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Synthesis of 1-(*N*-ethoxycarbonylamino)alkylphosphonic monoesters

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Summary. A series of 1-(*N*-ethoxycarbonylamino)alkylphosphonic monoesters were synthesized via three-component Mannich-type condensation of ethyl carbamate, aldehydes and dichlorophosphites in benzene, followed by hydrolysis.

Keywords: Amino acid – Aminoalkylphosphonic acid – Multiple-component condensation – Mannich-type reaction – Synthesis

Introduction

α-Aminoalkylphosphonic acids are not only important phosphorus analogues of naturally occurring amino acids, but also members of the most important types of them, which have been discovered in a wide range of living organisms, animals and even human tissues (Kafarski and Lejczak, 2000). Over recent decades, numerous aminoalkylphosphonic acids have been obtained from natural resources and by synthesis (Kafarski and Lejczak, 2000; Xu and Yu, 1999). Some of them have been found to show some antibiotic activities (Kafarski and Lejczak, 2000). Several methods for the synthesis of aminoalkylphosphonic acids and derivatives have been developed to date (Kafarski and Lejczak, 2000; Xu and Yu, 1999; Xu et al., 2000). In order to get structurally diverse aminoalkylphosphonic acids, a series of 1-(*N*-ethoxycarbonylamino)alkylphosphonic acid monoesters have been prepared using ethyl carbamate, aldehydes and dichlorophosphites as starting materials via a Mannich-type condensation and followed by hydrolysis.

Materials and methods

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

Synthesis of aminoalkylphosphonic monoester (General procedure)

To a stirred solution of ethyl carbamate (0.27 g, 3 mmol) and aldehyde (3 mmol) in 10 mL of anhydrous benzene, cooled by an ice bath, dichlorophosphite (3 mmol) was added dropwise. After stirring the reaction mixture for another 6 hours at below 10°C, the mixture was refluxed for 1 hour and then cooled to room temperature. 0.5 mL of water was added and the mixture was allowed to stir for at least 2 hours until a white solid precipitated thoroughly. The solid was filtered and recrystallized from water-ethanol to afford colorless crystals. The solid can also be purified by silica gel column with a mixture of petroleum ether (30–60°C) and ethyl acetate (1:1, v/v) as eluent.

Methyl 1-(*N*-ethoxycarbonylamino)phenylmethylphosphonate (**1a**)

White solid, yield 62%; mp 129–31°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.23 (t, $J = 7.0$ Hz, 3H, CH_3), 3.55 (d, $J_{PH} = 10.6$ Hz, 3H, POMe), 4.05–4.30 (m, 2H, OCH_2), 5.17 (d, $J_{PH} = 19.0$H, CHP), 5.80 (s, br, 1H, CONH), 7.25–7.55 (m, 5H, ArH).

IR ν (cm^{-1}): 3318 (O–H), 1716 (C=O), 1241 (P=O), 1077 and 1037 (P–O–C).

ESI-MS (m/z): 274 (MH^+).

Ethyl 1-(*N*-ethoxycarbonylamino)phenylmethylphosphonate (**1b**)

White solid, yield 74%; mp 158–60°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.19 (m, 6H, $2CH_3$), 3.85–3.96 (m, 2H, $POCH_2$), 4.13 (q, $J = 6.9$ Hz, 2H, OCH_2), 5.13 (d, $J_{PH} = 18.9$ Hz, 1H, CHP), 5.80 (s, br, 1H, CONH), 7.25–7.50 (m, 5H, ArH), 9.92 (s, br, 1H, POH).

IR ν (cm^{-1}): 3310 (O–H), 1714 (C=O), 1248 (P=O), 1076 and 1027 (P–O–C).

ESI-MS (m/z): 288 (MH^+).

Phenyl 1-(*N*-ethoxycarbonylamino)phenylmethylphosphonate (**1c**)

White solid, yield 68%; mp 141–3°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.23 (t, $J = 6.9$ Hz, 3H, CH_3), 4.08–4.18 (m, 2H, OCH_2), 5.57 (dd, $J = 10.0$ Hz, $J_{PH} = 21.7$ Hz, 1H, CHP), 5.76 (s, br, 1H, CONH), 6.80–7.55 (m, 10H, ArH).

IR ν (cm^{-1}): 3273 (O–H), 1714 (C=O), 1256 (P=O), 1037 (P–O–C).
ESI-MS (m/z): 336 (MH^+).

Methyl 1-(*N*-ethoxycarbonylamino)(4-chlorophenyl) methylphosphonate (**1d**)

White solid, yield 64%; mp 156–8°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.23 (t, $J = 7.0$ Hz, 3H, CH_3), 3.58 (d, $J_{PH} = 10.8$ Hz, 3H, POMe), 4.13 (q, $J = 6.9$ Hz, 2H, OCH_2), 5.13 (d, $J_{PH} = 20.7$ Hz, 1H, CHP), 5.79 (s, br, 1H, CONH), 7.25–7.40 (m, 5H, ArH), 9.80 (s, br, 1H, POH).
IR ν (cm^{-1}): 3320 (O–H), 1720 (C=O), 1244 (P=O), 1036 (P–O–C).
ESI-MS (m/z): 308 (MH^+).

Ethyl 1-(*N*-ethoxycarbonylamino)(4-chlorophenyl) methylphosphonate (**1e**)

White solid, yield 77%; mp 158–60°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.23 (m, 6H, CH_3), 3.91 (m, 2H, $POCH_2$), 4.13 (q, $J = 6.9$ Hz, 2H, OCH_2), 5.11 (d, $J_{PH} = 23.4$ Hz, 1H, CHP), 5.76 (s, br, 1H, CONH), 7.20–7.40 (m, 4H, ArH), 10.39 (s, br, 1H, POH).
IR ν (cm^{-1}): 3316 (O–H), 1719 (C=O), 1247 (P=O), 1024 (P–O–C).
ESI-MS (m/z): 322 (MH^+).

Phenyl 1-(*N*-ethoxycarbonylamino)(4-chlorophenyl) methylphosphonate (**1f**)

White solid, yield 68%; mp 157–9°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.22 (t, $J = 7.2$ Hz, 3H, CH_3), 4.12 (q, $J = 7.0$ Hz, 2H, OCH_2), 5.27 (d, $J_{PH} = 22.5$ Hz, 1H, CHP), 5.82 (s, br, 1H, CONH), 6.90–7.35 (m, 10H, ArH), 10.38 (s, br, 1H, POH).
IR ν (cm^{-1}): 3309 (O–H), 1722 (C=O), 1249 (P=O), 1038 (P–O–C).
ESI-MS (m/z): 370 (MH^+).

Methyl 1-(*N*-ethoxycarbonylamino)(4-methoxyphenyl) methylphosphonate (**1g**)

White solid, yield 73%; mp 112–4°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.22 (t, $J = 6.9$ Hz, 3H, CH_3), 3.55 (d, $J_{PH} = 10.8$ Hz, 3H, POMe), 3.78 (s, 3H, OCH_3), 4.12 (q, $J = 7.2$ Hz, 2H, OCH_2), 5.10 (d, $J_{PH} = 19.5$ Hz, 1H, CHP), 5.81 (s, br, 1H, CONH), 6.88 (d, $J = 8.4$ Hz, 2H, ArH), 7.30 (d, $J = 8.4$ Hz, 2H, ArH), 9.24 (s, br, 1H, POH).
IR ν (cm^{-1}): 3305 (O–H), 1715 (C=O), 1235 (P=O), 1057 and 1029 (P–O–C).
ESI-MS (m/z): 304 (MH^+).

Ethyl 1-(*N*-ethoxycarbonylamino)(4-methoxyphenyl) methylphosphonate (**1h**)

White solid, yield 62%; mp 138–40°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21 (m, 6H, $2CH_3$), 3.78 (s, 3H, OCH_3), 3.90 (m, 2H, $POCH_2$), 4.12 (q, $J = 6.9$ Hz, 2H, OCH_2), 5.07 (d, $J_{PH} = 20.1$ Hz, 1H, CHP), 5.75 (s, br, 1H, CONH), 6.87 (d, $J = 8.4$ Hz, 2H, ArH), 7.29 (d, $J = 8.4$ Hz, 2H, ArH).
IR ν (cm^{-1}): 3313 (O–H), 1715 (C=O), 1237 (P=O), 1029 (P–O–C).
ESI-MS (m/z): 318 (MH^+).

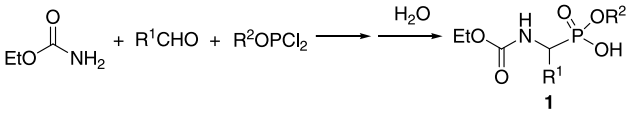
Phenyl 1-(*N*-ethoxycarbonylamino)(4-methoxyphenyl) methylphosphonate (**1i**)

White solid, yield 88%; mp 138–40°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.21 (t, $J = 7.0$ Hz, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.11 (q, $J = 7.0$ Hz, 2H, OCH_2), 5.24 (d, $J_{PH} = 21.9$ Hz, 1H, CHP), 5.76 (s, br, 1H, CONH), 6.85 (d, $J = 8.4$ Hz, 2H, ArH), 6.96 (d, $J = 8.4$ Hz, 2H, ArH), 7.10–7.35 (m, 5H, ArH), 9.03 (s, br, 1H, POH).
IR ν (cm^{-1}): 3374 (O–H), 1721 (C=O), 1238 (P=O), 1031 (P–O–C).
ESI-MS (m/z): 366 (MH^+).

Results and discussion

Multiple component condensation is one of important methods for preparing structurally diverse compounds because different types of structurally diverse starting materials could be used in one reaction. Mannich reaction is an important three-component condensation and has been widely used to synthesize α-amino ketone derivatives. The Mannich-type reactions of carbamates, aldehydes, and phosphite have been used to synthesize α-aminoalkylphosphonic acids and derivatives. In this case, the three-component condensations were followed by hydrolysis (Yuan and Wang, 1990; Dai and Chen, 1997a, b), alcoholysis (Xu and Fu, 2001; Xu and Wei, 2000) and aminolysis (Xu and Fu, 2000). Thus, these one-pot reactions can be considered as pseudo-four-component reactions. Herein, the one-pot reaction was used to prepare structurally diverse aminoalkylphosphonic acid monoesters **1** via simple starting materials, ethyl carbamate, aldehydes, dichlorophosphites, and followed by hydrolysis (shown in Scheme 1).

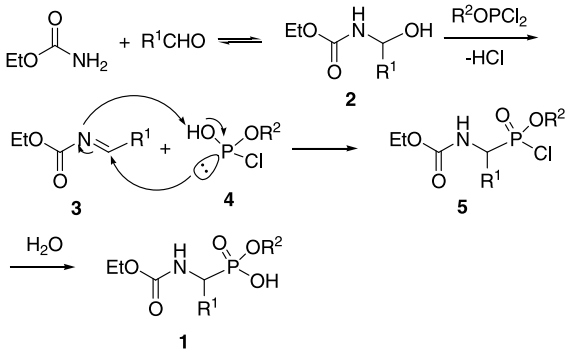
On the basis of our previous investigation (Xu and Fu, 2001), the reaction mechanism could be proposed as shown in Scheme 2. Ethyl carbamate and aldehydes could undergo an addition to form intermediates **2**, which could be dehydrolyzed to generate imines **3** in the presence of dichlorophosphites served as dehydrolyzing agents, and the dichlorophosphites were converted to chlorophosphites **4** at the same time. The imines **3** and chlorophosphites **4** underwent a nucleophilic addition and followed by hydrogen transfer to give rise to aminoalkylphosphonate chlorides



1

1a, R^1 = Ph, R^2 = Me; **1b**, R^1 = Ph, R^2 = Et; **1c**, R^1 = Ph, R^2 = Ph
1d, R^1 = 4-ClPh, R^2 = Me; **1e**, R^1 = 4-ClPh, R^2 = Et; **1f**, R^1 = 4-ClPh, R^2 = Ph
1g, R^1 = 4-MeOPh, R^2 = Me; **1h** R^1 = 4-MeOPh, R^2 = Et; **1i**, R^1 = 4-MeOPh, R^2 = Ph

Scheme 1. Synthesis of aminoalkylphosphonic acid monoesters



Scheme 2. Proposed reaction mechanism for the synthesis of aminoalkylphosphonic acid monoesters

5, which were converted to the desired products **1** after hydrolysis. In our method, benzene was used as a solvent instead of irritative acetyl chloride previously used in the reaction (Yuan and Wang, 1990; Dai and Chen, 1997a, b).

It has been found that all reactions give satisfactory to good yields. We attempted to extend the application of the three component condensation to amines and amides. A variety of amines, including primary amines: aniline, benzylamine, *tert*-butylamine; secondary amines: diethylamine, piperidine, morpholine, and acetamide were tested in the reaction. However, no desired product was obtained under the same reaction conditions and other attempted reaction conditions. In comparison with carbamates, amides show weaker basicity and nucleophilicity. They cannot undergo an addition to aldehydes in the first step. Thus, no desired product was obtained for amides.

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