Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic Chemistry 34 (2006) 167–172
BIOORGANIC CHEMISTRY
www.elsevier.com/locate/bioorg

An improved route to the synthetic of diphenyl α-(diethoxythiophosphorylamino) methylphosphonates

Zhiwei Miao, Bin Wang, Gaihong Zhang, Ruyu Chen *

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

Received 24 February 2006

Abstract

An improved method for the synthesis of Diphenyl α-(diethoxythiophosphorylamino)methylphosphonates under mild conditions is described. It consists of the reaction of diethyl thiophosphoramidate (**1**) with triphenyl phosphite (**3**) and a substituted benzylaldehyde or ketone (**2**) by a one-pot procedure with the aid of acetyl chloride.

Keywords: Mannich type reaction; Thiophosphate-phosphonate derivatives; Acetyl chloride; X-ray crystal structure

1. Introduction

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates [1–4]. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds. α-Aminophosphonates are important compounds due to their applications as enzyme inhibitors, antibiotics, pharmacological agents and many other applications are well

* Corresponding author. Fax: +86 22 23503627.
E-mail address: miaozhiwei@nankai.edu.cn (R. Chen).

0045-2068/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bioorg.2006.05.003

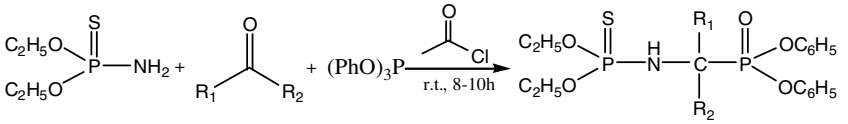
documented [5,6]. α-Aminophosphoryl compounds have recently been proved to be biologically active and have been shown to inhibit the enzymes renin, EPSP synthase and HIV protease [7,8]. Also a large number of thiophosphate-phosphonate derivatives, bearing a P–N–C–P bond structure were synthesized and their significant herbicidal, antiviral, and fungicidal activities were reported [9–12].

Among numerous synthetic methods for the preparation of α-aminophosphonic acids derivatives, the three-component condensation involving substituted amide, aldehyde (or ketone) and phosphorus ester is of significant interest [13–16]. We report here a facile synthetic method for the preparation of α-amino-substituted thiophosphate-phosphonates derivatives with the aids of a versatile reagent acetyl chloride.

2. Results and discussion

The Mannich type reaction of trivalent phosphines has proved facile for the preparation of new phosphorus α-aminoalkanephosphonate compounds. As shown in Scheme 1, diethyl thiophosphoramidate (**1**) was allowed to react with triphenyl phosphite (**3**) and various substituted ketones or benzaldehyde (**2**) in acetyl chloride to give the target Diphenyl α-(diethoxythiophosphorylamino)methylphosphonates **4a–g** in moderate to good yields ranging from 56 to 90%. It was found that the use of aromatic adehydes led to much better yields than that of ketones. The reactions were carried out using one-pot procedure. All the products were isolated from reaction mixture by column chromatography, and their structures were characterized by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, and mass spectrum.

The ^{31}P NMR spectra of compound **4** showed two doublets due to the P–P splitting as shown by identical coupling constants. Similar results were reported by C.Y. Yuan [13–15]. The ^{31}P NMR spectra showed at around $\delta = 20$ and at $\delta = 69$ ppm, the first one being attributable to the P-atom of the diphenoxyphosphinyl group, and the second one to the P-atom of the *N*-thiophosphoryl group. In the ^{1}H NMR spectra of **4**, the CHP proton appears as a doublet–triplet ($\delta = 5.03$–5.15) due to the pair of phosphorus atoms coupling with coupling constant $^{2}J_{P,CH}$ of 23.2 Hz and $^{3}J_{P,CH}$ of 11 Hz and NH coupling with a coupling constant $^{3}J_{NH,CH}$ of 11 Hz. The IR spectra of **4** show normal



1 **2** **3** **4**

4	R_1	R_2	Yield (%)	4	R_1	R_2	Yield (%)
4a	H	Ph	89	**4e**	$(CH_2)_4$		76
4b	H	4-MeC_6H_4	90	**4f**	$(CH_2)_5$		67
4c	H	4-MeOC_6H_4	77	**4g**	$(CH_2)_6$		63
4d	Ph	CH_3	56				

Scheme 1. Preparation of diphenyl α-(diethoxythiophosphorylamino) methylphosphonates.

stretching absorption bands, indicating the existence of the NH (~3320 cm^{-1}), C–N (~1310 cm^{-1}), P=O (1220–1230 cm^{-1}), P–O–Ar (930 cm^{-1}), and P=S (660–680 cm^{-1}) groups. The EI-MS spectra of **4a–g** show the existence of strong molecular ion peaks, indicating that the molecular skeletons have some stability.

In order to confirm the structure of products **4**, the product **4f** was recrystallized and determined by X-ray diffraction analysis (Fig. 1) [18]. The unit cell of **4f** contains four molecules. The analysis shows typical bond lengths and bond angles, such as P(1)–S(1) of 1.925 Å, P(2)–O(4) of 1.456 Å, P(1)–N(1) of 1.627 Å, P(1)–O(1) of 1.570 Å, N(1)–C(5) of 1.477 Å, P(2)–C(5) of 1.825 Å, and P(2)–C(5)–N(1) of 108.27°, O(1)–P(1)–N(1) of 104.30°. The configuration of hexane ring in the molecule is in chair form and the angles of O(3)–P(2)–O(5) and O(1)–P(1)–O(2) are 99.82° and 98.97°, respectively.

Because of the difference of the two substitutes (R_1, R_2) of carbonyl compound (**3**), two enantiomers should be found for the reason that there is one stereogenic center created. However, only one isomer was found as white solid by column chromatography. In order to confirm the structure of **4c**, the isolated one isomer of product **4c** was recrystallized and determined by X-ray diffraction analysis (Fig. 2) [18]. The structure of **4c** is similar as **4f**, and the main difference is the unit cell of **4c** contains two molecules. The analysis shows typical bond lengths and bond angles, such as P(2)–S(1) of 1.904 Å, P(1)–O(1) of 1.460 Å, P(2)–N(1) of 1.624 Å, P(2)–O(15) of 1.562 Å, N(1)–C(13) of 1.460 Å, P(1)–C(13) of 1.811 Å, and P(1)–C(13)–N(1) of 105.40°, O(5)–P(2)–N(1) of 105.43°.

In conclusion, we have developed an improved route of the synthesis of diphenyl α-(diethoxythiophosphorylamino)methylphosphonates by using acetyl chloride. The reactions take place under mild conditions with good yields, and this makes it possible to introduce a wide range of substituents at the α-position to the phosphorus atom. The intermolecular pathway of the formation of the P–C bond in the P–C–N fragment gives a good example of Mannich type reaction.

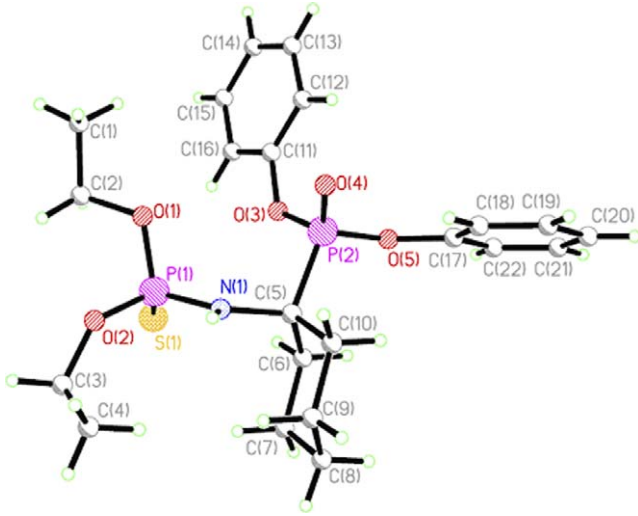


Fig. 1. X-ray crystal structure of **4f**.

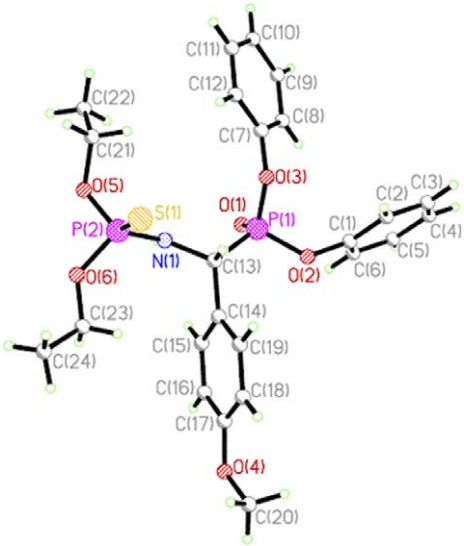


Fig. 2. X-ray crystal structure of **4c**.

3. Materials and methods

All melting points were determined on a Yanaco apparatus and were uncorrected. NMR spectra were measured on a Varian AS400 NMR instrument in $CDCl_3$ and chemical shifts were expressed as δ. Coupling constants J are given in Hz. Tetramethyl silane was used as an internal standard for ^1H NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Mass spectra were recorded on a Polaris-Q instrument of Thermofinnigan. X-ray analysis was done on a Bruker SMART 1000 CCD diffractometer with MoKα radiation ($\lambda = 0.71073$ Å). IR Spectra were recorded on an Equinox55 Spectrometer, and band positions were reported in wave numbers (cm^{-1}). Column chromatography was performed using silica gel H (10–40 μm, Haiyang chemical Factory of Qingdao). The solvent was dried with sodium and redistilled. All the ketones and benzaldehyde were redistilled before use. Diethyl thiophosphoramidate was synthesized according to the document [17].

3.1. General procedure for synthesis of diphenyl α-(diethoxythiophosphorylamino)-methylphosphonates

Freshly distilled ketones or benzaldehyde (1 mmol) is added dropwise to a stirred mixture of diethyl thiophosphoramidate (1 mmol, 0.17 g), triphenyl phosphite (1 mmol, 0.31 g), and acetyl chloride (5 ml) at room temperature. The process of the reaction is monitored by TLC on silica gel. After 8–12 h stirring at RT, the resulting mixture is filtered and the filtrate concentrated in vacuo. The residue is purified by column chromatography on silica gel, eluting with EtOAc/petroleum ether (bp 60–90 °C, 1:2) to afford pure products.

*3.2. Diphenyl (diethoxythiophosphorylamino) (phenyl)methylphosphonate (**4a**)*

^{31}P NMR (121 MHz, $CDCl_3$): δ 69.23 (*d*, $^3J = 23.8$ Hz), 14.92 (*d*, $^3J = 23.8$ Hz). ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.11 (*m*, 15H, $3C_6H_5$), 5.32 (*m*, 1H, C*H*), 4.33

(br. 1H, NH), 3.92 (*m*, 2H, OCH_2CH_3), 3.54 (*m*, 2H, OCH_2CH_3), 1.15 (*t*, 3H, $^3J = 7.2$ Hz, OCH_2CH_3), 1.01 (*t*, 3H, $^3J = 7.2$ Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.73, 137.02, 135.74, 130.65, 130.09, 128.95, 126.50, 124.13 (3Ph), 59.48 (*d*, $^1J = 158$ Hz, NH*C*HP), 55.37 (OCH_2CH_3), 53.29 (OCH_2CH_3), 17.11 (OCH_2CH_3), 16.23 (OCH_2CH_3). ESI/MS: $[M+1]^+$ *m/z* 492.

3.3. Diphenyl (diethoxythiophosphorylamino) (p-tolyl)methylphosphonate (**4b**)

^{31}P NMR (121 MHz, $CDCl_3$): δ 71.78 (*d*, $^3J = 33.2$ Hz), 16.04 (*d*, $^3J = 33.2$ Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–6.70 (*m*, 14H, $2C_6H_5$, C_6H_4), 5.13 (*ddd*, 1H, $J = 23.6$, 11.8, 11.6 Hz, C*H*), 4.49 (br. 1H, NH), 3.96 (*m*, 2H, OCH_2CH_3), 3.61 (*m*, 2H, OCH_2CH_3), 2.34 (*s*, 3H, CH_3), 1.18 (*t*, 3H, $^3J = 6.8$ Hz, OCH_2CH_3), 1.04 (*t*, 3H, $^3J = 7.2$ Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.59, 132.61, 129.98, 129.78, 129.63, 128.44, 128.38, 125.62, 125.43, 120.87, 120.54, 120.10, 115.66 (3Ph), 63.41 (*d*, $^1J = 141$ Hz, NH*C*HP), 54.83 (OCH_2CH_3), 53.25 (OCH_2CH_3), 21.42 (CH_3), 16.03 (OCH_2CH_3), 15.80 (OCH_2CH_3). ESI/MS: $[M+1]^+$ *m/z* 506.

3.4. Diphenyl (diethoxythiophosphorylamino) (4-methoxyphenyl)methylphosphonate (**4c**)

^{31}P NMR (121 MHz, $CDCl_3$): δ 71.87 (*d*, $^3J = 33.9$ Hz), 15.99 (*d*, $^3J = 33.9$ Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–6.79 (*m*, 14H, $2C_6H_5$, C_6H_4), 5.09 (*ddd*, 1H, $J = 23.2$, 11.6, 11.2, C*H*), 4.48 (br. 1H, NH), 3.93 (*m*, 2H, OCH_2CH_3), 3.79 (*s*, 3H, OCH_3), 3.61 (*m*, 2H, OCH_2CH_3), 1.17 (*t*, 3H, $^3J = 7.2$ Hz, OCH_2CH_3), 1.05 (*t*, 3H, $^3J = 7.2$ Hz, OCH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.96, 129.75, 127.82, 125.56, 125.37, 120.85, 120.53, 114.33 (3Ph), 63.38 (*d*, $^1J = 121$ Hz, NH*C*HP), 55.56 (OCH_3), 54.47 (OCH_2CH_3), 52.89 (OCH_2CH_3), 16.01 (OCH_2CH_3), 15.83 (OCH_2CH_3). ESI/MS: $[M+1]^+$ *m/z* 522.

3.5. Diphenyl (diethoxythiophosphorylamino) 1-phenylethyl phosphonate (**4d**)

^{31}P NMR (121 MHz, $CDCl_3$): δ 70.41 (*d*, $^3J = 34.1$ Hz), 17.78 (*d*, $^3J = 34.1$ Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–6.81 (*m*, 15H, $3C_6H_5$), 6.08 (*s* 1H, NH), 4.27 (*m*, 2H, OCH_2CH_3), 4.12 (*m*, 2H, OCH_2CH_3), 1.39 (*t*, 3H, $^3J = 6.8$ Hz, OCH_2CH_3), 1.32 (*t*, 3H, $^3J = 5.2$ Hz, OCH_2CH_3), 0.97 (*t*, $^3J = 6.8$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.71, 128.62, 128.53, 126.64, 121.43, 120.96, 120.88, 118.62, 117.23, 115.56, 115.37 (3Ph), 56.55 (*d*, $^1J = 158$ Hz, NH*C*P), 51.83 (OCH_2CH_3), 50.85 (OCH_2CH_3), 16.12 (OCH_2CH_3), 15.89 (OCH_2CH_3), 14.62 (CH_3). ESI/MS: $[M+1]^+$ *m/z* 506.

3.6. Diphenyl (diethoxythiophosphorylamino) cyclopentyl phosphonate (**4e**)

^{31}P NMR (121 MHz, $CDCl_3$): δ 69.55 (*d*, $^3J = 16.5$ Hz), 22.08 (*d*, $^3J = 16.5$ Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.11 (*m*, 10H, $2C_6H_5$), 4.12 (*m*, 4H, $2OCH_2CH_3$), 3.62 (*d*, $^2J = 14.4$ Hz, 1H, NH), 2.36 (*m*, 4H, $2 \times CH_2$), 1.94 (*m*, 4H, $2 \times CH_2$), 1.27 (*t*, 6H, $^3J = 6.8$ Hz, $2OCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.76, 136.54, 132.71, 130.15, 128.55, 126.53 (2Ph), 63.82 (OCH_2CH_3), 63.76 (OCH_2CH_3), 56.78 (*d*, $^1J = 121$ Hz, NH*C*P), 37.24 (CH_2), 24.96 (CH_2), 19.15 (OCH_2CH_3), 16.27 (OCH_2CH_3). ESI/MS: $[M+1]^+$ *m/z* 470.

3.7. Diphenyl (diethoxythiophosphorylamino) cyclohexyl phosphonate (**4f**)

^{31}P NMR (121 MHz, $CDCl_3$): δ 69.74 (*d*, $^3J = 11.5$ Hz), 20.56 (*d*, $^3J = 11.5$ Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.12 (*m*, 10H, $2C_6H_5$), 4.13 (*m*, 4H, $2OCH_2CH_3$), 3.37 (*d*, $^2J = 10.8$ Hz, 1H, NH), 2.16 (*m*, 4H, $2 \times CH_2$), 1.76 (br., 4H, $2 \times CH_2$), 1.48 (*m*, 2H, CH_2), 1.26 (*t*, 6H, $^3J = 7.2$ Hz, $2OCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.88, 125.25, 120.86 (2Ph), 61.52 (OCH_2CH_3), 61.37 (OCH_2CH_3), 59.57 (*d*, $^1J = 157$ Hz, NHCP), 31.94 (CH_2), 25.25 (CH_2), 21.16 (OCH_2CH_3), 16.10 (OCH_2CH_3). ESI/MS: $[M+1]^+$ *m*/*z* 484.

3.8. Diphenyl (diethoxythiophosphorylamino) cycloheptyl phosphonate (**4g**)

^{31}P NMR (121 MHz, $CDCl_3$): δ 70.15 (*d*, $^3J = 16.3$ Hz), 21.55 (*d*, $^3J = 16.3$ Hz). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.16 (*m*, 10H, $2C_6H_5$), 4.03 (*m*, 4H, $2OCH_2CH_3$), 3.15 (*d*, $^2J = 11.2$ Hz, 1H, NH), 2.10 (*m*, 4H, $2 \times CH_2$), 1.66 (*m*, 4H, $2 \times CH_2$), 1.37 (*m*, 4H, CH_2), 1.21 (*t*, 6H, $^3J = 7.2$ Hz, $2OCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.77, 129.92, 129.58, 128.85, 122.86, 120.05 (2Ph), 62.32 (OCH_2CH_3), 62.17 (OCH_2CH_3), 60.19 (*d*, $^1J = 129$ Hz, NHCP), 32.04 (CH_2), 29.65 (CH_2), 25.25 (CH_2), 19.66 (OCH_2CH_3), 17.10 (OCH_2CH_3). ESI/MS: $[M+1]^+$ *m*/*z* 498.

Acknowledgment

This work was supported by Nankai University (J02044 to Zhiwei Miao).

References

[1] F. Ekström, C. Akfur, A.K. Tunemalm, S. Lundberg, Biochemistry 45 (2006) 74–81.
[2] S. Pignard, C. Lopin, G. Gouhier, S.R. Piettre, J. Org. Chem. 71 (2006) 31–37.
[3] V.A. Milyukov, Y.H. Budnikova, O.G. Sinyashin, Russ. Chem. Rev. 74 (2005) 859–885.
[4] O.I. Kolodiazhnyi, Tetrahedron-Asymmetry 16 (2005) 3295–3340.
[5] K. Moonen, I. Laureyn, C.V. Stevens, Chem. Rev. 104 (2004) 6177–6215.
[6] H. Gröger, B. Hammer, Chem. Eur. J. 6 (2000) 943–948.
[7] C.F. Shuman, L. Vrang, U.H. Danielson Vrang, J. Med. Chem. 47 (2004) 5953–5961.
[8] A.C. Pierce, G. Rao, G.W. Bemis, J. Med. Chem. 47 (2004) 2768–2775.
[9] A. De La Cruz, K.J. Koeller, N.P. Rath, C.D. Spilling, I.C.F. Vasconcelos, Tetrahedron 54 (1998) 10513–10524.
[10] J. Zhou, R.Y. Chen, X.F. Yang, Heteroatom Chem. 9 (1998) 369–375.
[11] J. Zhou, R.Y. Chen, J. Chem. Soc. Perkin Trans. 1 (1998) 2917–2921.
[12] M.M. Kabachnik, E.V. Zobnina, I.P. Beletskaya, SYNLETT 9 (2005) 1393–1396.
[13] C.Y. Yuan, Y.M. Qi, Synthesis (1986) 821–823.
[14] C.Y. Yuan, Y.M. Qi, Synthesis (1988) 472–474.
[15] C.Y. Yuan, S.J. Chen, G.H. Wang, Synthesis (1991) 490–493.
[16] R.A. Cherkasov, V.I. Galkin, Russ. Chem. Rev. 67 (1998) 857–882.
[17] Z.G. Li, Q.M. Wang, J.M. Huang, Synth. Org. Intermediates (2001) 207.
[18] Crystallographic data were deposited at Cambridge Crystallographic data Center, 12 Union Road, Cambridge CB2 1EZ, UK and are available from there under the deposition number CCDC 293785 for **4f** and CCDC 293786 for **4c**.