Research Article

Interconversion of Aminophosphonates via Biomimetic 1, 3-H Transfer in 1,3-Diphosphorylated Azapropenes

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Abstract: The condensation of 1-amino-1-arylmethylphosphonates and aroylphosphonates results in the formation of 1,3-diaryl-1,3-diphosphorylated azapropenes, which incorporate iminophosphonate and aminophosphonate fragments in their structure. A reversible 1,3-proton shift in the C=N-C triad enables interconversion between various aminophosphonates. The control over this interconversion can be achieved through substituents present in the 1,3-diaryl rings.

Keywords: Aminophosphonates, iminophosphonate, transamination, H-transfer, biomimetic

1. Introduction

Aminophosphonic acid derivatives are recognized as bioisosteres of α-amino acids, where the planar carboxylic group is substituted with a tetrahedral phosphonic acid residue. This substitution allows them to act as substitutes for α-amino acids in peptides, altering their properties [1]. These derivatives exhibit a broad range of biological activities and find numerous applications in medicinal and pharmaceutical sciences, including serving as haptens for catalytic antibodies, enzyme inhibitors, antibacterial, antioxidant, and anticancer agents, as well as agrochemicals [1-8]. In our previous works, we introduced a novel conceptual approach to aminophosphonic acid derivatives by utilizing a proton shift in the C=N-C triad of N-benzyl iminophosphonates (Scheme 1) [9,10].

\[
\begin{align*}
\text{R} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{P} & \quad \text{R} \\
\end{align*}
\]

Scheme 1. The irreversible 1,3-H transfer in C=N-C triad of iminophosphonates.

It is important to highlight that the proton transfer in aminophosphonates with a stereodirecting group at the nitrogen atom exhibits stereoselectivity, resulting in the formation of enantiomerically enriched aminophosphonates [9-12] (Scheme 2). The successful application of biomimetic reductive amination, based on 1,3-H transfer in imines derived from α-trifluoromethyl-containing carbonyl compounds, has been extensively demonstrated in the seminal
works of the Soloshonok group [13 and references therein]. These studies showcase the synthetic utility of this approach for the synthesis of fluorinated amines and amino acids.

Thus, the proton transfer within the C=NCH triad is a fundamental characteristic of iminophosphonates and plays a pivotal role in the synthesis of α-aminoalkylphosphonic acid derivatives. The irreversibility of 1,3-H transfer in Schemes 1 and 2 is attributed to the electron-withdrawing properties of the phosphonyl group. However, when both the 1 and 3 positions of the C=NCH triad contain phosphonyl groups, reversible proton transfer occurs, leading to the mutual conversion of two aminophosphonates. Previous research has demonstrated that the reaction between aminophosphonates 1a,b and ketophosphonate 2a yields an equilibrium mixture of bisphosphonates 3a,b and 4a,b, with nearly equal proportions of both isomers (3/4 ~ 1-1.3). The same equilibrium ratios have been achieved through the reaction of aminophosphonate 1c with ketophosphonates 2b,c (Scheme 3) [9, 14].

We hypothesized that through careful selection of substituents in the aryl rings of aminophosphonates 1 and ketophosphonates 2, it would be feasible to greatly increase the equilibrium ratio between 3 and 4. Consequently, this would enable the efficient conversion of one aminophosphonate into another.

2. Results and Discussion

Using the previously described procedure [14], we synthesized a series of 1,3-diaryl-1,3-diphosphorylated azapropene derivatives (Scheme 4).

Scheme 2. The stereoselective 1,3-H transfer in fluorinated iminophosphonates.

Scheme 3. The reversible 1,3-H transfer in diphosphorylated azapropenes.
In order to investigate the impact of substituents in the phosphonyl group on the prototropic equilibrium, we conducted a reaction between O,O-dimethyl ketophosphonate 5a and aminophosphonate 1c. Interestingly, we observed that the equilibrium ratios of 6a/7a (Scheme 4) and 4a/3a (Scheme 3) were identical. This implies that the replacement of one diethoxyphosphonyl group with a methoxyphosphonyl substituent does not influence the equilibrium.

It is important to note that the 1H and 31P NMR spectral data of isomers 3 and 4 exhibit close similarities, making them challenging to distinguish. However, the 31P NMR signals of the (MeO)2P(O) group are shifted approximately 2 ppm to the low-field region compared to the diethoxyphosphonyl substituent (Table). This result provides an opportunity to easily monitor the prototropic equilibrium using 31P NMR without altering the isomeric ratio by employing compounds with non-equivalent phosphonyl groups. For derivatives 3a, 4a, 6a,b, and 7a,b, containing fluorophenyl substitutions, the prototropic isomers can be readily differentiated using 19F NMR. The chemical shifts of the fluorine atoms in compounds 3a and 6a,b are shifted approximately 4 ppm to the high-field region compared to isomers 4a and 7a,b, respectively. This shift is attributed to the bonding of the fluorophenyl ring to the donor alkyl or acceptor imidoyl substituent, respectively (Table).

The results obtained demonstrate that the equilibrium ratio of prototropic isomers 6 and 7 can be modulated by substituents in the aryl rings (Scheme 4). To shift the equilibrium towards one side or the other, it is important for the electronic parameters of the substituents X and Y to differ significantly. For instance, the reaction of aminophosphonate 1d, which contains an electron-releasing MeO group (σp -0.27), with ketophosphonate 5d, bearing an electron-withdrawing CF3 group (σm 0.43), leads to a substantial increase in the equilibrium ratio of the isomeric diphosphonates (7d/6d, 9:1). In practical terms, Scheme 4 represents the conversion of N-protected 4-methoxybenzyl-α-aminophosphonate 6d into N-protected 3-trifluoromethylbenzyl-α-aminophosphonate 7d. This conversion can be performed as a one-pot procedure. Consequently, the condensation of ketophosphonate 2d with aminophosphonate 1d, followed by hydrolysis, yields aminophosphonate 8 and aminophosphonic acid 9. This signifies that the trifluoromethyl-substituted ketophosphonate 2d has been transformed into the corresponding trifluoromethyl-substituted aminophosphonate 2d and the respective aminophosphonic acid 9 through reductive amination (Scheme 5). This reaction can be considered as a phosphorus model of the biomimetic transformation of ketocarboxylic acid into the respective α-amino acid. The pivotal step of the overall process involves the proton shift within the C=N-C triad, leading to the transposition of the imine functionality. It is noteworthy that both aminophosphonates [1-8] and ketophosphonates [15-20] exhibit diverse biological activities and are of significant interest for biomedical applications. They are regarded as mimetics of α-aminophosphonic and α-ketophosphonic fragments, respectively.
Scheme 5. Conversion of ketophosphonate 2d to aminophosphonate 8 and aminophosphonic acid 9.

Aminophosphonate 8 and acid 9 were synthesized using an alternative approach outlined in Scheme 6. The reaction between imidoyl chloride 10 and triethyl phosphite resulted in the formation of iminophosphonate 11, which, under the reaction conditions (150-160 °C), underwent an irreversible 1,3-H shift, yielding benzylidene aminophosphonate 11. Subsequent N- and O-deprotection of the latter compound afforded α-amino-(3-trifluoromethylbenzyl)phosphonate 8 and the corresponding aminophosphonic acid 9.

Scheme 6. Synthesis of aminophosphonates 8, 12 and aminophosphonic acid 9 from imidoyl chloride 10.

The key step of the process involves the irreversible biomimetic H-transfer occurring in iminophosphonate 11, even in the absence of a basic catalyst. The intermediate iminophosphonate 11 was only detected in the reaction mixture by 1H, 31P NMR (δP 7.6 ppm, δCH2N 4.62 ppm, d, 4JHP 4.6 Hz) as it isomerizes to iminophosphonate 12 under the reaction conditions (150-160 °C). The prototropic isomerizations observed in Schemes 5 and 6 provide environmentally friendly alternatives for C=N bond reduction, as they do not require any metal or organic catalyst. These isomerizations can be considered as phosphorus models of biological transamination processes, offering a unique chemical solution to the reduction-oxidation processes that all living organisms have adopted throughout evolution [13 and references therein].

Table 1. 1H, 31P, 19F NMR spectral data of compounds 6a-d, 7a-d.

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<th>δH, ppm; J, Hz</th>
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<td>6a-d</td>
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<td>7a-d</td>
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3. Conclusions

The conversion of ketophosphonates to the respective aminophosphonates can be accomplished through the condensation of α-keto and α-aminophosphonates, followed by the transfer of the amino functionality in intermediate 1,3-diphosphorylated azapropenes via 1,3-H transfer. The reversible transfer of the amino functionality in 1,3-diaryl-1,3-diphosphorylated azapropenes can be controlled by the substituents in the aryl rings. The presence of electron-withdrawing substituents in the benzene ring of α-ketophosphonates and electron-releasing substituents in α-aminophosphonates favors the transamination process. Furthermore, the interconversion of two distinct aminophosphonates can be achieved through the reversible biomimetic H-transfer within the C=NCH triad of 1,3-diphosphorylated azapropenes.

4. Experimental Section

4.1 General

The $^1$H, $^{19}$F, $^{31}$P and $^{13}$C NMR spectra were recorded using Varian VXR 400, Bruker Avance DRX 300, Bruker Avance DRX 500 and Agilent 600 spectrometers. Chemical shifts are reported relative to internal TMS ($^1$H, $^{13}$C), CFCl$_3$ ($^{19}$F) and external 85%-H$_3$PO$_4$ ($^{31}$P) standards. LCMS analyses were carried out on an Agilent 1200 LC system equipped with a G6140 MSD detector (ESI mode). Preparative HPLC was performed on a Shimadzu LC-8A equipped with a Phenomenex C18 column (30×150 mm). HRMS spectra were obtained on Agilent 6200 (Q-ToF) MS system. Melting points are uncorrected. Solvents were dried before use according to standard methods. Elemental analysis was carried out in the analytical laboratory of Institute of Organic Chemistry, NAS of Ukraine.

4.2 General procedure for the preparation 6a-d, 7a-d
The mixture of respective aminophosphonate 1a, 1c or 1d (5 mmol), ketophosphonate (5 mmol) and TsOH (5 mg) in benzene (30 mL) was refluxed in Dean-Stark apparatus for 4 hrs. The resulting mixture was washed with saturated NaHCO₃, water and dried over MgSO₄. The solvent was evaporated, the residue was triturated with petroleum ether and washed with small amounts of ether. Spectral data for isomeric mixtures of 6a-d, 7a-d are presented in Table and respective equilibrium ratios in Scheme 4.

4.3 N-Benzyl-3-(trifluoromethyl)benzenecarboximidoyl chloride (10)

A mixture of freshly distilled thionyl chloride (20 g, 0.17 mol) and N-benzyl-3-(trifluoromethyl)benzamide (5 g, 17.9 mmol) was stirred and heated at reflux for 4h. The excess of SOCl₂ was removed under vacuum and the residue was distilled. Yield 3.77 g (70%), colorless liquid, bp 105–110°C (0.07 mmHg). ¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm: 8.45-8.33 (m, 1 H, Ar), 8.29-8.26 (m, 1 H, Ar), 7.76-7.73 (m, 1 H, Ar), 7.58-7.54 (m, 1 H, Ar), 7.47-7.43 (m, 2 H, Ar), 7.42-7.38 (m, 2 H, Ar), 7.34-7.30 (m, 1 H, Ar), 4.96 (s, 2 H, CH₂). ¹⁹F NMR spectrum (376 MHz, CDCl₃), δ, ppm: -62.5. ¹³C NMR spectrum (150 MHz, CDCl₃), δ, ppm: 141.9, 137.7, 136.4, 132.2 (q, JCF 1.1 Hz), 130.0 (q, JCF 32.5 Hz), 128.9, 128.6, 128.0 (q, JCF 3.6 Hz). 127.8, 127.3, 125.9 (q, JCF 4.0 Hz), 123.8 (q, JCF 272.2 Hz), 57.9.

4.4 Diethyl phenylmethyleneamino(3-(trifluoromethyl)phenyl)methylphosphonate (12)

A mixture of N-benzyl-3-(trifluoromethyl)benzenecarboximidoyl chloride (10) (1.5 g, 5 mmol) and triethyl phosphite (1 g, 6 mmol) was stirred and heated at 150–160°C for 4h to afford crude 12 in a 90% yield. An analytically pure sample of the compound 12 was obtained from 0.2g of reaction mixture by preparative HPLC (CH₃CN–H₂O) performing gradient elution from 50 to 100% of CH₃CN. Yield 45 mg (23%), colorless oil. ¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm: 8.44 (d, 1 H, 4JHP 4.6 Hz, CH=N), 7.91-7.88 (m, 1 H, Ar), 7.87-7.82 (m, 3 H, Ar), 7.57-7.52 (m, 1 H, Ar), 7.5-7.41 (m, 3 H, Ar), 4.96 (d, 1 H, 2JHP 18.8 Hz, CHP), 4.11-3.99 (m, 4 H, OCH₂), 1.25 (t, 3 H, J 7.1 Hz, CH₃), 1.2 (t, 3 H, J 7.1 Hz, CH₃). ¹³P NMR spectrum (162 MHz, CDCl₃), δ, ppm: 18.3. ¹⁹F NMR spectrum (376 MHz, CDCl₃), δ, ppm: -62.6. ¹³C NMR spectrum (100 MHz, CDCl₃), δ, ppm: 164.8 (d, JCP 15.1 Hz), 133.7 (d, JCP 5.4 Hz), 133.3 (d, JCP 4.7 Hz), 129.9, 129.5 (qd, JCF 32 Hz, JCP 2 Hz), 126.0 m, 125.9 m, 124.4 m, 124.1 (q, JCF 32 Hz, JCF 272.2 Hz), 73.1 (d, JCP 151.8 Hz), 63.4 (d, JCF 7.1 Hz), 16.3 (d, JCF 6.2 Hz). HRMS (ESI): m/z 400.1211 [M + H]+; calcld for C₁₉H₂₁F₃NO₃P: 400.1269 [M + H]+.

Intermediate iminophosphonate 11 was detected in reaction mixture when reaction was carried out at 100 °C for 2 hrs: δP 7.6 ppm, δCH₂N 4.62 ppm (d, 4JHP 4.6 Hz), 11/12 ~ 0.7:1.

4.5 Diethyl amino(3-(trifluoromethyl)phenyl)methylphosphonate hydrochloride (8)

A. To a crude diethyl phenylmethyleneamino(3-(trifluoromethyl)phenyl)methylphosphonate (12) 8 mL HCl (15%) was added, and the mixture was stirred for 4 hrs. Water was evaporated to 50%, the resulting white precipitate was filtered, dried and recrystallized from acetone. Yield 0.5 g (43%), white powder, mp 165°C. ¹H NMR spectrum (300 MHz, DMSO-d₆), δ, ppm: 9.31 (br, 3 H, NH₃+), 8.57-7.98 (m, 1 H, Ar), 7.91-7.85 (m, 1 H, Ar), 7.81-7.76 (m, 1 H, Ar), 7.73-7.66 (m, 1 H, Ar), 5.18 (d, 1 H, 3JHP 17.8 Hz, CHP), 4.15-4.04 (m, 2 H, OCH₂), 4.01-3.89 (m, 2 H, OCH₂), 1.23 (t, 3 H, J 6.9 Hz, CH₃), 1.10 (t, 3 H, J 6.9 Hz, CH₃). ³¹P NMR spectrum (162 MHz, DMSO-d₆), δ, ppm: 17.3. ¹⁹F NMR spectrum (376 MHz, DMSO-d₆), δ, ppm: -61.7. ¹³C NMR spectrum (150 MHz, DMSO-d₆), δ, ppm: 133.7 (d, JCF 5.4 Hz), 133.3 (d, JCF 4.7 Hz), 129.9, 129.5 (qd, JCF 32 Hz, JCF 2 Hz), 126.0 m, 125.9 m, 124.4
(q, JCP 272.2 Hz), 63.9 (d, JCP 6.4 Hz), 63.8 (d, JCP 6.4 Hz), 49.8 (d, JCP 150.2 Hz), 16.5 (d, JCP 5.7 Hz), 16.3 (d, JCP 5.7 Hz). HRMS (ESI): m/z 312.0898 [M + H]+; calcd for C12H17F3NO3P: 312.0962 [M + H]+.

B. To a solution of 1.37 g (5 mmol) of 1d and 1.55 g (5 mmol) of 2d in benzene (30 mL) 5 mg of TsOH was added. The mixture was refluxed in Dean-Stark apparatus for 4 hrs. After cooling, the mixture was washed with aq. NaHCO3, brine, and water. The solvent was evaporated in vacuum, the residue was triturated with petroleum ether and washed with Et2O (0.5 mL) to give 2.0 g of a crude mixture of 3c and 4c which was stirred with 5% HCl for 3 hrs. The resulting solution was washed with ether (3x5 mL), water was evaporated in vacuum, the residue was triturated with dry acetone to afford hydrochloride salt of aminophosphonate 8, yield 0.65 g (37%, based on ketophosphonate 2d). Spectral data were identical with a sample prepared by method A.

4.6 Amino(3-(trifluoromethyl)phenyl)methylphosphonic acid hydrochloride (9)

A mixture of diethyl amino(3-(trifluoromethyl)phenyl)methylphosphonate hydrochloride 8 (0.2 g, 0.58 mmol) and conc. HCl was stirred and heated at reflux for 8h. Water was evaporated, the resulting white solid was dried under vacuum. Yield 170 mg ( 85%), white powder, mp 270-273°C. 1H NMR spectrum (400 MHz, DMSO-d6), δ, ppm: 8.50 ( br, 5Н), 7.94-7.91 (m, 1Н, Ar), 7.84 -7.81 (m, 1Н, Ar), 7.72 -7.68 (m, 1Н, Ar), 7.65 -7.60 (m, 1Н, Ar), 4.58 (d, 1Н, 2JHP 17.1 Hz, CHP). 31P NMR spectrum (162 MHz, DMSO-d6), δ, ppm: 10.9. 19F NMR spectrum (376 MHz, DMSO-d6), δ, ppm: -63.3. 13C NMR spectrum (150 MHz, DMSO-d6), δ, ppm: 135.9, 133.1, 129.6, 129.3 (q, JCF 31 Hz), 125.5, 125.1, 124.4 (q, JCF 272.2 Hz), 52.3 (d, JCP 140 Hz).

Conflict of interest

There is no conflict of interest for this study.

References


