthesis of primary diethyl α-aminophosphonates **11–13** from acid-sensitive aldehydes such as thiophene-2-carbaldehyde, furan-2-carbaldehyde, and indol-3-carbaldehyde without any decomposition or polymerization. The present method is also suitable for the preparation of primary 1-aminophosphonates from aliphatic aldehydes (Table 2, Entries 13 and 14). In addition to aldehydes, some ketones were also screened to examine the direct coupling by $Al(OTf)_3$ under these reaction conditions. The results showed that the reactions involving alkyl aryl ketones, acyclic dialkyl ketones, and cyclic ketones worked well and the expected products could be obtained smoothly in 70% to 96% yields (Table 2, Entries 15–23). (In the case of ketones, no imine was formed, according to the spectral data of the isolated product by plate chromatography before acidic workup.) However, no product was obtained when diaryl ketones such as benzophenone or 9*H*-fluoren-9-one (Table 2, Entries 24 and 25) were used in this one-pot reaction under the same conditions.

In conclusion, we have introduced $Al(OTf)_3$ as a new and efficient catalyst for the selective synthesis of primary 1-aminophosphonates by the one-pot reaction of various types of aldehydes/ketones, HMDS, and diethyl phosphite. The applicability of diethyl phosphite as a phosphorus nucleophile instead of the foul-smelling triethyl phosphite, high yields, the suppression of side products and tar formation, the simple extractive workup, and the nonrequirement of additional promoters other than a catalytic amount of $Al(OTf)_3$ make this method an attractive and useful contribution to the present methodologies.

EXPERIMENTAL

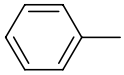
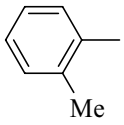
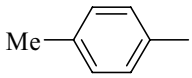
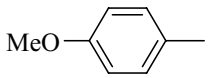
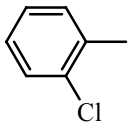
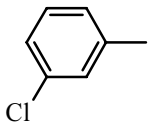
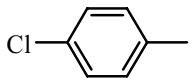
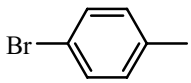
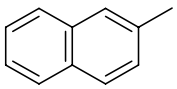
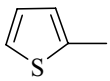
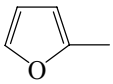
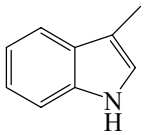
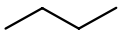
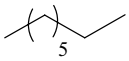
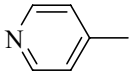
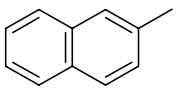
General

Chemicals were purchased from the Merck and Fluka chemical companies. All of the products were identified by their physical and spectral data. IR spectra were measured on a Perkin Elmer 780 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250 NMR spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP5050A gas chromatograph mass spectrometer. The purity of the products and the progress of the reactions were determined by thin layer chromatography (TLC) on silica-gel polygram $SILG/UV_{254}$ plates or by gas chromatography (GC) on a Shimadzu model GC-14A gas chromatograph.

General Procedure for the Preparation of Primary Diethyl 1-Aminophosphonates

A mixture of an aldehyde/ketone (1.5 mmol), HMDS (1.2 mmol), diethyl phosphite (1.2 mmol), and $Al(OTf)_3$ (0.01 mmol) was stirred in an oil bath at 80°C for an appropriate amount of time (Table 2). Progress of the reaction was monitored with TLC or GC [In the case of aldehydes, the progress of the reaction was also monitored by ^1H NMR measurements (conversion = 90%–100%)]. The reaction mixture was cooled and acidified to pH 1 by HCl (aq). The solution was washed with EtOAc (2 × 10 mL). The aqueous phase was then made alkaline with NaOH (aq) and the product was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give diethyl 1-aminophosphonates as pale yellow oils with high purity [R_f = 0.2–0.35 [*n*-hexane:ethyl acetate (1:3)].

TABLE 2 One-Pot Synthesis of Primary 1-Aminophosphonates from Aldehydes/Ketones, HMDS and Diethyl Phosphite in the Presence of $Al(OTf)_3$ at 80°C under Solvent-Free Conditions

Entry	*R^1*	*R^2*	*Product*	*Time*	*Yield[a,b] (%)*
1		H	**2**	30 min	96[c]
2		H	**3**	25 min	94
3		H	**4**	2 h	86[c]
4		H	**5**	30 min	92
5		H	**6**	15 min	99
6		H	**7**	30 min	91
7		H	**8**	1.5 h	93[c]
8		H	**9**	20 min	83[c]
9		H	**10**	45 min	90
10		H	**11**	30 min	92
11		H	**12**	1 h	98
12		H	**13**	2 h	92
13		H	**14**	40 min	88
14		H	**15**	35 min	93
15		Me	**16**	45 min	83[d]
16		Me	**17**	2 h	70[d]
17	*iso*-Butyl	Et	**18**	30 min	96[d]
18	Et	Me	**19**	35 min	92[d]
19	Me	MeO_2C	**20**	15 min	95[d]

(Continued)

TABLE 2 Continued

Entry	*R^1*	*R^2*	*Product*	*Time*	*Yield[a,b] (%)*
20			**21**	30 min	87[d]
21			**22**	2 h	84[d]
22			**23**	45 min	85[d]
23			**24**	1 h	83[d]
24			**25**	24 h	0
25			**26**	24 h	0

[a]Isolated yield based on half of aldehyde.
[b]Conditions: carbonyl compound (1.5 mmol), HMDS (1.2 mmol), and diethyl phosphite (1.2 mmol).
[c]Conditions: carbonyl compound (2 mmol), HMDS (1.2 mmol), and diethyl phosphite (1.2 mmol).
[d]Isolated yield based on diethyl phosphite.

Spectral Data for Selected Diethyl 1-Aminophosphonates

*Diethyl 1-Aminophenylmethylphosphonate (**2**).* ^{1}H NMR ($CDCl_3$, TMS): δ 1.16 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.26 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 2.37 (bs, NH_2), 3.82–4.09 (m, 4H, OCH_2CH_3), 4.24 (d, 1H, $^1J_{PH}$ = 17.2 Hz, CH), 7.21–7.46 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 54.0 (d, $^1J_{CP}$ = 149.5 Hz, CH), 62.7 (d, $^2J_{CP}$ = 7.7 Hz, OCH_2CH_3), 62.8 (d, $^2J_{CP}$ = 7.7 Hz, OCH_2CH_3), 127.6, 128.1 (d, $^3J_{CP}$ = 2.5 Hz, C_6H_5), 137.3 (d, $^2J_{CP}$ = 3.8 Hz, C_6H_5); IR: 3375, 3293 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 243 (M^+), 106 [M—P(O)$(OEt)_2$].

*Diethyl 1-Amino(*p*-methoxyphenyl)methylphosphonate (**5**).* ^{1}H NMR ($CDCl_3$, TMS): δ 1.16 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.26 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.88 (bs, NH_2), 3.78 (s, 3H, OCH_3), 3.82–4.08 (m, 4H, OCH_2CH_3), 4.18 (d, 1H, $^1J_{PH}$ = 16.2 Hz, CH), 6.85–6.88 (m, 2H, C_6H_4), 7.33–7.45 (m, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{CP}$ = 6.3 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ = 6.3 Hz, OCH_2CH_3), 53.4 (d, $^1J_{CP}$ = 150.9 Hz, CH), 55.2 (s, OCH_3), 62.6 (d, $^2J_{CP}$ = 6.9 Hz, OCH_2CH_3), 62.7 (d, $^2J_{CP}$ = 6.9 Hz, OCH_2CH_3), 128.7, 128.8 (C_6H_5), 113.8 (d, $^3J_{CP}$ = 2.5 Hz, C_6H_5), 159.2 (d, $^2J_{CP}$ = 3.1 Hz, C_6H_5); IR: 3371, 3300 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 273 (M^+), 136 [M—P(O)$(OEt)_2$].

*Diethyl 1-Amino(*p*-chlorophenyl)methylphosphonate (**8**).* ^{1}H NMR ($CDCl_3$, TMS): δ 1.07 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.13 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.82 (bs, NH_2), 3.73–3.97 (m, 4H, OCH_2CH_3), 4.10 (d, 1H, $^1J_{PH}$ = 17.2 Hz, CH), 7.15–7.19 (m, 2H, C_6H_4), 7.24–7.27 (m, 2H, C_6H_4); ^{13}C NMR ($CDCl_3$, TMS): δ 16.2 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 16.3 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 53.3 (d, $^1J_{CP}$ = 150.3 Hz, CH), 62.6 (d, $^2J_{CP}$ = 5.1 Hz, OCH_2CH_3), 62.8 (d, $^2J_{CP}$ = 5.1 Hz, OCH_2CH_3), 128.4, 129 (C_6H_5), 133.4 (d, $^2J_{CP}$ = 4.4 Hz, C_6H_5), 136.3 (d, $^3J_{CP}$ = 3.7 Hz, C_6H_5); IR: 3350, 3280 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 279 (M + 2), 277 (M^+), 140 [M—P(O)$(OEt)_2$].

*Diethyl 1-Amino(2-naphthyl)methylphosphonate (**10**).* ^{1}H NMR ($CDCl_3$, TMS): δ 1.15 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.25 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 2.19 (bs, NH_2), 3.78–4.10 (m, 4H, OCH_2CH_3), 4.43 (d, 1H, $^1J_{PH}$ = 17.5 Hz, CH), 7.44–7.48 (m, 2H, $C_{10}H_7$), 7.56–7.60 (m, 1H, $C_{10}H_7$), 7.80–7.90 (m, 4H, $C_{10}H_7$); ^{13}C NMR ($CDCl_3$, TMS):

δ 16.3 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 54.2 (d, $^1J_{CP}$ = 149.7 Hz, CH), 62.8 (d, $^2J_{CP}$ = 6.3 Hz, OCH_2CH_3), 62.9 (d, $^2J_{CP}$ = 6.3 Hz, OCH_2CH_3), 125.7–126.6 (m, $C_{10}H_7$), 127.6–128.1 (m, $C_{10}H_7$), 132.9–133.2 (m, $C_{10}H_7$), 135.1 (d, $^2J_{CP}$ = 3.8 Hz, $C_{10}H_7$); IR: 3371, 3292 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 293 (M^+), 156 [M—P(O)$(OEt)_2$].

Diethyl 1-Amino(2-thienyl)methylphosphonate (**11**). ^{1}H NMR ($CDCl_3$, TMS): δ 1.11–1.20 (m, 6H, OCH_2CH_3), 2.27 (bs, NH_2), 3.82–4.03 (m, 4H, OCH_2CH_3), 4.42 (d, 1H, $^1J_{PH}$ = 16.7 Hz, CH), 6.87 (t, $^2J_{HH}$ = 4.0 Hz, 1 H, C_4H_3S), 7.03 (s, 1H, C_4H_3S), 7.14 (d, 1H, $^2J_{HH}$ = 5.0 Hz, C_4H_3S); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{CP}$ = 3.8 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ = 3.8 Hz, OCH_2CH_3), 49.9 (d, $^1J_{CP}$ = 156.2 Hz, CH), 62.9 (d, $^2J_{CP}$ = 7.6 Hz, OCH_2CH_3), 124.9, 125.5, 126.8 (C_4H_3S), 141 (d, $^2J_{CP}$ = 3.8 Hz, C_4H_3S); IR: 3374, 3302 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 249 (M^+), 112 [M—P(O)$(OEt)_2$].

Diethyl 1-Amino(2-furyl)methylphosphonate (**12**). ^{1}H NMR ($CDCl_3$, TMS): δ 1.19 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.26 (t, 3H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 3.28 (bs, NH_2), 3.84–4.13 (m, 4H, OCH_2CH_3), 4.23 (d, 1H, $^1J_{PH}$ = 18.3 Hz, CH), 6.10–6.12 (m, 1H, C_4H_3O), 6.45–6.47 (m, 1H, C_4H_3O), 7.33–7.34 (m, 1H, C_4H_3O); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{CP}$ = 5.1 Hz, OCH_2CH_3), 16.4 (d, $^3J_{CP}$ = 5.1 Hz, OCH_2CH_3), 48.2 (d, $^1J_{CP}$ = 155.0 Hz, CH), 62.8 (d, $^2J_{CP}$ = 6.9 Hz, OCH_2CH_3), 110.1, 110.6, 141.8, 151.0 (C_4H_3O); IR: 3378, 3268 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 233 (M^+), 96 [M—P(O)$(OEt)_2$].

*Diethyl 1-Amino(1*H*-3-indolyl)methylphosphonate* (**13**). ^{1}H NMR ($CDCl_3$, TMS): δ 1.24–1.29 (m, 6H, OCH_2CH_3), 3.03 (bs, NH_2), 4.09–4.15 (m, 4H, OCH_2CH_3), 4.63 (d, 1H, $^1J_{PH}$ = 15.0 Hz, CH), 7.04–7.17 (m, 2H, C_8H_6N), 7.33–7.41 (m, 2H, C_8H_6N), 7.63–7.66 (m, 1H, C_8H_6N), 9.33 (bs, NH); ^{13}C NMR ($CDCl_3$, TMS): δ 16.3 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 16.2 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 45.9 (d, $^1J_{CP}$ = 158.7 Hz, CH), 62.9 (d, $^2J_{CP}$ = 6.3 Hz, OCH_2CH_3), 63.4 (d, $^2J_{CP}$ = 6.3 Hz, OCH_2CH_3), 110.7, 118.8, 119.5, 119.3, 122.0, 124.3 (C_8H_6N), 126.1 (1H, $^2J_{CP}$ = 5.7 Hz, C_8H_6N), 136.1 (C_8H_6N); IR: 3396, 3252 (NH_2, NH) cm^{-1}; MS (70 eV), *m/z*: 282 (M^+), 145 [M—P(O)$(OEt)_2$].

Diethyl 1-Amino-1-pyridin-4-ylethylphosphonate (**16**). ^{1}H NMR ($CDCl_3$, TMS): δ 0.91 (t, 6H, $^2J_{HH}$ = 7.5 Hz, OCH_2CH_3), 1.28 (d, 3H, $^2J_{PH}$ = 17.1 Hz, CH_3), 1.64 (bs, NH_2), 4.19–4.23 (m, 4H, OCH_2CH_3), 7.50–7.54 (m, 2H, C_5H_4N), 7.68–7.72 (m, 2H, C_5H_4N); IR: 3377, 3299 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 258 (M^+), 121 [M—P(O)$(OEt)_2$].

Diethyl 1-Amino-1-ethyl-3-methylbutylphosphonate (**18**). ^{1}H NMR ($CDCl_3$, TMS): δ 0.95 (t, 6H, $^2J_{HH}$ = 6.7 Hz, OCH_2CH_3), 1.23–1.33 (m, 9H, CH_3), 1.46–1.63 (m, 6H, CH_2, NH_2), 1.89–1.99 (m, 1H, CH), 4.05–4.17 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.6 (d, $^3J_{CP}$ = 5 Hz, OCH_2CH_3), 22.1 (d, $^3J_{CP}$ = 1.9 Hz, CH_3), 23.2 (d, $^2J_{CP}$ = 10.1 Hz, CH_2), 25.2 (s, CH_3), 45.5 (d, $^3J_{CP}$ = 3.1, CH), 52.5 (d, $^1J_{CP}$ = 145.3 Hz,), 62.2 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2CH_3); IR: 3390, 3302 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 251 (M^+), 114 [M—P(O)$(OEt)_2$].

Diethyl 1-Amino-1-methylpropylphosphonate (**19**). ^{1}H NMR ($CDCl_3$, TMS): δ 0.98 (t, 3H, $^2J_{HH}$ = 7.5 Hz, CH_3), 1.24 (d, 3H, $^2J_{PH}$ = 16 Hz, CH_3), 1.32 (t, 6H, $^2J_{HH}$ = 7 Hz, OCH_2CH_3), 1.59–1.73 (m, 4H, CH_2, NH_2); 4.07–4.19 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 7.3 (d, $^3J_{CP}$ = 7.6 Hz, CH_3), 16.6 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 21.7 (d, $^2J_{CP}$ = 21.7 Hz, CH_3), 30.0 (d, $^2J_{CP}$ = 3.8 Hz, CH_2), 52.0 (d, $^1J_{CP}$ = 147.4 Hz, C), 62.2 (d, $^2J_{CP}$ = 7.6 Hz, OCH_2CH_3); IR: 3378, 3307 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 209 (M^+), 72 [M—P(O)$(OEt)_2$].

Methyl 2-Amino-2-(diethoxyphosphoryl)-propanoate (**20**). ^{1}H NMR ($CDCl_3$, TMS): δ 1.33 (t, 6H, $^2J_{HH}$ = 7.0 Hz, OCH_2CH_3), 1.58 (d, 3H, $^3J_{PH}$ = 16.2 Hz, CH_3), 2.11 (bs, NH_2), 3.78 (s, 3H, CO_2CH_3), 4.06–4.23 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{CP}$ = 5.0 Hz, OCH_2CH_3), 21.9 (s, CH_3), 52.9 (s, CH_3), 58.4 (d, $^1J_{CP}$ = 145.5 Hz, C), 63.4 (d, $^2J_{CP}$ = 3.2 Hz, OCH_2CH_3), 63.5 (d, $^2J_{CP}$ = 3.2 Hz, OCH_2CH_3), 172.2 [d, $^2J_{CP}$ = 3.8 Hz, C(O)]; IR: 3394, 3316 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 239 (M^+), 102 [M—P(O)$(OEt)_2$].

Diethyl 1-Aminocyclopentylphosphonate (**21**). ^{1}H NMR ($CDCl_3$, TMS): δ 1.29 (t, 6H, $^2J_{HH}$ = 7.2 Hz, OCH_2CH_3), 1.54–1.69 (m, 4H, C_5H_8), 1.87–2.04 (m, 6H, C_5H_8, NH_2), 4.08–4.20 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.6 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 24.6 (d, $^2J_{CP}$ = 11.3 Hz, C_5H_8), 36.3 (d, $^3J_{CP}$ = 6.9 Hz, C_5H_8), 58.7 (d, $^1J_{CP}$ = 154.7 Hz, C_5H_8), 62.2 (d, $^2J_{CP}$ = 6.9 Hz, OCH_2CH_3); IR: 3368, 3294 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 221 (M^+), 84 [M—P(O)$(OEt)_2$].

Diethyl 1-Aminocyclohexylphosphonate (**22**). ^{1}H NMR ($CDCl_3$, TMS): δ 1.29 (t, 6H, $^2J_{HH}$ = 7.2 Hz, OCH_2CH_3), 1.52–1.72 (m, 12H, C_6H_{10}, NH_2), 4.04–4.15 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 19.8 (d,

$^3J_{CP}$ = 11.3 Hz, C_6H_{10}), 25.5, 31.3 (C_6H_{10}), 51.6 (d, $^1J_{CP}$ = 151 Hz, C_6H_{10}), 62.1 (d, $^2J_{CP}$ = 8.2 Hz, OCH_2CH_3); IR: 3385, 3290 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 235 (M^+), 98 [M—P(O)$(OEt)_2$].

*Diethyl 1-Aminocycloheptylphosphonate (**23**).* ^{1}H NMR ($CDCl_3$, TMS): δ 1.21 (t, 6H, $^2J_{HH}$ = 7 Hz, OCH_2CH_3), 1.42–1.52 (m, 12H, C_7H_{12}), 1.90 (bs, NH_2), 3.96–4.08 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 21.9 (d, $^2J_{CP}$ = 9.4 Hz, C_7H_{12}), 30.3 (s, C_7H_{12}), 35.5 (d, $^3J_{CP}$ = 3.1 Hz, C_7H_{12}), 54.5 (d, $^1J_{CP}$ = 144 Hz, C_7H_{12}), 62.1 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2CH_3); IR: 3369, 3300 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 249 (M^+), 112 [M—P(O)$(OEt)_2$].

*Diethyl 1-Aminocyclooctylphosphonate (**24**).* ^{1}H NMR ($CDCl_3$, TMS): δ 1.24 (t, 6H, $^2J_{HH}$ = 7 Hz, OCH_2CH_3), 1.34–1.80 (m, 16H, C_8H_{14}, NH_2), 3.99–4.11 (m, 4H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, TMS): δ 16.5 (d, $^3J_{CP}$ = 5.7 Hz, OCH_2CH_3), 21.6 (d, $^2J_{CP}$ = 8.2 Hz, C_8H_{14}), 24.9, 28.1 (C_8H_{14}), 30.9 (d, $^3J_{CP}$ = 3.1 Hz, C_8H_{14}), 54.9 (d, $^1J_{CP}$ = 144.0 Hz, C_8H_{14}), 62.0 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2CH_3); IR: 3368, 3295 (NH_2) cm^{-1}; MS (70 eV), *m/z*: 263 (M^+), 126 [M—P(O)$(OEt)_2$].

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