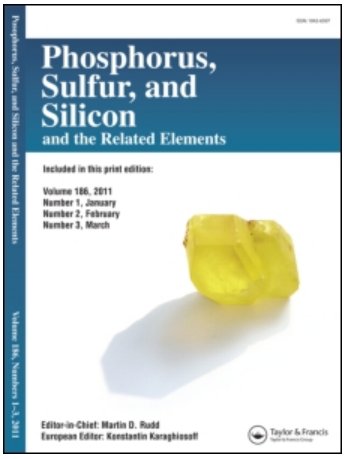

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Synthesis and Mass Spectrometry of 2-Hydroxyethyl 1-Aminoalkylphosphonates

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Mannich-type condensation of benzyl carbamate, aldehydes, and chlorophosphite has been widely used in the synthesis of 1-(N-benzyloxycarbonylamino)arylmethylphosphonic derivatives. Reactions of benzyl carbamate, aldehydes, and cyclic

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chlorophosphite 2-chloro-1,3,2-dioxaphospholane were conducted in benzene to afford a mixture of benzyl [(2-oxido-1,3,2-dioxaphospholane-2-yl)arylmethyl]-carbamates and 2-hydroxyethyl 1-(N-benzoxycarbonylamino)arylmethylphosphonate monoesters. 2-hydroxyethyl 1-(N-benzoxycarbonylamino)arylmethylphosphonate monoesters were obtained exclusively after the addition of water under stirring. The reaction mechanism was discussed. Their mass spectrometric fragmentations were also described.

Keywords Alkylphosphonate; amino acid; aminoalkylphosphonic acid; Mannich-type reaction; mass spectrometry; multiple component condensation; synthesis

INTRODUCTION

Many naturally occurring aminoalkylphosphonic acids have been discovered in a wide range of living organisms, animals, and even human tissues.[1] They are not only important phosphorus analogues of naturally occurring amino acids, but also members of the most important types of them. α-aminoalkylphosphonic acids are important phosphorus analogues of naturally occurring amino acids. To date, several methods for the synthesis of α-aminoalkylphosphonic acids and their derivatives have been developed.[1,2] Among them, the Mannich-type reaction of carbamates, aldehydes, and phosphite/phosphorus trichloride is considered a very useful method and has been widely used to synthesize α-aminoalkylphosphonic acids and their monoesters,[3–7] symmetric[8–10] and mixed diesters,[11,12] amidates,[13] phosphonopeptide, and depsiphosphonopeptides.[14–16] Herein we present the reaction of benzyl carbamate, aldehydes, and 2-chloro-1,3,2-dioxaphospholane to prepare functionalized 2-hydroxyethyl aminoalkylphosphonate monoesters and their formation mechanism and mass spectrometry.

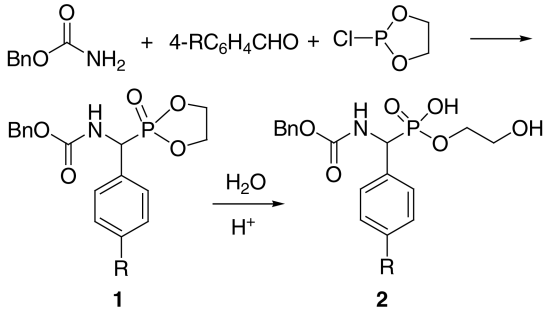
RESULTS AND DISCUSSION

The Mannich-type reactions of carbamates, aldehydes, and phosphite have been widely used to synthesize α-aminoalkylphosphonic acids and their derivatives. The three-component condensations of carbamates, aldehydes, and monochlorophosphite generally afforded *N*-Cbz protected α-aminoalkylphosphonate diesters.[8–10] For example, the condensations of benzyl carbamate, aldehydes, and dialkyl monochlorophosphite afforded *N*-Cbz protected symmetric α-aminoalkylphosphonate diesters.[9] The condensations of benzyl carbamate, aldehydes, aromatic cyclic monochlorophosphite, and 2-chloro-benzo[1,3,2]dioxaphosphole afforded *N*-Cbz protected symmetric cyclic α-aminoalkylphosphonate diesters, benzyl *N*-[(2-oxido-benzo[1,3,2]dioxaphosphol-2-yl)phenylmethyl]carbamate.[8] The reaction of benzyl carbamate, aldehydes, and 2-chloro-1,3,2-dioxaphospholane, an aliphatic cyclic monochlorophosphite, was

TABLE I The Reaction of Benzyl Carbamate, Aldehydes, and 2-Chloro-1,3,2-Dioxaphospholane

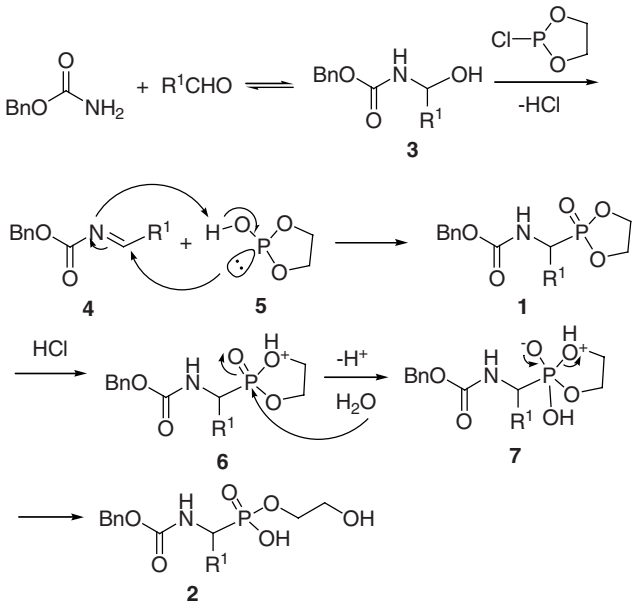
	Reaction Without the Addition of Water		Reaction Followed by the Addition of Water
Entry	Yield of **1** (%)	Yield of **2** (%)	Yield of **2** (%)
a	48	—	64
b	13	30	89
c	14	33	92
d	34	43	89
e	30	53	52

assumed to be used to prepare α-aminoalkylphosphonate cyclic diesters **1** without any experiment data.[17] However, when the three-component condensation of benzyl carbamate, aldehydes, and 2-chloro-1,3,2-dioxaphospholane was used to hope to prepare α-aminoalkylphosphonate cyclic diesters **1**. The results indicate that a mixture of the desired cyclic diesters, benzyl *N*-[aryl-(2-oxido-1,3,2-dioxaphospholane-2-yl)methyl]carbamates **1**, and 2-hydroxyethyl *N*-Cbz protected α-aminoalkylphosphonate monoesters **2** were obtained in most cases (Table I, columns 2 and 3). Monoesters **2** should be 1,3,2-dioxaphospholane ring-opening products by water during workup. In order to improve the yields of monoesters **2**, a type of functionalized monoesters, water was added into the reaction mixture, and the resulting mixture was stirred before workup. Monoesters **2** were obtained exclusively in moderate to good yields (Table I, column 4). The current route provides a general and convenient method to prepare 2-hydroxyethyl *N*-Cbz protected α-aminoalkylphosphonate monoesters **2**, a type of functionalized monoesters (Scheme 1).



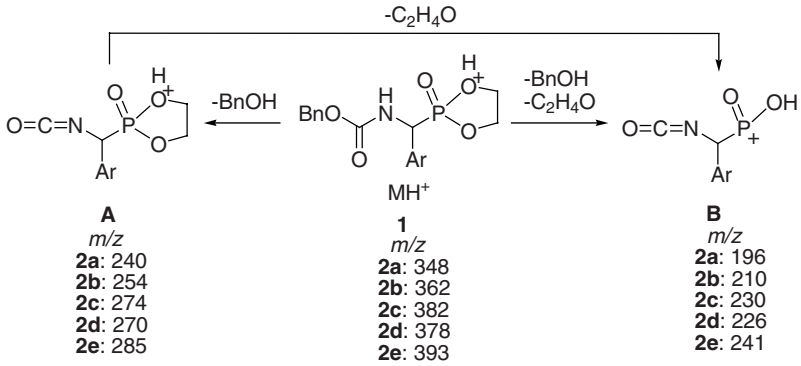
a: R = H; **b**: R = 4-Me; **c**: R = 4-Cl; **d**: R = 4-MeO; **e**: R = 4-NO_2

SCHEME 1 The reaction of benzyl carbamate, aldehydes, and 2-chloro-1,3,2-dioxaphospholane.



SCHEME 2 The proposed reaction mechanism for the formation of benzyl *N*-[aryl-(2-oxido-1,3,2-dioxaphospholane-2-yl)methyl]carbamates **1** and 2-hydroxyethyl 1-(*N*-benzoxycarbonylamino)arylmethylphosphonate monoesters **2**.

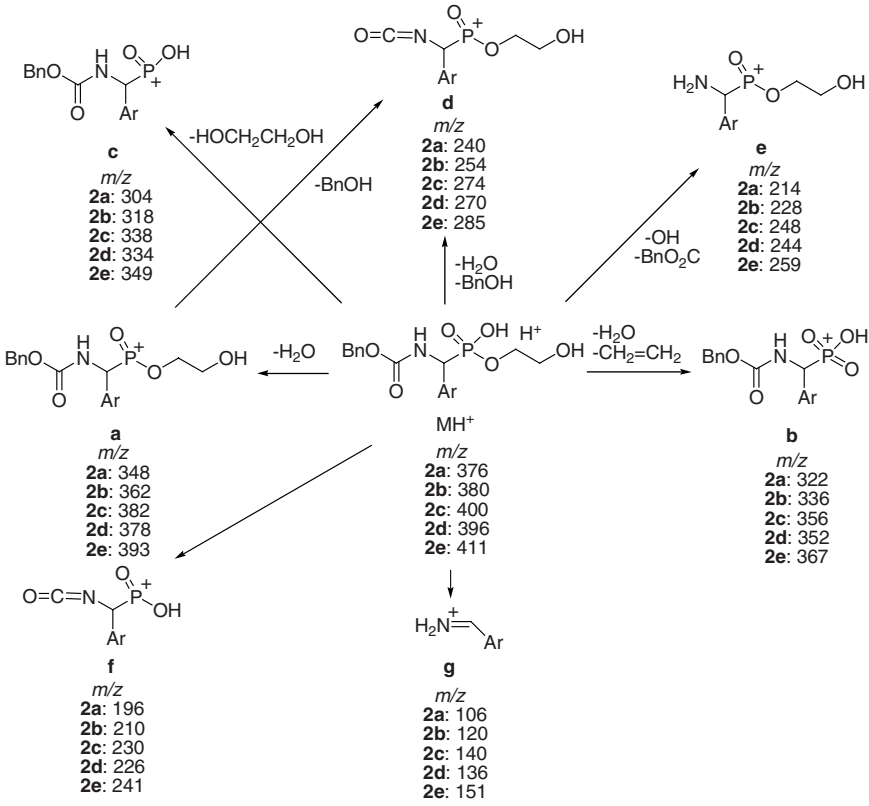
On the basis of our previous investigation,[7,12] the reaction mechanism could be proposed as shown in Scheme 2. Benzyl carbamate and aldehydes could undergo an addition to form intermediates **3**, which could be dehydrolyzed to generate imines **4** in the presence of 2-chloro-1,3,2-dioxaphospholane serving as a dehydrolyzing agent, and 2-chloro-1,3,2-dioxaphospholane was converted to hydroxyphosphite **5** at the same time. Imines **4** and hydroxyphosphite **5** underwent a nucleophilic addition followed by a hydrogen transfer to give rise to aminoalkylphosphonate cyclic diesters **1** as described previously,[12] some of which were converted to monoesters **2** during workup due to the presence of hydrochloric acid and moisture during workup. Actually the conversion from cyclic diesters **1** to monoesters **2** is an acid-catalyzed hydrolysis via protonated cyclic diesters **6** and pentacoordinated phosphorus intermediates **7**. Although the five-membered ring compounds are generally stable and their formation is favorable in most cases, 1,3,2-dioxaphospholane is not so stable in the current case and undergoes predominant hydrolysis in the presence of acid.



SCHEME 3 Mass spectral fragmentation of benzyl *N*-[aryl-(2-oxido-1,3,2-dioxaphospholane-2-yl)methyl]carbamates **1**.

Pure cyclic diesters **1** were not obtained, and their structure was confirmed by crude ^{1}H NMR spectra and their mass spectral fragmentation under positive ion Electrospray Ionization (ESI) conditions. The mass spectral fragmentation mechanisms of both cyclic diesters **1** and 2-hydroxyethyl *N*-Cbz protected α-aminoalkylphosphonate monoesters **2** were investigated via tandem mass spectra under ESI conditions. Protonated cyclic diesters **1** showed a simple mass spectral fragmentation pattern. They formed protonated aryl-(2-oxido-1,3,2-dioxaphospholane-2-yl)methyl isocyanate ions (A) by a loss of benzyl alcohol and 1-aryl-1-isocyanomethylphosphonic ions (B) by a loss of ethene oxide. The ions (A) could also yielded ions (B) by a loss of ethene oxide (Scheme 3). Their fragmentation was obviously different from that of the corresponding dimethyl and diethyl esters,[18] which could undergo the common eliminations of ether, benzyl alcohol, phosphite, and an ether plus benzyl alcohol from their protonated molecular ions and could also undergo an interesting intramolecular benzyl rearrangement to yield benzylphosphonate ions.

All protonated monoesters **2** could eliminate a molecule of water to yield 2-hydroxyethyl 1-(*N*-Cbzamino)arylmethylphosphonic ions (a), a molecule of water, plus ethene, to give rise to 1-(*N*-Cbzamino)arylmethylphosphonic ions (b), a molecule of 1,2-ethanediol to produce 1-(*N*-Cbzamino)arylmethylphosphonic ions (c), a molecule of water plus benzyl alcohol to generate 2-hydroxyethyl 1-aryl-1-isocyanomethylphosphonic ions (d), a molecule of 1,2-ethanediol plus benzyl alcohol to form 1-aryl-1-isocyanomethylphosphonic ions (f). The protonated monoesters **2** could also form 2-hydroxyethyl 1-aminoarylmethylphosphonic ions (e) and protonated aryliminium ions



SCHEME 4 Mass spectral fragmentation of 2-hydroxyethyl *N*-Cbz protected α-aminoalkylphosphonate monoesters **2**.

(g) (Scheme 4). The hydoxyethyl monoesters **2** showed obviously different fragmentation from that of the corresponding methyl and ethyl monoesters,[19] which predominantly undergo four-membered ring rearrangements to yield mainly nitrogen-containing fragment ions by a loss of a carbon dioxide, phosphite, carbon dioxide plus phosphite, or benzyloxycarbonylphosphonate monoester.

EXPERIMENTAL

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H NMR and ^{31}P NMR spectra were recorded on a Mercury Plus 300 (300 MHz) spectrometer in $CDCl_3$. IR spectra were obtained on Nicolet AVATAR 330 FTIR spectrometer. ESI mass spectra were acquired using a Bruker ESQUIRE∼LC^{TM} ESI ion trap

spectrometer. CHN analyses were recorded on an Elementar Vario EL analyzer.

The Synthesis of 2-hydroxyethyl 1-aryl-1-(*N*-benzyloxycarbonylamino)methylphosphonates from benzyl carbamate, aldehydes, and 2-chloro-1,3,2-dioxaphospholane (General Procedure)

To a stirred solution of benzyl carbamate (0.50 g, 3 mmol) and aldehyde (3 mmol) in 10 mL of anhydrous benzene was added dropwise 2-chloro-1,3,2-dioxaphospholane (0.38 g, 3 mmol) at r.t. The resulting mixture was stirred for 5 h. After an addtition of water (0.1 g), the resulting mixture was stirred for another 5 h. After removal of the solvent, the residue was recrystallized from water-ethanol to afford colorless crystals.

Benzyl *N*-[phenyl-(2-oxido-1,3,2-dioxaphospholane-2-yl)methyl]carbamate (1a)[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.54 (m, 2 H, CH_2), 3.87 (m, 2 H, CH_2), 5.00–5.14 (m, 3 H, CH_2 & CHP), 6.28 (s, br, 1 H, NH), 7.20–7.50 (m, 10 H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 23.1. IR υ (cm^{-1}): 1722 (C═O), 1249 (P═O), 1038 (P─O─C). ESI-MS (m/z): 348 (MH^+). Anal. calcd. for $C_{17}H_{18}NO_5P$: C, 58.79; H, 5.22; N, 4.03. Found: C, 58.77; H, 5.15; N, 3.89.

2-Hydroxyethyl 1-(*N*-benzyloxycarbonylamino)-phenylmethylphosphonate (2a)

White solid, yield 64%; m.p. 118–120°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.47 (m, 2 H, CH_2), 3.80 (m, 3 H, OH & CH_2), 5.03 (s, 2 H, CH_2), 5.08–5.23 (m, 1 H, CHP), 6.38 (s, br, 1 H, POH), 6.61 (s, br, 1 H, NH), 7.05–7.46 (m, 9 H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 22.3. IR υ (cm^{-1}): 3318 (O─H), 1716 (C═O), 1241 (P═O), 1077 and 1037 (P─O─C). ESI-MS (m/z): 366 (MH^+). Anal. calcd. for $C_{17}H_{20}NO_6P1/2H_2O$: C, 54.55; H, 5.65; N, 3.74. Found: C, 54.64; H, 5.46; N, 3.90.

2-Hydroxyethyl 1-(*N*-benzyloxycarbonylamino)(4-methylphenyl)methylphosphonate (2b)

White solid, yield 89%; m.p. 151–153°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.34 (s, 3 H, CH_3), 3.93 (m, 3 H, OH & CH_2), 4.41 (m, 2 H, CH_2), 5.05–5.18 (m, 2 H, CH_2), 5.31 (dd, $J = 9.0$, 20.4 Hz, 1 H, CHP),

5.88 (s, br, 1 H, NH), 7.04–7.24 (m, 9 H, ArH), 9.98 (s, br, 1 H, POH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 21.6. IR υ (cm^{-1}): 3310 (O-H), 1714 (C=O), 1248 (P=O), 1076 and 1027 (P–O–C). ESI-MS (m/z): 380 (MH^+). Anal. calcd. for $C_{18}H_{22}NO_6P1/2H_2O$: C, 55.67; H, 5.97; N, 3.61. Found: C, 56.06; H, 5.70; N, 3.95.

2-Hydroxyethyl 1-(*N*-benzyloxycarbonylamino)(4-chlorophenyl)methylphosphonate (2c)

White solid, yield 92%; m.p. 144–146°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.95 (m, 3 H, OH & CH_2), 4.43 (m, 2 H, CH_2), 5.11 (m, 2 H, CH_2), 5.31 (dd, $J = 8.4$, 21.3 Hz, 1 H, CHP), 5.90 (s, br, 1 H, NH), 7.10–7.42 (m, 9 H, ArH), 9.09 (s, br, 1H, POH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 21.2. IR υ (cm^{-1}): 3273 (O–H), 1714 (C=O), 1256 (P=O), 1037 (P–O–C). ESI-MS (m/z): 400 (MH^+). Anal. calcd. for $C_{17}H_{19}NClO_6P$: C, 51.08; H, 4.79; N, 3.50. Found: C, 51.30; H, 4.72; N, 3.62.

2-Hydroxyethyl 1-(*N*-benzyloxycarbonylamino)(4-methoxyphenyl)methylphosphonate (2d)

White solid, yield 89%; m.p. 150–152°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.70 (s, br, 1 H, OH), 3.80 (s, 3 H, CH_3), 3.90 (m, 2 H, CH_2), 4.41 (m, 2 H, CH_2), 5.03–5.20 (m, 2 H, CH_2), 5.29 (dd, $J = 9.0$, 19.8 Hz, 1 H, CHP), 5.80 (s, br, 1 H, NH), 6.80–7.44 (m, 9 H, ArH), 9.91 (s, br, 1 H, POH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 21.8. IR υ (cm^{-1}): 3320 (O–H), 1720 (C=O), 1244 (P=O), 1036 (P–O–C). ESI-MS (m/z): 396 (MH^+). Anal. calcd. for $C_{18}H_{22}NO_7P$: C, 54.68; H, 5.61; N, 3.54. Found: C, 54.33; H, 5.52; N, 3.55.

2-Hydroxyethyl 1-(*N*-benzyloxycarbonylamino)(4-nitrophenyl)methylphosphonate (2e)

White solid, yield 52%; m.p. 170–172°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.05 (m, 3 H, OH & CH_2), 4.43 (m, 2 H, OCH_2), 5.11 (m, 2 H, CH_2), 5.43 (dd, $J = 8.8$, 21.1 Hz, 1 H, CHP), 6.26 (s, br, 1 H, NH), 7.22–8.24 (m, 9 H, ArH). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ (ppm): 20.4. IR υ (cm^{-1}): 3316 (O–H), 1719 (C=O), 1247 (P=O), 1024 (P–O–C). ESI-MS (m/z): 411 (MH^+). Anal calcd for $C_{17}H_{19}N_2O_8P3/2H_2O$: C, 46.69; H, 5.07; N, 6.41. Found: C, 46.99; H, 4.69; N, 6.69.

REFERENCES

[1] V. P. Kukhar and H. R. Hudson, Eds., *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, (John Wiley, Chichester, 2000).
[2] J. X. Xu and L. Yu, *Chin. J. Synth. Chem. (Hecheng Huaxue)*, **7,** 153 (1999) and references cited therein.
[3] J. Oleksyszyn, R. Tyka, and P. Mastalez, *Synthesis*, 479 (1978).
[4] C. Y. Yuan and G. H. Wang, *Synthesis*, 256 (1990).
[5] Q. Dai and R. Y. Chen, *Synth. Commun.*, **27,** 1653 (1997).
[6] Q. Dai and R. Y. Chen, *Synth. Commun.*, **27,** 3341 (1997).
[7] H. Liu and J. X. Xu, *Amino Acids*, **29,** 241 (2005).
[8] Q. Dai, R. Y. Chen, C. X. Zhang, and Z. Liu, *Synthesis*, 405 (1998).
[9] J. X. Xu, Y. Ma, and L. F. Duan, *Heteroat. Chem.*, **11,** 417 (2000).
[10] K. C. Kumara Swanmy, S. Kumaraswanmy, K. Senthil Kumar, and C. Muthiah, *Tetrahedron Lett.*, **46,** 3347 (2005).
[11] J. X. Xu and M. Wei, *Synth. Commun.*, **31,** 1489 (2000).
[12] J. X. Xu and N. Y. Fu, *J. Chem. Soc. Perkin. Trans 1*, 1223 (2001).
[13] J. X. Xu and N. Y. Fu, *Synth. Commun.*, **30,** 4137 (2000).
[14] N. Y. Fu, Q. H. Zhang, L. F. Duan, and J. X. Xu, *J. Peptide Sci.*, **12,** 303 (2006).
[15] J. X. Xu and Y. H. Gao, *Synthesis*, 783 (2006).
[16] H. Liu, S. Z. Cai, and J. X. Xu, *J. Peptide Sci.*, **12,** 337 (2006).
[17] R. Y. Chen and Q. Dai, *Chin. Chem. Lett.*, **6,** 561 (1995).
[18] Y. Ma, Y. Chen, M. Su and Y. F. Zhao, *Rapid Commun. Mass Spectrom.*, **17,** 1449 (2003).
[19] Y. Ma, W. Liu, and Y. F. Zhao, *Int. J. Mass Spectrom.*, **248,** 17 (2006).