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Research Article

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

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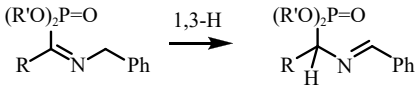
Abstract: The condensation of 1-amino-1-arylmethylphosphonates and aroylphosphonates results in the formation of 1,3-diaryl-1,3-diphosphorylated azapropenes, which incorporate iminophosphonate and aminophosphonate fragments in their structure. A reversible 1,3-proton shift in the C=N-C triad enables interconversion between various aminophosphonates. 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]



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 iminophosphonates 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

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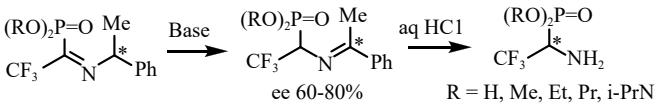
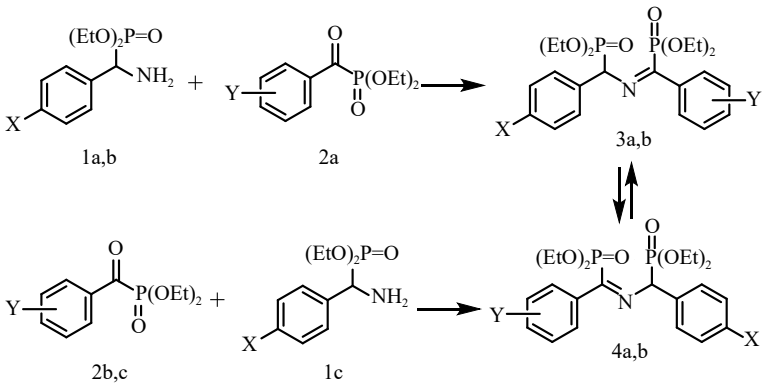
the Soloshonok group[13] (and references therein). These studies showcase the synthetic utility of this approach for the synthesis of fluorinated amines and amino acids.



Scheme 2. The irreversible 1,3-H transfer

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]



Scheme 3. The reversible 1,3-H transfer in diphosphorylated azapropenes

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. Experimental section

2.1 *General*

The ^{1}H, ^{19}F, ^{31}P and ^{13}C nuclear magnetic resonance spectroscopy (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 tetramethylsilane (TMS) (^{1}H, ^{13}C), $CFCl_3$ (^{19}F), and external 85%-H_3PO_4 (^{31}P) standards. liquid chromatography-mass spectrometry (LCMS) analyses were carried out on an Agilent 1200 LC system equipped with a G6140 MSD detector (ESI mode). Preparative high-performance liquid chromatography (HPLC) was performed on a

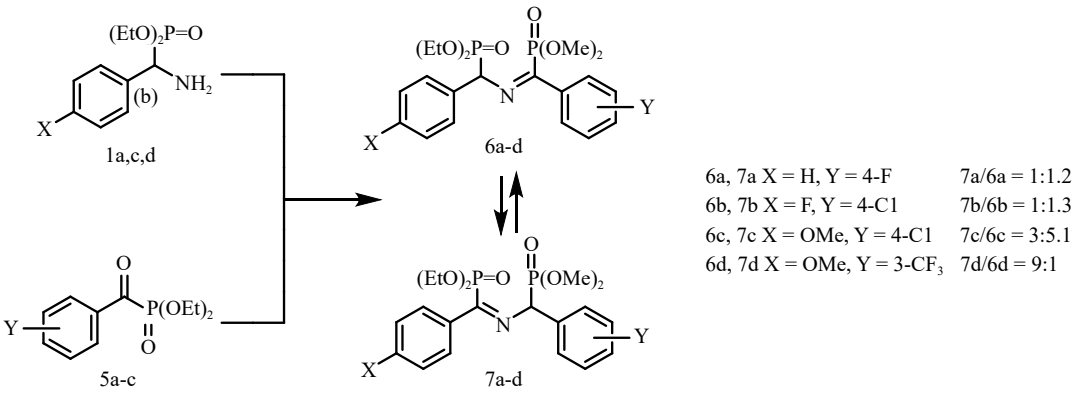
Shimadzu LC-8A equipped with a Phenomenex C18 column (30 × 150 mm). High-resolution mass spectrometry (HRMS) spectra were obtained on the Agilent 6200 (Q-ToF) mass spectrometry (MS) system. Melting points are uncorrected. Solvents were dried before use according to standard methods. Elemental analysis was carried out in the analytical laboratory of the Institute of Organic Chemistry, NAS of Ukraine.

2.2 *General procedure for the preparation 6a-d and 7a-d*

The mixture of respective aminophosphonates 1a, 1c, or 1d (5 mmol), ketophosphonate (5 mmol), and TsOH (5 mg) in benzene (30 mL) was refluxed in the Dean-Stark apparatus for 4 hours. The resulting mixture was washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. The solvent was evaporated, the residue was triturated with petroleum ether, and it was washed with small amounts of ether. Spectral data for isomeric mixtures of 6a-d and 7a-d are presented in Table 1, and respective equilibrium ratios are in Scheme 4.

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

Compound	δ_H, ppm; *J*, Hz			δ_P		δ_F
	CHP ($^2J_{HP}$; $^4J_{HP}$)	MeO-P ($^3J_{HP}$)	MeO-C	CHP	N=CP	
6a	5.08 (15; 3.2)	3.84 (11) 3.88 (11)	-	18.1	7.1	-110.4
7a	5.10 (14.7; 2.7)	3.67 (10.5) 3.68 (10.5)	-	20.6	4.9	-114.3
6b	5.10 (14.7; 2.7)	3.82 (10.9) 3.86 (11)	-	18.3	7.5	-114.4
7b	5.12 (14.7; 3.0)	3.68 (11) 3.70 (11)	-	20.5	5.3	-110.6
6c	4.99 (14.7; 3.0)	3.83 (11) 3.87 (11)	3.80	18.8	7.6	-
7c	5.18 (14.7; 2.9)	3.66 (10.8) 3.69 (10.8)	3.84	20.8	5.7	-
6d	5.00 (14.7; 3.0)	3.84 (11) 3.87 (11)	3.82	18.6	7.1	-63.0
7d	5.21 (14.7; 3.0)	3.68 (11) 3.72 (11)	3.85	20.3	5.5	-63.2



1: X = F (a), H (c), OMe (d); 5 Y = 4-F (a), 4-C1 (b), 3-CF_3 (c)

Scheme 4. Interconversions of X-substituted *α*-aminobenzylphosphonates 6 and Y-substituted *α*-aminobenzylphosphonates 7

2.3 *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 4 hours. The excess $SOCl_2$ was removed under vacuum, and the residue was distilled. Yield 3.77 g (70%), colorless liquid, bp 105-110 °C (0.07 mmHg). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), 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, 2H, Ar), 7.42-7.38 (m, 2H, Ar), 7.34-7.30 (m, ^{1}H, Ar), 4.96 (s, 2H, CH_2). ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: -62.5. ^{13}C NMR spectrum (150 MHz, $CDCl_3$), δ, ppm: 141.9, 137.7, 136.4, 132.2 (q, J_{CF} 1.1 Hz), 130.0 (q, J_{CF} 32.5 Hz), 128.9, 128.6, 128.0 (q, J_{CF} 3.6 Hz). 127.8, 127.3, 125.9 (q, J_{CF} 4.0 Hz), 123.8 (q, J_{CF} 272.2 Hz), 57.9.

2.4 *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 4 hours to afford crude **12** in a 90% yield. An analytically pure sample of compound 12 was obtained from 0.2 g of reaction mixture by preparative HPLC (CH_3CN–H_2O) performing gradient elution from 50 to 100% of CH_3CN. Yield 45 mg (23%), colorless oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.44 (d, ^{1}H, $^4J_{HP}$ 4.6 Hz, CH=N), 7.91-7.88 (m, ^{1}H, Ar), 7.87-7.82 (m, 3H, Ar), 7.57-7.52 (m, ^{1}H, Ar), 7.51-7.41 (m, 3H, Ar), 4.96 (d, ^{1}H, $^2J_{HP}$ 18.8 Hz, CHP), 4.11-3.99 (m, 4H, OCH_2), 1.25 (t, 3H, J 7.1 Hz, CH_3), 1.20 (t, 3H, J 7.1 Hz, CH_3). ^{31}P NMR spectrum (162 MHz, $CDCl_3$), δ, ppm: 18.3. ^{19}F NMR spectrum (376 MHz, $CDCl_3$), δ, ppm: -62.6. ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 164.8 (d, J_{CP} 15.1 Hz), 137.8 (d, J_{CP} 7.9 Hz), 135.6 (d, J_{CP} 3.9 Hz), 131.8 (d, J_{CP} 5.4 Hz), 131.4, 130.5 (qd, J_{CP} 3 Hz, J_{CF} 32 Hz), 128.8 (d, J_{CP} 2.5 Hz), 128.69, 128.65 (d, J_{CP} 1.6 Hz), 125.2 m, 124.4 m, 124.1 (q, J_{CF} 272.2 Hz), 73.1 (d, J_{CP} 151.8 Hz), 63.4 (d, J_{CP} 7.1 Hz), 16.3 (d, J_{CP} 6.2 Hz). HRMS (ESI): *m/z* 400.1211 $[M + H]^+$; calculated for $C_{19}H_{21}F_3NO_3P$: 400.1269 $[M + H]^+$.

Intermediate iminophosphonate **11** was detected in the reaction mixture when the reaction was carried out at 100 °C for 2 hours: δ_P 7.6 ppm, δ_{CH2N} 4.62 ppm (d, $^4J_{HP}$ 4.6 Hz), **11**/**12** ~ 0.7:1.

2.5 *Diethyl amino(3-(trifluoromethyl)phenyl)methylphosphonate hydrochloride (8)*

A. To a crude diethyl phenylmethyleneamino(3-(trifluoromethyl)phenyl)methylphosphonate (12), 8 mL of HCl (15%) was added, and the mixture was stirred for 4 hours. Water was evaporated to 50%, and the resulting white precipitate was filtered, dried, and recrystallized in acetonitrile. Yield 0.5 g (43%), white powder, mp 165 °C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 9.31 (br, 3H, NH_3^+), 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, $^2J_{HP}$ 17.8 Hz, CHP), 4.15-4.04 (m, 2H, OCH_2), 4.01-3.89 (m, 2H, OCH_2), 1.23 (t, 3H, J 6.9 Hz, CH_3), 1.10 (t, 3H, J 6.9 Hz, CH_3). ^{31}P NMR spectrum (162 MHz, DMSO-d_6), δ, ppm: 17.3. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: -61.7. ^{13}C NMR spectrum (150 MHz, DMSO-d_6), δ, ppm: 133.7 (d, J_{CP} 5.4 Hz), 133.3 (d, J_{CP} 4.7 Hz), 129.9, 129.5 (qd, J_{CF} 32 Hz, J_{CP} 2 Hz), 126.0 m, 125.9 m, 124.4 (q, J_{CF} 272.2 Hz), 63.9 (d, J_{CP} 6.4 Hz), 63.8 (d, J_{CP} 6.4 Hz), 49.8 (d, J_{CP} 150.2 Hz), 16.5 (d, J_{CP} 5.7 Hz), 16.3 (d, J_{CP} 5.7 Hz). HRMS (ESI): *m/z* 312.0898 $[M + H]^+$; calculated for $C_{12}H_{17}F_3NO_3P$: 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 the Dean-Stark apparatus for 4 hours. After cooling, the mixture was washed with aqueous $NaHCO_3$, brine, and water. The solvent was evaporated in vacuum, and the residue was triturated with petroleum ether and washed with Et_2O (0.5 mL) to give 2.0 g of a crude mixture of **3c** and **4c** which was stirred with 5% HCl for 3 hours. The resulting solution was washed with ether (3 × 5 mL), water was evaporated in vacuum, and the residue was triturated with dry acetone to afford the hydrochloride salt of aminophosphonate **8**, yielding 0.65 g (37% based on ketophosphonate **2d**). Spectral data were identical to a sample prepared by method A.

2.6 *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 8 hours. Water was evaporated, and the resulting white solid was dried under vacuum. Yield 170 mg (85%), white powder, mp 270-273 °C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm:

8.50 (br, 5H), 7.94-7.91 (m, ^{1}H, Ar), 7.84-7.81 (m, ^{1}H, Ar), 7.72-7.68 (m, ^{1}H, Ar), 7.65-7.60 (m, ^{1}H, Ar), 4.58 (d, ^{1}H, $^{2}J_{HP}$ 17.1 Hz, CHP). ^{31}P NMR spectrum (162 MHz, DMSO-d_6), δ, ppm: 10.9. ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm: -63.3. ^{13}C NMR spectrum (150 MHz, DMSO-d_6), δ, ppm: 135.9, 133.1, 129.6, 129.3 (q, J_{CF} 31 Hz), 125.5, 125.1, 124.4 (q, J_{CF} 272.2 Hz), 52.3 (d, J_{CP} 140 Hz).

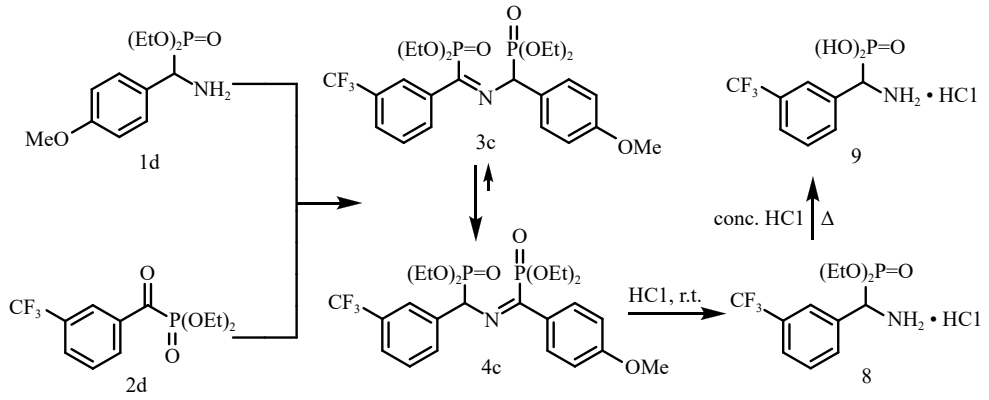
3. Results and discussion

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

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.

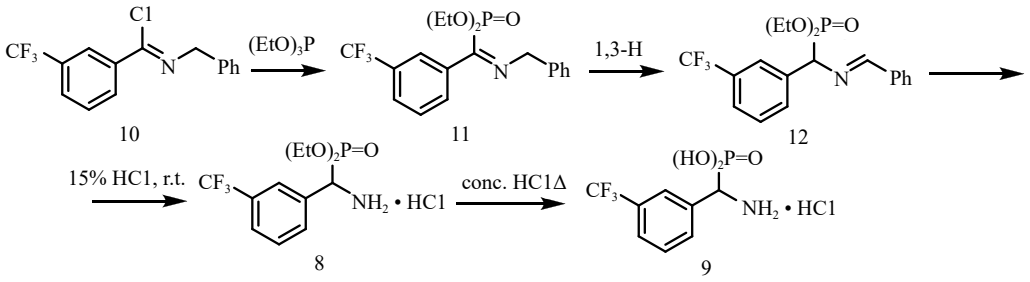
It is important to note that the ^{1}H and ^{31}P NMR spectral data of isomers 3 and 4 exhibit close similarities, making them challenging to distinguish. However, the ^{31}P NMR signals of the $(MeO)_2P(O)$ group are shifted approximately 2 ppm to the low-field region compared to the diethoxyphosphonyl substituent (Table 1). This result provides an opportunity to easily monitor the prototropic equilibrium using ^{31}P 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 ^{19}F 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 1).

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 toward 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 CF_3 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 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 ^{1}H, ^{31}P NMR (δ_p 7.6 ppm, δ_{CH2N} 4.62 ppm, d, $^{4}J_{HP}$ 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 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).

4. 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 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.

Conflict of interest

There is no conflict of interest for this study.

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