Short Note

Diethyl (2-(4-Phenyl-1H-1,2,3-triazol-1-yl)benzyl) Phosphate

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Abstract: Here we describe a full structural elucidation of the diethyl (2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzyl) phosphate. This compound is a common by-product present in the synthetic protocols to access the α-hydroxy phosphonate compounds through of a Phospha-Brook rearrangement. Thus, a complete NMR structural characterization of this rearrangement by-product was performed by 1H, 13C{1H}, 31P{1H}, COSY, HSQC, and HMBC NMR experiments. Additionally, we have demonstrated that the 1H-31P HMBC is a 2D heteroatom NMR experiment which combines the simple identification by 31P chemical shift with the detection sensitivity by 1H spectrum in a practical procedure.

Keywords: 1,2,3-triazoles; click-chemistry; hydroxyphosphonates; NMR spectroscopy; phospha-brook rearrangement

1. Introduction

Organophosphonate compounds present a singular application in medicinal chemistry [1–4], especially in the agrochemical field [5–7]. Based on the Abramov and Pudovik reactions, the synthetic protocols to prepare these compounds usually employ hydrophosphoryl reagents as starting materials, which are simple and practical, with an ample substrate scope [8–10]. Additionally, hydrophosphoryl reagents are easily prepared by industrial sector through the oxidative coupling of hypophosphorous acids with alcohols, affording a cheaper and readily available scope of starting materials [11–13].

Based on the peculiar reactivity of hydrophosphoryl compounds [14,15], bioactive targets are constantly produced [16,17], mainly those containing nitrogen heterocycles [18–21]. Routinely, no full assignments are present, resulting in the absence of the precise structural data, that could be useful information for the identification of products and by-products, as well as for the recognition of biological processes [22,23].

In this sense, we have recently prepared α-hydroxyphosphonates containing functionalyzed 1,2,3-triazoles under mild conditions [24]. This nitrogen heterocycle is amply applied as a bioactive compound [25–27], and a precise structural assignment is an imperative task to evaluate the regioselectivity of the 1,3-dipolar cycloaddition reaction [28,29].

A routine inconvenience in the synthesis of α-hydroxyphosphonate compounds is the occurrence of the Phospha-Brook rearrangement, which produces a by-product that demonstrates a similar backbone structure (Scheme 1), hampering the identification and quantification of this by-product. In this sense, a full comprehension of this by-product is important to evaluate the presence of impurities in the synthesis of the α-hydroxyphosphonates.

Herein, we present a full structural characterization of the diethyl (2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzyl) phosphate derived from the Phospha-Brook rearrangement through 1H, 13C{1H}, 31P{1H}, COSY, HSQC, and HMBC NMR experiments, due the structural similarities with α-hydroxyphosphonate [28]. Additionally, the 1H-31P HMBC 2D correlation experiment was carried out for the Phospha-Brook rearrangement to demonstrates the simplicity and additional information of this alternative 2D NMR protocol. The spectral data provided herein can be used for the identification of organophosphonate compounds, as well as pharmacological 1,2,3-triazoles [30] from copper catalyzed azide-alkyne cycloaddition (CuAAC) reactions [29].
2. Results

The α-hydroxyphosphonate compounds were obtained previously by us, through the reaction between triazole 1 and diethyl phosphite 2 in a ratio of 1:3 in the presence of Na₂CO₃ (10 mol%) as catalyst at 70 °C for 3.0 h under conventional heating. Using these free-solvent conditions, the α-hydroxyphosphonate containing α-functionalized 1,2,3-triazole 3 was isolated in a high yield (93%) by column chromatography (see the Supporting Information to access also the full assignment of product 3 for a proper data comparison), while compound 4 was obtained in 90% yield by Phospha-Brook rearrangement of product 3, after treatment with KOH (10 mol%) in DMSO at 70 °C for 3.0 h. Posteriorly, the complete NMR structural characterization of this common by-product 4 was performed by 1H, 13C{1H}, 31P{1H}, COSY, HSQC, and HMBC NMR experiments. The sample was prepared employing 5 mg of the respective product 4 in 600 µL deuterated chloroform. The 90° pulse width was calibrated, and the resolution used in the 2D experiments was 4 K/512 (l2 × l1) data points. For the 1H-31P HMBC experiment, the same pulse sequence of carbon-13 was used, replacing the parameters relating to the specific nuclide.

3. Discussion

Initially, the α-hydroxyphosphonate containing functionalized 1,2,3-triazoles 3 was prepared (Scheme 1). In this moment, the main by-product was not detected by thin-layer-chromatography, but the 31P{1H} spectrum of the crude reaction showed several small peaks. Thus, product 3 was purified and submitted to a strong base (KOH) in a DMSO solvent to favor the formation of the Phospha-Brook rearrangement (Scheme 1). Under this condition, the main by-product 4 was isolated by chromatographic column and obtained in a high yield (90%). The plausible mechanism for this reaction (Scheme 2) starts with the deprotonation of the α-hydroxyl group of compound 3 by the base A, forming the oxynion compound B. This oxynion of intermediate B performs a nucleophilic attack on the electrophilic phosphorus center, giving the intermediate C. After the occurrence of P-C bond cleavage, the intermediate D, a short-lived carbanion (carbanion stabilizing by the phenyl group), was generated. Finally, after protonation of the intermediate D, the desired Phospha-Brook rearrangement product 4 was formed, and the base A was regenerated for the catalytic cycle [31,32].

Next, we performed the complete structural characterization of the Phospha-Brook product (Table 1, compound 4) through the 1H, 13C{1H}, 31P{1H}, COSY, HSQC, and HMBC NMR experiments. The structural profile can be a useful data for comparison with α-hydroxyphosphonate [24], especially to evaluate its influence in other organic functions, as the 1,2,3-triazole heterocycle. Firstly, the 1H spectrum demonstrates a clear signal profile, which can easily identify the aliphatic protons and the aromatic protons. In a downfield 1H chemical shift, it is possible to detect the triazole proton in a singlet multiplicity. The aromatic ring which connects the phosphonate group with the 1,2,3-triazole ring can be identified by the standard multiplicity, but an overlapping of signals can occur due to the same backbone profile of α-hydroxyphosphonate (see the NMR spectra in Supplementary).
According to the $^{13}$C($^1$H) spectrum, eighteen peaks can be visualized, because of the presence of carbon-phosphorus scalar couplings. All aliphatic carbons demonstrate coupling constants with phosphorus nuclide due to the proximity. When the aromatic carbons are evaluated, only one $^{13}$C-$^{31}$P coupling is perceived in carbon-2 (Table 1, entry 2). This is an important profile variation in the carbons in the aromatic ring when compared with the structural elucidation of the of $\alpha$-hydroxyphosphonate 3 (see Support Information), which. Due to the shorter distance between the phosphonate group and the aromatic ring in compound 3, there are various $^{13}$C-$^{31}$P scalar couplings.

Although, the NMR profile can provide distinct data, a full structural elucidation is necessary to identify all carbons signals, and for this purpose 2D NMR experiments
were carried out. As can be seen in Table 1, proton-carbon correlations are a valuable information to recognize all carbons. The stronger $^{3}J_{1H-13C}$ scalar coupling can be used to identify not only the quaternary carbons C-2 and C-7, but also to confirm the primary carbons C-3, C-4, C-5, and C-6. The C-9 can be easily detected by the correlation with the proton singlet derived from 1,2,3-triazole moiety (Table 1, entry 8). It is important to note that the quaternary carbon C10 of the phenyl bound in the triazole ring overlaps on C4 (Table 1, entry 4 and 10). At the end, the aliphatic carbons’ chemical shifts are easily identified, but the presence of similar carbons in the α-hydroxyphosphonate 3 emphasizes that they are not good options to differentiate between product and by-product.

An interesting alternative to check the structure of these phosphonate compounds is through the $^{31}P^{[1H]}$ spectrum. The phosphorus-31 chemical shift of the Phospha-Brook rearrangement (Supplementary, Figure S9: $−6.95$ ppm) demonstrates a significant change derived from the stronger diamagnetic anisotropy caused by the new bond formed between oxygen and phosphorus, even though misinterpretations could occur in the proton spectra because of the same backbone. In this sense, a simple and practical $^{1}H-^{31}P$ HMBC experiment was performed to highlight the advantages of this 2D long-range experiment (Figure 1), which shows these correlations are useful for the discrimination of signals around to the phosphorus element, providing also the $^{31}P$ chemical shift. To carry out the $^{1}H-^{31}P$ HMBC experiment, the same $^{1}H-^{13}C$ HMBC parameters should be optimized. Based on the proximity between protons with the phosphorus heteroatom, it is possible to detect the proton neighborhood around the phosphorus element, with protons 1, 14/14’ and 15/15’ giving new details about the structural assignment. The long-range parameter could be optimized for the cases in which the scalar couplings ($^{2}J_{1H-31P}$ and $^{3}J_{1H-31P}$) are far from the values commonly observed.

![Figure 1. $^{1}H-^{31}P$ HMBC NMR experiment of compound 4.](image-url)

4. Materials and Methods

The nuclear magnetic resonance (NMR) data were collected on a Bruker Avance III HD spectrometer operating at 400.0 MHz for $^{1}H$, 100 MHz for $^{13}C$, and 161 MHz for $^{31}P$. The concentration of all samples was approximately 20 mg/0.7 mL of CDCl$_3$. NMR data were recorded at 25 °C, with chemical shifts $\delta$ reported in parts per million and coupling constants $J$ in Hertz. The chemical shifts of the $^{1}H$ and $^{13}C^{[1H]}$ NMR experiments were referenced by TMS (tetramethylsilane) at $\delta = 0.0$ ppm. The chemical...
shifts of the $^{31}$P-$^1$H NMR experiments were referenced by triphenyl phosphate at $\delta = 77.0$ ppm. 2D NMR experiments COSY, HSQC, HMBC were performed using the standard Bruker pulse sequence with gradient. The relaxation delay, 90° pulse, spectral width, and number of data points for $^1$H-NMR were 1 s, 9.43 µs, 5580 Hz, and 64 K, respectively. The corresponding parameters for the $^{13}$C-NMR experiments were 0.5 s, 10.0 µs, 26,041 Hz, and 64 K, respectively. The parameters for the $^{31}$P NMR experiments were 3.0 s, 15.0 µs, 21,000 Hz, and 64 K, respectively. Two-dimensional experiments including COSY, HSQC, and HMBC were performed with 4 K $\times$ 512 ($t_2 \times t_1$) data points. The long-range coupling time for $^1$H-$^{13}$C HMBC was 100 ms, and for $^1$H-$^{31}$P HMBC 70 ms. All data were analyzed using the MNova 7.1.1 (2012) software.

Spectral Data of Compounds 3 and 4

Diethyl (hydroxy(2-(4-phenyl-1H-1,2,3-triazol-1-yl)phenyl)methyl) phosphonate 3, Yield: 93%; white solid, m.p.: 124–126 °C. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 8.43 (s, 1H), 7.99 (d, $J_{\text{H-H}}$ = 8.0 Hz, 1H), 7.82 (d, $J_{\text{H-H}}$ = 7.0 Hz, 2H), 7.54 (dd, $J_{\text{H-P}}$ = 13.1, 5.8 Hz, 1H), 5.02 (dd, $J_{\text{H-P}}$ = 16.5, 5.8 Hz, 1H), 4.16–4.00 (m, 4H), 1.28 (t, $J_{\text{H-H}}$ = 7.0 Hz, 3H), 1.21 (t, $J_{\text{H-H}}$ = 7.1 Hz, 3H). $^{13}$C-$^1$H NMR (101 MHz, CDCl$_3$) $\delta$ = 147.6, 135.6 (d, $J_{\text{C-P}}$ = 9.1 Hz), 133.4, 130.2 (d, $J_{\text{C-P}}$ = 2.4 Hz), 130.1, 129.9 (d, $J_{\text{C-P}}$ = 4.1 Hz), 129.2 (d, $J_{\text{C-P}}$ = 2.6 Hz), 129.1 (2C), 128.5, 126.2, 125.9 (2C), 123.3, 65.2 (d, $J_{\text{C-P}}$ = 165.0 Hz), 63.7 (d, $J_{\text{C-P}}$ = 7.2 Hz), 63.4 (d, $J_{\text{C-P}}$ = 7.1 Hz), 16.6 (d, $J_{\text{C-P}}$ = 5.5 Hz), 16.5 (d, $J_{\text{C-P}}$ = 5.6 Hz). $^{31}$P-$^1$H NMR (162 MHz, CDCl$_3$) $\delta$ = 21.3. MS (rel. int., %) m/z: 387 (0.3), 342 (0.4), 220 (60.4), 193 (89.5), 165 (71.1), 111 (52.9), 105 (57.4), 83 (100.0). HR-MS (APCI-QTOF) calculated mass for C$_{19}$H$_{23}$N$_3$O$_4$P [M + H]$^+$: 388.1421, found: 388.1437.

Diethyl (2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzyl) phosphate 4 [33], Yield: 90%; colorless oil, $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 8.15 (s, 1H), 7.92 (d, $J_{\text{H-H}}$ = 8.0 Hz, 2H), 7.74 (d, $J_{\text{H-H}}$ = 7.0 Hz, 1H), 7.60–7.54 (m, 2H), 7.53–7.51 (m, 1H), 7.49–7.45 (m, 2H), 7.40–7.36 (m, 1H), 5.08 (d, $J_{\text{H-P}}$ = 16.5 Hz, 2H), 4.12–3.99 (m, 4H), 1.25 (t, $J_{\text{H-H}}$ = 7.1 Hz, 6H). $^{13}$C-$^1$H NMR (101 MHz, CDCl$_3$) $\delta$ = 148.1, 135.9, 131.5 (d, $J_{\text{C-P}}$ = 7.6 Hz), 130.5, 130.2 (2C), 129.8, 129.1, 128.6, 126.0, 125.9, 121.6, 65.0 (d, $J_{\text{C-P}}$ = 5.1 Hz), 64.2 (d, $J_{\text{C-P}}$ = 5.8 Hz), 16.2 (d, $J_{\text{C-P}}$ = 6.6 Hz). $^{31}$P-$^1$H NMR (162 MHz, CDCl$_3$) $\delta$ = -6.95.

5. Conclusions

In conclusion, we have synthesized the diethyl (2-(4-phenyl-1H-1,2,3-triazol-1-yl)benzyl) phosphate and performed a full structural elucidation of its $^1$H, $^{13}$C, and $^{31}$P NMR signals. This is an important contribution to facilitate the purity assessment of $\alpha$-hydroxyphosphonate compounds, which have consolidated pharmacological applications—especially in the agrochemical field, due to the organophosphonate herbicides, because it is the major by-product derived from the Phospha-Brook rearrangement. Thus, the full assignments are an imperative task in the development of new bioactive compounds, not only for the products, but also for the impurities formed during the synthesis. Additionally, we have demonstrated the utility of the $^1$H-$^{31}$P HMBC experiment, which is a simple and practical 2D experiment that combines the simple identification by the $^{31}$P chemical shift with the detection sensitivity by the $^1$H spectrum in a practical procedure.

Supplementary Materials: The following are available online. Figures S1–S13: $^1$H, $^{13}$C and $^{31}$P, COSY, HSQC and HMBC spectrum.

Author Contributions: M.S.S., as supervisor, designed, conceived the whole experiments, and wrote, reviewed, and edited the manuscript; D.A. wrote, reviewed, and edited the manuscript; and G.P.d.C. developed the methodology and performed the experiments. All authors have read and agreed to the published version of the manuscript.

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