Short Note

Diethyl(benzamido(diisopropoxyphosphoryl)methyl)phosphonate

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Abstract: Bisphosphonates are widely used in medicine and related areas, mainly for the treatment of bone diseases, such as osteoporosis. However, their synthesis is usually performed under harsh reaction conditions. In order to overcome this limitation, the present work illustrates a new synthetic route to access the title α-aminobisphosphonate in milder reaction conditions using α-phosphorylated imines as key intermediates.

Keywords: bisphosphonates; α-aminophosphonates; Pudovik reaction

1. Introduction

Phosphonate-containing organic molecules such as aminophosphonate and bisphosphonate derivatives are well-known for their biological activities [1–5]. Consequently, many routes have been reported for their synthesis [6–10]. In particular, bisphosphonates have shown high potential as enzyme inhibitors [11–13], anti-inflammatory agents [14] or cancer treatments [15–17]. In particular, zoledronic acid, considered an essential medicine by the World Health Organization [18,19], and other bisphosphonate analogues, are broadly used for the treatment of osteoporosis and other bone diseases (Figure 1).

![Figure 1. Bisphosphonate drugs.](https://example.com/figure1.png)

Concerning the synthetic routes to α-hydroxy and α-aminobisphosphonates, the most widely used methods make use of carboxylic acids, amides or amines as starting materials (Scheme 1) [6,8]. However, these methodologies often require harsh reaction conditions or high temperatures.

In this context, α-aminophosphonates have emerged as promising substrates to access α-aminobisphosphonate derivatives [20,21] that allow phosphorylated imine intermediates and make them suitable for subsequent transformations [22–24]. It should be noted that all those methodologies require milder reaction conditions when compared with the previously known strategies (Scheme 1B,C). Over the last decade, our group has been working on the synthesis of organophosphorus compounds [22,25–30]. Based on Steglich’s [31] and Kobayashi’s reports [32–34], as well as our previous experience with nucleophilic additions to imines [22,26,28,35,36], in this case, we propose the synthesis of chiral diethyl (benzamido(diisopropoxyphosphoryl)methyl)phosphonate through a Pudovik reaction using α-bromo aminophosphonates as the starting material of the corresponding imine (Scheme 2).
Scheme 1. Main synthetic routes to bisphosphonates. (A) Synthesis of α hydroxy bisphosphonates from carboxylic acids; (B) Synthesis of α aminobisphosphonates from amides; (C) Synthesis of α amino bisphosphonates from amines.

Scheme 2. Our proposal to access amino bisphophonates.

Scheme 3. Synthesis of diethyl (benzamido (diisopropoxyphosphoryl) methyl) phoshonate 3.

Aminobisphosphonate 3 was extensively characterized by $^1$H, $^{13}$C[$^1$H] NMR, DEPT, $^{31}$P NMR, 2D-COSY NMR [$^1$H-$^1$H], 2D-HSQC NMR [$^1$H-$^{13}$C], 2D-HMBC NMR [$^1$H-$^{13}$C], FTIR spectra and HRMS experiments (Supplementary Materials).

The most relevant signal of compound 3 in the $^1$H NMR spectrum (CDCl$_3$) is the proton corresponding to the P-CH-P moiety, which is seen as a representative triplet doublet at $\delta_H = 5.19$ ppm ($J_{PH} = 21.5$ Hz and $J_{HH} = 10.2$ Hz), the result of the coupling...
between CH and the NH of the amide moiety and the coupling of CH with each of the contiguous phosphonates. In addition, due to the low interchange ratio of the NH belonging to the amide group, a doublet is observed at 6.54 ppm, showing coupling only with the neighboring CH moiety ($^3J_{HH} = 10.2$ Hz). Likewise, in the $^{13}$C NMR spectrum of phosphorylated derivative 3, the two doublets corresponding to the two diastereotopic CH carbons of the isopropyl moiety appear at $\delta_C = 72.8$ ppm ($^3J_{CP} = 17.4$ Hz) and $\delta_C = 72.7$ ppm ($^3J_{CP} = 17.7$ Hz). The methylene carbons corresponding to the two ethoxy groups can be also detected as two doublets with chemical shifts at $\delta_C = 63.7$ ppm (d, $^3J_{CP} = 29.3$ Hz) and $\delta_C = 63.6$ ppm (d, $^3J_{CP} = 29.7$ Hz). A very characteristic signal corresponding to the CH carbon appears as a double doublet at $\delta_C = 44.9$ ppm with strong coupling with the two adjacent phosphorus atoms ($^3J_{CP} = 148.4$ Hz and $^3J_{CP} = 146.6$ Hz). Finally, due to the presence of a chiral center in the structure, the two carbons corresponding to the four methyl groups at the isopropyl moieties appear as two doublets at 24.7 ppm ($^3J_{CP} = 3.3$ Hz) and 23.9 ppm ($^3J_{CP} = 5.4$ Hz) for isopropyl groups. However, both methyl groups of the ethoxy group appear overlapped as one doublet at 16.5 ppm ($^3J_{CP} = 6.0$ Hz). As expected, the $^{31}$P NMR spectrum of substrate 3 shows two doublets at $\delta_P = 16.5$ and 14.3 ppm ($^3J_{PP} = 31.3$ Hz).

The FTIR spectrum of compound 3 shows a stretching vibration around $\nu = 3218$ cm$^{-1}$, which is typical for N-H moiety. In addition, several absorptions within the interval $\nu = 3056$–2986 cm$^{-1}$ correspond to the stretching vibration of aromatic and aliphatic C-H bonds. One of the most relevant absorption signals observed in the IR spectrum corresponds to the stretching vibration of the amide C=O bond at $\nu = 1657$ cm$^{-1}$. The vibration of the P=O bonds corresponding to the ethyl and isopropyl phosphonates results in moderate absorption bands at $\nu = 1258$ cm$^{-1}$ and $\nu = 1163$ cm$^{-1}$. Due to the presence of the phosphorylated groups, the IR spectrum shows two signals at $\nu = 1144$ cm$^{-1}$ and $\nu = 1109$ cm$^{-1}$ which correspond to the P-O-C stretching bands of both phosphate moieties.

The high-resolution mass spectrometry (HRMS (ESI-TOF) m/z) experiment shows a peak corresponding to the molecular ion with an exact mass of 436.1642 (M + H)$^+$ that fits with the predicted mass ((M + H)$^+$ = 436.1654) of the calculated molecular formula $(C_{18}H_{32}NO_7P_2)$ far within the standard tolerated deviation.

3. Materials and Methods

3.1. General Experimental Information

Solvents used for extraction and chromatography were technical grade. All the solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F254 plates. Visualization was accomplished by UV light. $^1$H and $^{13}$C-NMR spectra were recorded on a Varian Unity Plus (Varian Inc., NMR Systems, Palo Alto, Santa Clara, CA, USA) (at 300 MHz, 75 MHz, 120 MHz and 282 MHz) and on a Bruker Avance 400 (Bruker BioSpin GmbH, Rheinstetten, Germany) (at 400 MHz for $^1$H and 100 MHz for $^{13}$C). Chemical shifts ($\delta$) were reported in ppm relative to residual CHCl$_3$ ($\delta = 7.26$ ppm for $^1$H and $\delta = 77.16$ ppm for $^{13}$C NMR). Coupling constants (J) were reported in Hertz. Data for $^1$H NMR spectra were reported as follows: chemical shift, multiplicity, coupling constant and integration. Multiplicity abbreviations were as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. $^{13}$C-NMR peak assignments were supported by distortionless enhanced polarization transfer (DEPT). High resolution mass spectra (HRMS) were obtained by positive-ion electrospray ionization (ESI). Data were reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were taken in a Nicolet iS10 Thermo Scientific spectrometer (Thermo Scientific Inc., Waltham, MA, USA) as neat solids. Peaks were reported in cm$^{-1}$.
3.2. Experimental Procedures and Characterization Data for Aminobisphosphonate 3

Synthetic procedure: To a solution of 1 (2 mmol, 756 mg, 1.0 equiv.) in dry CH₂Cl₂ (3 mL) under N₂ atmosphere, triethylamine (2.2 mmol, 307 µL, 1.1 equiv.) and diethyl phosphite 2 (2 mmol, 260 µL, 1 equiv.) were sequentially added. Then, the reaction was stirred at room temperature for 16 h, concentrated under vacuum and purified by column chromatography (hexane/EtOAc) to afford 662 mg (76%) of 3 as a white solid.

1H-NMR (400 MHz, CDCl₃) δ 7.78 (d, JHH = 7.2 Hz, 2H, 2 × CH₆Ar), 7.46 (t, JHH = 7.4 Hz, 2H, 2 × CH₆Ar), 6.54 (d, JHH = 10.2 Hz, 1H, NH), 5.19 (td, JIP = 21.5 Hz, 3JHH = 10.2 Hz, 1H, CH), 4.87–4.74 (m, 2H, 2 × CH OPr), 4.35–4.11 (m, 4H, 2 × CH₂ OEt), 1.65–0.97 (m, 18H, 2 × CH₂ Pr).

13C-NMR (101 MHz, CDCl₃) δ 166.5 (t, 3JCP = 4.0 Hz, C = O), 133.7 (Cquat), 132.2 (CH₆Ar), 128.9 (2 × CH₆Ar), 127.2 (2 × CH₆Ar), 72.8 (d, JCP = 17.4 Hz, CH OPr), 72.7 (d, JCP = 17.7 Hz, CH OPr), 63.7 (d, JCP = 29.3 Hz, CH₂ OEt), 63.6 (d, JCP = 29.7 Hz, CH₂ OEt), 49.9 (dd, JCP = 148.4 Hz, JCP = 146.6 Hz, CH), 24.7 (d, JCP = 3.3 Hz, 2 × CH₃ OPr), 23.9 (d, JCP = 5.4 Hz, 2 × CH₂ OPr).

31P-NMR (162 MHz, CDCl₃) δ 16.5 (d, JPP = 31.3 Hz, 14.3 (d, JPP = 31.3 Hz) ppm.

M.p. (Et₂O) = 153–155 °C.

FTIR (neat) vmax: 3218 (NH), 3056 (=CH), 2987 (C-H), 1657 (C=O), 1258 (P=O), 1163 (P=O-C), 1109 (P-O-C) cm⁻¹.

HRMS (ESI-TOF) m/z: [M + H] + calcld for C₁₈H₃₂NO₇P₂ 436.1654, Found 436.1642.

4. Conclusions

The synthesis of bisphosphonate derivative 3 was accomplished by the direct addition of diethyl phosphite 2 to a solution of α-bromo aminophosphonate 1 under the presence of an excess of triethylamine. 1H, 13C, 31P and 2D-NMR, and FTIR and HRMS experiments unequivocally confirm the structure of the obtained compound.

Supplementary Materials: The following are available online, 1H, 13C, 31P and 2D-NMR, and FTIR, HRMS and UV spectra copies of compound 3.

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Data Availability Statement: The data presented in this study are available in the supplementary materials file or on request from the corresponding author (1H, 13C, 31P, 2D-COSY, 2D-HSQC and 2D-HMBC NMR, FTIR, HRMS and HPLC spectra).

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Conflicts of Interest: The authors declare no conflict of interest.

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