Heteroatom Chemistry
Volume 11, Number 6, 2000

A Novel Synthetic Route to N-Protected 1-Aminoalkylphosphonates

Jiaxi Xu,[1] Yuan Ma,[2] and Lifang Duan[1]

[1]*College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China*

[2]*Bioorganic Phosphorus Chemistry Laboratory, Department of Chemistry, Tsinghua University, Beijing 100084, P.R. China*

Received 08 May 2000; revised 29 June 2000

ABSTRACT: *Dialkyl and dithioalkyl N-protected 1-aminoalkylphosphonates were synthesized using reactions of benzyl carbamate, aldehydes and chlorophosphites, or dithioalkyl chlorophosphite, respectively. This represents a novel synthetic method for 1-aminoalkylphosphonates.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:417–421, 2000

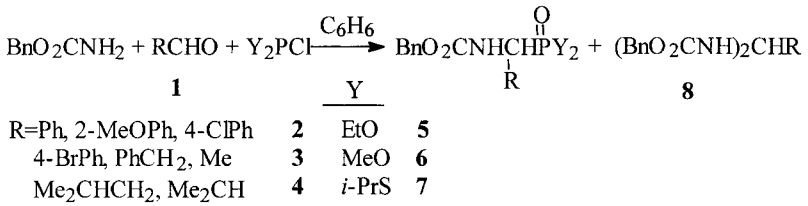
INTRODUCTION

1-Aminoalkylphosphonates have received an increasing amount of attention because they are phosphorus analogs of naturally occurring amino carboxylic acids [1–4]. Indeed, a number of potent antibiotics and pharmacological agents [5,6], herbicides [7], enzyme inhibitors [1,3,4,8,9], and haptens of catalytic antibodies [10–12] are 1-aminoalkylphosphonic acids, as well as their derivatives, notably peptides [13–14]. These important compounds have also been used in ingenious ways as peptidomimetics [13–14]. Up to now, a number of synthetic methods for the preparation of 1-aminoalkylphosphonates have been available [15–16]. They were, in general, synthesized using (a) Arbuzov and Michaelis-Becker reactions and reductive aminations [17,18]; (b) addition of phosphites to imines and enamines [19,20]; (c) Mannich-type reactions of aldehydes, amines, and dialkyl or trialkyl phosphites [21–23]; (d) ester exchange reactions from diphenyl 1-aminoalkylphosphonates into dialkyl 1-aminoalkylphosphonates [24]; (e) Curtius and Hoffmann rearrangements of substituted phosphonoacetic esters [25,26]; (f) conversion of the corresponding 1-hydroxyalkylphosphonates to 1-aminoalkylphosphonates [27,28]; (g) alkylation of Schiff base derivatives of aminomethylphosphonates and their anionic or cationic equivalents [29–31]; (h) aziridination of vinylphosphonates with [*N*-(*p*-toluenesulfonyl)imino]-phenyliodonane (TsN=IPh), followed by the reductive ring opening of the azirinylphosphonates formed [32]; (i) electrophilic amination of anions of alkylphosphonates [33,34]; and (j) aldol reactions of (isocyanomethyl)phosphonates with aldehydes, followed by hydrolysis [35]. Among the methods just mentioned, Mannich-type three-component condensation reactions involving aldehydes, benzyl carbamate, and trialkyl phosphites in acetic acid or in acetyl chloride are a very important and a convenient method [21–23,36]. They have been used in synthesis of a variety of N-protected 1-aminoalkylphosphonates. Herein we report a novel synthetic method for synthesis of N-protected 1-aminoalkylphosphonates, a convenient and modified synthetic approach to known Mannich-type three-component condensation reactions.

RESULTS AND DISCUSSION

In previous papers [21–23,36], a number of N-protected 1-aminoalkylphosphonates have been synthesized using Mannich-type reactions, namely, three-

Correspondence to: Jiaxi Xu.
Contract Grant Sponsor: NSFC.



SCHEME 1

component condensation reactions involving aldehydes, benzyl or alkyl carbamates, and trialkyl phosphites in acetic acid or in acetyl chloride. These are simple and convenient methods. In these reactions, a dehydrating agent was usually necessary. When we carried out in situ syntheses of N-protected 1-aminoalkylphosphonamidates using one-pot reactions of aldehydes, dichlorophosphites, and benzyl carbamate in benzene, followed by aminolysis, we found that dichlorophosphites functioned as dehydrating agents [37]. Thus, we reason that chlorophosphites should also be dehydrating agents, and they might be used in syntheses of N-protected 1-aminoalkylphosphonates instead of trialkyl phosphites in Mannich-type reactions. After we tested reactions of aldehydes, chlorophosphites, and benzyl carbamate in benzene, we succeeded in obtaining N-protected 1-aminoalkylphosphonates in good yields. It is a novel method for the synthesis of N-protected 1-aminoalkylphosphonates. (See Scheme 1).

Various kinds of 1-aminoalkylphosphonic acid derivatives are necessary in the combinatorial syntheses of phosphonates, phosphonamidates, and phosphonopeptides in the search for efficient enzyme inhibitors and pharmacological agents. Up to now, only a few articles have been found to report the synthesis of N-protected 1-aminoalkylphosphonate monothioesters by chloridization of the phosphonic moiety with thionyl chloride, followed by thiolysis [13]. As far as we know, no report on the synthesis of N-protected 1-aminoalkylphosphonate dithioesters has appeared in the literature. We extended our method to synthesize dithioalkyl N-protected 1-aminoalkylphosphonates, and also we succeeded in the syntheses of several N-protected 1-aminoalkylphosphonate dithioesters in moderate yields using dithioisopropyl chlorophosphite instead of a chlorophosphite. By-products, bis(benzyloxycarbonylamino)methylbenzene derivatives, $(BnO_2CNH)_2CHR$, were also obtained in low yields [38]. See Table 1.

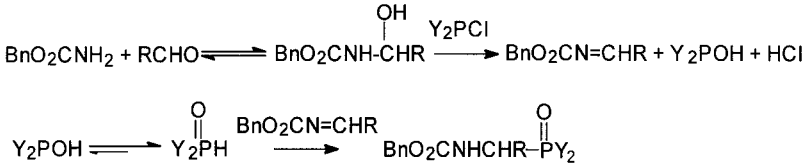
According to ^{31}P NMR tracing results of in situ syntheses of N-protected 1-aminoalkylphosphonamidates using reactions of benzyl carbamate, aldehydes, and dichlorophosphites, followed by aminolysis [37], the reaction mechanism might involve the chlorophosphites **2** and **3** or dithioalkyl chlorophosphite **4** as dehydrating agents in these reactions and thus can promote the reactions of benzyl carbamate and aldehydes to form the imines $BnO_2CN=CHR$ and Y_2POH. The latter could further tautomerize into the dialkyl/dithioalkyl phosphite $Y_2P(O)H$ and then undergo addition reactions with the imines to yield symmetric phosphonates **5, 6, and 7.** See Scheme 2.

TABLE 1 Syntheses of N-Protected 1-Amino-Alkylphosphonates **5,6,** and **7**

Entry	*R*	*Y*	*Yield* (%)	*m.p.* (°C)	*m.p.* (°C) *in lit.*
5a	Ph	EtO	87	112–113	113–114 [24]
5b	2-MeOPh	EtO	71	86–88	
5c	4-ClPh	EtO	69	108–110	
5d	4-BrPh	EtO	74	94–96	
5e	$PhCH_2$	EtO	67	oil	oil [13]
5f	Me_2CHCH_2	EtO	69	40–42	41–43 [24]
5g	Me_2CH	EtO	67	83–84	85–86 [24]
5h	Me	EtO	56	oil	oil [24]
6a	Ph	MeO	78	117–118	117–118.5 [24]
6b	2-MeOPh	MeO	64	100–101	
6c	4-ClPh	MeO	66	106–108	
6d	4-BrPh	MeO	64	109–111	
6e	$PhCH_2$	MeO	50	67–69	67–69.5 [13]
6f	Me_2CHCH_2	MeO	57	33–35	34–35 [24]
6g	Me_2CH	MeO	58	oil	oil [24]
6h	Me	MeO	55	oil	oil [24]
7a	Ph	i-PrS	43	16	
7b	2-MeOPh	i-PrS	38	21	
7c	4-ClPh	i-PrS	40	19	

All products were characterized by ^1H NMR, ^{31}P NMR, and MS spectroscopy and elemental analyses. The data of known compounds are well in agreement with the proposed structures and/or the data in the literature [23,24].

In summary, N-protected 1-aminoalkylphosphonate diesters and dithioesters have been synthesized using one-pot reactions of benzyl carbamate, aldehydes, and dialkoxyl/dialkylthiophosphine chlo-



SCHEME 2

rides in anhydrous benzene as a solvent. It is a convenient and novel synthetic route to N-protected 1-aminoalkylphosphonates.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario EL analyzer. The ^{1}H NMR spectra were recorded on a Varian mercury 200 spectrometer with TMS as an internal standard in $CDCl_3$. ^{31}P NMR spectra were obtained on the same apparatus at 81 MHz, and the chemical shifts values are referenced to 85% H_3PO_4 with negative shifts upfield. Mass spectra were recorded on a VG ZAB-HS mass spectrometer.

Methyl chlorophosphite and ethyl chlorophosphite were synthesized using commercially available phosphorus trichloride and trimethyl phosphite or triethyl phosphite, respectively [39]. Methyl chlorophosphite is not stable enough for long-time storage at room temperature. It is better to freshly prepare it prior to use. Dithioisopropyl chlorophosphite was synthesized as described in Ref. [40].

Synthesis of Dialkoxyl and Dialkylthio N-Protected 1-Aminoalkylphosphonate **5, 6,** *and* **7**

General Procedure. Dialkoxyl/dialkylthiophosphine chlorides **2, 3,** or **4** (3.3 mmol) was added dropwise to a stirred mixture of benzyl carbamate (0.45 g, 3 mmol) and aldehyde **1** (3.1 mmol) in anhydrous benzene (10 mL) at room temperature. After the reaction mixture had been stirred for 6 hours to overnight at room temperature, it was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ 10% aqueous $NaHSO_3$ solution, and brine, and then dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was recrystallized from a mixture of hexane and ethyl acetate to yield colorless crystals of symmetric 1-aminoalkylphosphonates **5–d, 5f, and 6a–d.** The other products were purified by flash chromatography on a silica gel column with elution by 5:1 to 1:1 of hexane and ethyl acetate to give colorless crystals or oils.

Diethyl 1-(N-benzyloxycarbonylamino)(2-methoxylphenyl)methylphosphonate (**5b**). ^{31}P NMR (81 MHz, $CDCl_3$) δ: 19.38; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.07 (t, J = 6.9 Hz, 3H, $OCH_2\mathbf{CH_3}$), 1.28 (t, J = 6.9 Hz, 3H, $OCH_2\mathbf{CH_3}$), 3.67–4.18 (m, 4H, $2\mathbf{OCH_2}CH_3$), 3.88 (s, 3H, CH_3OPh), 5.04 and 5.14 (d, J = 12.3, 2H, $Ph\mathbf{CH_2}O$), 5.64 (dd, J = 10.5, 21.9 Hz, 1H, CHP), 6.01 (br d, J = 10.5 Hz, 1H, CONH), 6.87–6.98 (m, 2H, ArH), 7.24–7.39 (m, 7H, ArH). EI-MS *m/z*: 407 (M^+). Anal. Calcd. for $C_{20}H_{26}NO_6P$ (407.40): C: 58.96, H: 6.43, N: 3.44; Found: C, 59.02; H, 6.69; N, 3.48.

*Diethyl 1-(N-benzyloxycarbonylamino)(4-chlorophenyl)*methylphosphonate (**5c**).

^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.35; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13 (t, J = 6.6 Hz, 3H, $OCH_2\mathbf{CH_3}$), 1.26 (t, J = 6.9 Hz, 3H, $OCH_2\mathbf{CH_3}$), 3.72–4.15 (m, 4H, $2\mathbf{OCH_2}CH_3$), 5.00–5.17 (m, 3H, $Ph\mathbf{CH_2}O$ and CHP), 5.94 (br, 1H, CONH), 7.22–7.40 (m, 9H, ArH). EI-MS *m/z*: 411 (M^+). Anal. Calcd. for $C_{19}H_{23}NClO_5P$ (411.82): C, 55.41; H, 5.63; N, 3.40; Found: C, 55.23; H, 5.69; N, 3.45.

Diethyl 1-(N-benzyloxycarbonylamino)(4-bromophenyl)methylphosphonate (**5d**).

^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.18; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13 (t, J = 7.2 Hz, 3H, $OCH_2\mathbf{CH_3}$), 1.25 (t, J = 6.9 Hz, 3H, $OCH_2\mathbf{CH_3}$), 3.69–4.15 (m, 4H, $2\mathbf{OCH_2}CH_3$), 5.01–5.17 (m, 3H, $Ph\mathbf{CH_2}O$ and CHP), 6.15 (br, 1H, CONH), 7.20–7.52 (m, 9H, ArH) EI-MS *m/z*: 456 (M^+). Anal. Calcd. for $C_{19}H_{23}NBrO_5P$ (456.27): C, 50.02; H, 5.08; N, 3.07; Found: C, 50.23; H, 5.00; N, 3.25.

Dimethyl 1-(N-benzyloxycarbonylamino)(2-methoxylphenyl)methylphosphonate (**6b**).

^{31}P NMR (81 MHz, $CDCl_3$) δ: 19.38; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.54 (d, J = 10.2 Hz, 3H, CH_3O), 3.79 (d, J = 10.8 Hz, 3H, CH_3O), 3.93 (s, 3H, CH_3OPh), 5.10 and 5.18 (d, J = 12.0 Hz, 2H, $Ph\mathbf{CH_2}O$), 5.71 (dd, J = 9.9, 21.6 Hz, 1H, CHP), 6.05 (br d, J = 9.9 Hz, 1H, CONH), 6.92–7.05 (m, 2H, ArH), 7.30–7.45

(m, 7H, ArH) EI-MS *m/z*: 379 (M^+). Anal. Calcd. for $C_{18}H_{22}NO_6P$ (379.35): C, 56.99; H, 5.85; N, 3.69; Found: C, 57.23; H, 5.69; N, 3.56.

Dimethyl 1-(*N-benzyloxycarbonylamino*)(*4-chlorophenyl*)*methylphosphonate* (**6c**).

^{31}P NMR (81 MHz, $CDCl_3$) δ: 20.61; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.51 (d, J = 10.5 Hz, 3H, CH_3O), 3.72 (d, J = 10.8 Hz, 3H, CH_3O), 5.03–5.22 (m, 3H, Ph**C**$\mathbf{H_2}$O & CHP), 6.11 (br, 1H, CONH), 7.28–7.45 (m, 9H, ArH) EI-MS *m/z*: 383 (M^+). Anal. Calcd. for $C_{17}H_{19}NClO_5P$ (383.77): C, 53.21; H, 4.99; N, 3.65; Found: C, 53.28; H, 4.79; N, 3.55.

Dimethyl 1-(*N-benzyloxycarbonylamino*)(*4-bromophenyl*)*methylphosphonate* (**6d**).

^{31}P NMR (81 MHz, $CDCl_3$) δ: 20.44; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.51 (d, J = 10.5 Hz, 3H, CH_3O), 3.72 (d, J = 10.8 Hz, 3H, CH_3O), 5.03–5.20 (m, 3H, Ph**C**$\mathbf{H_2}$O and CHP), 6.11 (br, 1H, CONH), 7.27–7.51 (m, 9H, ArH) EI-MS *m/z*: 428 (M^+). Anal. Calcd. for $C_{17}H_{19}NBrO_5P$ (428.22): C, 47.68; H, 4.47; N, 3.27; Found: C, 47.45; H, 4.58; N, 3.41.

Diisopropylthio 1-(*N-benzyloxycarbonylamino*)*methylphosphonate* (**7a**).

Yield: 76%; m.p. 150–152°C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 66.49; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.17–1.26 and 1.33–1.41 (m, 12H, 2CH**Me**$\mathbf{_2}$), 3.27 (m, 2H, 2SCH), 5.10–5.16 (m, 2H, PhCH_2O), 5.29–5.41 (m, 1H, CHP), 5.82 (br, 1H, CONH), 7.17–7.45 (m, 10H, ArH); EI-MS *m/z*: 438 (MH^+). Anal. Calcd. for $C_{21}H_{28}NO_3PS_2$ (437.55): C, 57.64; H, 6.45; N, 3.20; Found: C, 57.61; H, 6.43; N, 3.47.

Diisopropylthio 1-(*N-benzyloxycarbonylamino*)(*2-methoxy*)*phenylmethylphosphonate* (**7b**).

Yield: 68%; m.p. 165–167°C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 66.68; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.24 and 1.38 (d, J = 6.8 Hz, 12H, 2CH**Me**$\mathbf{_2}$), 3.30 (m, 2H, 2SCH), 3.81 (s, 3H, MeO), 5.07–5.15 (m, 2H, PhCH_2O), 5.21–5.34 (m, 1H, CHP), 5.81 (br, 1H, CONH), 6.90 (d, J = 8.4 Hz, 2H, ArH), 7.35 (s, 7H, ArH); FAB-MS *m/z*: 468 (MH^+). Anal. Calcd. for $C_{22}H_{30}NO_4PS_2$ (467.58): C, 56.51; H, 6.47; N, 3.00; Found: C, 56.37; H, 6.48; N, 3.17.

Diisopropylthio 1-(*N-benzyloxycarbonylamino*)(*4-chloro*)*phenylmethylphosphonate* (**7c**).

Yield: 55%; m.p. 135–137°C. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 66.27; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.24 and 1.38 (d, J = 6.4 Hz, 12H, 2CH**Me**$\mathbf{_2}$), 3.31 (m, 2H, 2SCH), 5.08–5.16 (m, 2H, Ph**C**$\mathbf{H_2}$O), 5.25–5.38 (m, 1H, CHP), 5.82 (br, 1H, CONH), 7.11–7.52 (m, 9H, ArH); FAB-MS *m/z*: 472 (MH^+). Anal. Calcd. for $C_{21}H_{27}ClNO_3PS_2$ (472.00): C, 58.95; H, 6.43; N, 3.44; Found: C, 58.79; H, 6.19; N, 3.20.

REFERENCES

[1] Kafarski, P.; Lejczak, B. Phosphorus Sulfur Silicon Relat Elem 1991, 63, 193.
[2] Boutin, J. A.; Cudennec, C. A.; Hautefaye, P.; Lavielle, G.; Pierre, A.; Schaeffer, C. J Med Chem 1991, 34, 1998.
[3] Morgan, B. P.; Scholtz, J. M.; Ballinger, M. D.; Zipkin, I. D.; Bartlett, P. A. J Am Chem Soc 1991, 113, 297.
[4] Chen, S. J.; Liu, C.-H.; Kwon, D. S. ; Walsh, C. T.; Coward, J. K. J Med Chem 1997, 40, 3842.
[5] Antherton, F. R.; Hassal, C. H.; Lambert, R. W. J Med Chem 1987, 30, 1603.
[6] Stauffer Co. U.S. Pat 4,170,463, 1979.
[7] Hassal, C. H. In Antibiotics; Hahn, F. E., Ed.; Springer-Verlag: Berlin, 1983; Vol. VI, 1.
[8] Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Lee, V. G.; Loots, M. J.; Petrillo, E. W. J Med Chem 1990, 33, 1459.
[9] Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. J Med Chem 1989, 32, 1652.
[10] Pollack, S. J.; Jacobs, J. W.; Schultz, P. G. Science 1986, 234, 1570.
[11] Tramontano, A.; Janda, K. D.; Lerner, R. A. Science 1986, 234, 1566.
[12] Hirschmann, R.; Smith III, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. Science 1994, 265, 234.
[13] Bartlett, P. A.; Lamden, L. A. Bioorg Chem 1986, 14, 356.
[14] Xu, J. X.; Xia, C. F.; Yu, L.; Zhou, Q. Z. Phosphorus Sulfur Silicon Relat Elem 1999, 152, 35.
[15] Maier, L. Phosphorus Sulfur Silicon 1990, 53, 43.
[16] Xu, J. X.; Yu, L. Chinese J Synthetic Chem (Hecheng Huaxue) 1999, 7, 153.
[17] Berlin, K. D.; Roy, N. K.; Claunch, R. T.; Bude, D. J Am Chem Soc 1968, 90, 4494.
[18] Kudzin, Z. H.; Kotynsi, A. Synthesis 1980, 1028.
[19] Lukszo, J.; Tyka, R. Synthesis 1977, 239.
[20] Ha, H.-J.; Nam, G.-S. Synth Commun 1992, 22, 1143.
[21] Oleksyszyn, J.; Tyka, R. Tetrahedron Lett 1977, 18, 2823.
[22] Oleksyszyn, J.; Subotkowsk, L.; Mastalerz, P. Synthesis 1979, 985.
[23] Yuan, C. Y.; Wang, G. H.; Chen, S. J. Synthesis 1990, 522.
[24] Szewczyk, J. Synthesis 1982, 409.
[25] Coutrot, P.; Grison, C.; Charbonnier-Gerardin, C. Tetrahedron 1992, 48, 9841.
[26] Soroka, M.; Mastalers, P. Tetrahedron Lett 1973, 5201.
[27] Gajda, T.; Matsusiak, M. Synth Commun 1992, 22, 2193.
[28] Gajda, T.; Nowalinska, M.; Zawadzki, S.; Zwierzak, A. Phosphorus Sulfur Silicon Relat Elem 1995, 105, 45.
[29] Ferrari, M.; Jommi, G.; Miglierini, G.; Pagliarin, R.; Sisti, M. Synth Commun 1992, 22, 107.

[30] Genet, J. P.; Uziel, J.; Touzin, A. M.; Juge, S. Synthesis 1990, 41.
[31] Cabella, G.; Jommi, G.; Pagliarin, R.; Sello, G.; Sisti, M. Tetrahedron 1995, 51, 1817.
[32] Kim, D. Y.; Rhie, D. Y. Tetrahedron 1997, 53, 13603.
[33] Hanessian, S.; Bennani, Y. L. Synthesis 1994, 1272.
[34] Denmark, S. E.; Chatani, N.; Pansare, S. V. Tetrahedron 1992, 48, 2191.
[35] Sawamura, M.; Ito, Y.; Hayashi, T. Tetrahedron Lett 1989, 30, 2247.
[36] Yuan, C. Y.; Chen, S. J.; Wang, G. H. Synthesis 1991, 490.
[37] Xu, J. X.; Fu, N. Y. Synth Commun 2000, 30 (in press).
[38] Dai, Q.; Chen, R. Y. Synth Commun 1997, 27, 1653.
[39] Jones, C. E.; Coskran, K. J. Inorg Chem 1971, 10, 1536.
[40] Ray, D.; Pizzolat, P. J Am Chem Soc 1950, 72, 4584.