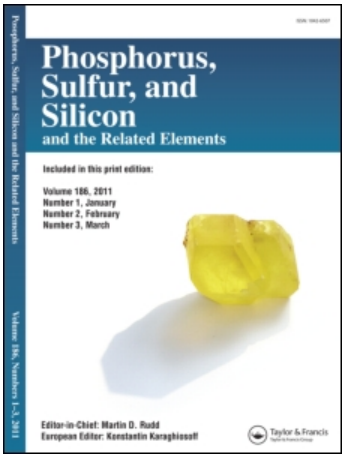

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Enamine-Imine Tautomerism in Cyclic (5-Alkyl-2,3,3-Trimethylpyrrolin-2-YL)Diethylphosphonate: A New Insight into Cyclization of β-Allenylaminophosphonates

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ENAMINE-IMINE TAUTOMERISM IN CYCLIC (5-ALKYL-2,3,3-TRIMETHYLPYRROLIN-2-YL)DIETHYLPHOSPHONATE: A NEW INSIGHT INTO CYCLIZATION OF β-ALLENYLAMINOPHOSPHONATES

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(5-alkyliden-2,3,3-trimethylpyrrolin-2-yl)diethylphosphonate ***3*** *were obtained by rearrangement of (5-alkyl-2,3,3-trimethylpyrrolin-2-yl)diethylphosphonate* ***2****. Rearrangement of* ***2*** *was induced at high temperature under an inert atmosphere. This air sensitive transformation requires a methyl group on the α position adjacent to the phosphonyl group. These results give new insight into cyclization of β-allenylaminophosphonates* ***1****.*

Keywords: β-allenylaminophosphonate; aminophosphonate; iminophosphonate; pyrrolines; tautomerism

INTRODUCTION

Because of their structural analogy to α-amino acids, α-amino phosphonates have received an increasing amount of attention. The potential of α-amino phosphonates as peptide mimics, enzyme inhibitors, and antibiotics and pharmacological agents has been established.[1–4]

Although a variety of synthetic methods of α-amino phosphonates are available, there are few reports about their reactivity and their

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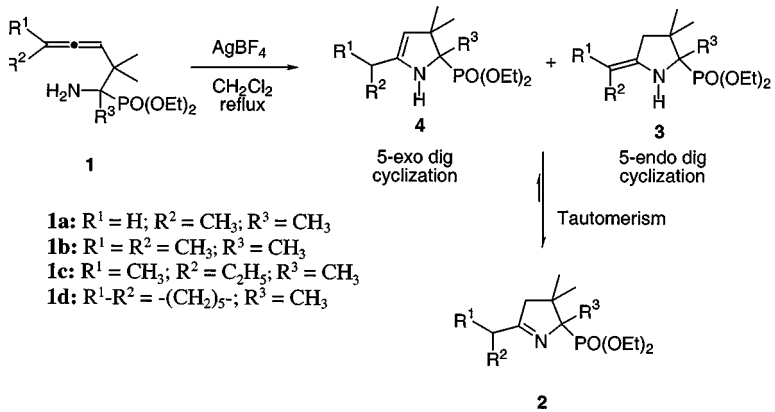
use in synthesis.[5,6] However iminophosphonates are somewhat even less known. They have been reported to undergo rearrangement into *N*-phosphoramidates.[7,8] But to the best of our knowledge no imine-enamine rearrangement was reported for these compounds.

Imines are known to exist in equilibrium with their enamine tautomers.[9–11] However, little is known about the factors governing this tautemorism and the relative energies of the tautomers. Thus many studies have been carried out by Clark and Parker[12] and by Ahlbrecht et al.[13,14] for the understanding of the imine-enamine equilibrium.

In connection with our interest in preparation of phosphonylated nitoxides, we have recently reported a strategy for the synthesis of 2,3,4-alkyl-5-phosphinylpyrrolines **2**. The latter arise from cyclization of the corresponding phosphonylated β-allenylamines **1**.[15,16] During the course of this synthesis, we showed that the cyclization of these β-allenylaminophosphonates **1** led to either 1-pyrrolines **2** by 5-*exo* cyclization or 1,2,3,6-tetrahydripyridines rings through a 6-*endo* cyclization. Formation of the iminophosphonate **2** was assumed to result from an enamine-imine tautomeric equilibrium of non characterized intermediates as outlined in Scheme 1. In this article, we wish to report on our preliminary results of this isomerization in the iminophosphonate series of type **2**.



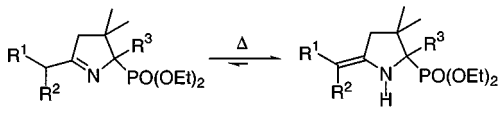
SCHEME 1

RESULTS AND DISCUSSION

A previously proposed mechanism for cyclization of amines **1** involved intermediates such **3** and **4** following a tautomeric equilibrium in which **2** was the favored form (Scheme 1).[9–11] On the other hand, considering

the geometry of amines **1** the probability of direct formation of **3** from **1** should be considered thoroughly, since we did not isolate **3** or **4** at that time.

Indeed, during purification procedure and after evaporation of the solvent, pyrrolines **2** were kept under high vacuum at 60°C (bath temperature) over 6 h, we observed a change in the ^{1}H and ^{31}P NMR spectra of this compound. The resulting spectra were assigned to the isomerized compound **3** following a tautomeric equilibrium from the iminophosphonate **2** (Scheme 2).



2 or 5 **3**

2a: $R^1 = H$; $R^2 = CH_3$; $R^3 = CH_3$; **5a:** $R^3 = H$
2b: $R^1 = R^2 = CH_3$; $R^3 = CH_3$; **5b:** $R^3 = H$
2c: $R^1 = CH_3$; $R^2 = C_2H_5$; $R^3 = CH_3$; **5c:** $R^3 = H$
2d: R^1-R^2 = -$(CH_2)_5$-; $R^3 = CH_3$; **5d:** $R^3 = H$

SCHEME 2

Under these conditions and using pure iminophosphonates **2b** and **2c** the results were even more convincing. The isomerization took place and could be considered as complete. However, when applied to **2a** and **2d** the rearrangement did not occur.

A new series of experiments was performed with **2b** and **2c**. Parameters were varied in order to settle the best conditions for the isomerization. Reactions were monitored by ^{1}H NMR based on the chemical shifts changes of the two methyl groups (d 1.12 ppm) and the proton on the isopropyl (2.66 ppm) for **2b** and methyl group (d 1.11 ppm) and the proton at (2.47 ppm) for **2c** as well as with ^{31}P NMR.

When heated at different temperatures up to 80°C for 4 to 8 h in presence of air, no isomerization was observed. In some cases complicated and broad ^{1}H NMR were recorded. Neither acidic or basic catalysis did help, and the starting material was recovered unchanged, even when several runs were carried out at different acid concentration for each solution. Moreover, the reaction was performed under argon at atmospheric pressure and 60°C (as it was under vacuum conditions when this tautomerism was observed in the first place) and led to the rearranged compounds **3b** and **3c**.

In order to identify the most significant factors affecting this tautomerism a series of experiments was carried out under argon atmosphere as outlined in Table I. Analysis of Table I shows the

TABLE I Optimization of the Rearrangement of **2b** under Different Conditions

Entry	T (°C)	Acid catalysis	Solvent[a]	Reaction time (h)	Ratio (imine-enamine)
1	60	+	Benzene	6	(50-50)
2	80	+	Benzene	6	(10-90)
3	60	−	Benzene	6	(60-40)
4	80	−	Benzene	6	(05-95)
5	60	+	—	6	(52-48)
6	80	+	—	6	(10-90)
7	60	−	—	6	(40-60)
8	80	−	—	6	(20-80)

[a]Changing solvent to chloroform or ethanol does not influence the reaction outcome.

preponderant effect of the temperature and of the inert atmosphere on this tautomerism. The interconversion reaction occurs at 60°C but is much faster at 80°C. Below 60°C the reaction evolves slowly and over 80°C no improvement is noticed but rather a decomposition of the enamine. Use of solvent or of acidic or basic catalysis did not show any effect. Thus the best conditions for the rearrangement are an inert atmosphere at 80°C using neat pyrroline.

Under these conditions **3** was generated quantitatively from **2** within 8 h. The changes in the chemical shifts that occurred in the ^{1}H NMR spectra are shown in Figure 1. Thus, for the generation of the enamine **3b** the signal of the CH_2 group on β position corresponding to an AB system at δ 2.25 ppm and 2.90 ppm undergoes a shift to δ 2.33 ppm

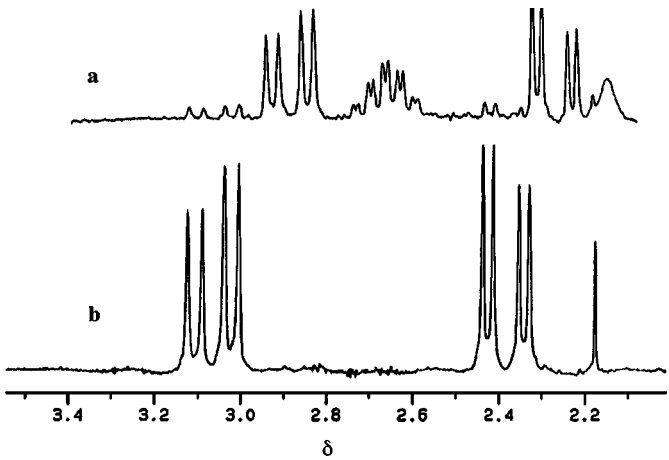


FIGURE 1 ^{1}H NMR (400 MHz) spectra in $CDCl_3$ of imine **2b**-enamine **3b** conversion: (a) sample after 30 min; (b) pure sample of enamine **3b** after isolation.

and 3.12 ppm as depicted in Figure 1. Regarding the isopropyl group, the signal of the two methyl groups at δ 1.12 was replaced by that at δ 1.45 ppm, whereas the signal of the proton completely disappeared (Figure 1). The enamines **3b** and **3c** were isolated after purification using silica gel column chromatography and were stable for several weeks, no back reaction was observed. Compound **3c** was obtained as a mixture of two isomers syn:anti (46:54) as shown by both ^{1}H and ^{13}C NMR.

Similarly, cyclization of **1b** proceeded under the same conditions at reflux in chloroform (61°C) leading to **2b** that started to rearrange into **3b**, but the tautomerism was much slower.

These results confirm that enamine **3** does not form as an intermediate in the cyclization of **1**, but arose through the tautomeric rearrangement of **2** under the specified conditions. It has been shown that one of the most important factors in the properties of enamines is the ability of the system to achieve a near planar conformation and to maximize overlap between the π-orbital of the double bond and the lone pair on the nitrogen. Bulky substituents on the double bond make it difficult to reach the most favorable conformation in the ground state or the transition state.[17–21] The rearrangement of **2** (*endo* C=N) to **3** (*exo* C=C) with less constraint allows a stabilization of the latter bond by its conjugation with the nitrogen lone pair. In contrast with pyrrolines **2**, compounds **5** (R^1 and R^2 = Alkyl, R^3 = H) (Scheme 2) did not give any rearrangement. Perhaps the lack of the methyl on the α position to the phosphonyl group involves less hindrance on the pyrroline ring. Regarding compounds **2a** and **2d**, the presence of only one methyl and a cyclohexyl group respectively does not stabilize enough the *exo* (C=C).

Semiempirical calculations AM1[10] and PM3[11] were carried out with complete geometry optimization (Table II). All the methods are in agreement with the experimental results except for compound **2d** and **3d**.

TABLE II Optimized Heat of Formation of Enamines and Imines Calculated by the PM3 and AM1 Methods

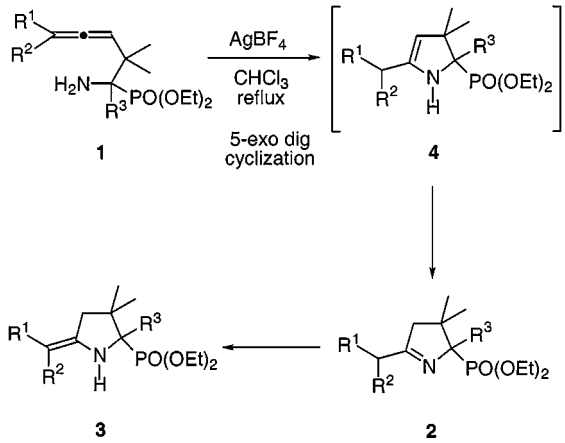
Method	Imine	Heat of formation (kcal/mol)	Enamine	Heat of formation (kcal/mol)	Stability of 3 over 2 (kcal/mol)
AM1	**2a**	−196.32	**3a**	−195.87	+0.45
PM3		−184.80		−182.69	+2.11
AM1	**2b**	−198.12	**3b**	−201.18	−3.06
PM3		−192.35		−193.58	−1.23
AM1	**2c**	−206.83	**3c**	−208.83	−2.00
PM3		−193.95		−194.59	−0.64
AM1	**2d**	−212.94	**3d**	−215.92	−2.98
PM3		−195.09		−196.33	−1.24

Much more than PM3, AM1 particularly strongly emphasizes the stability of the enamine form over the imine structure, even in the case of **2d** and **3d**. In the latter, since the isopropyl and cyclohexyl could be considered to be similar, we must conclude that the rearrangement in compound **2d** and **3d** is controlled mainly by steric interactions and not by electronic factors.

CONCLUSION

In summary, we have shown that enamines **3** are not formed directly from β-allenylaminophosphonates **1**, but result from the tautomeric rearrangement of the pyrrolines **2**. Thus β-allenylaminophosphonates **1** lead by cyclization to enamines **4**, and the latter isomerizes rapidly to afford imines **2** stable enough to be isolated. Furthermore when **2** is subjected to high temperatures enamine **3** was obtained as the thermodynamically stable compound. The case of iminophosphonates **2** ($R^3 = CH_3$) and **5** ($R^3 = H$) demonstrate the role played by the phosphenyl group and its environment. Indeed the steric effect in **2** leads to an imine-enamine rearrangement under specific conditions, but when this steric hindrance is weaker as it is in **5** this rearrangement is not observed.

We also showed that the rearrangement could occur sequentially without isolation of the pyrroline intermediate by running the cyclization of the aminophosphonate **1** at higher temperature under an inert atmosphere and longer reaction time.



SCHEME 3

Finally, from a mechanistic point of view, we could say that β-allenylaminophosphonates first undergo 5-exo-dig cyclization affording 2-pyrrolines **4** intermediates which instantly isomerizes to 1-pyrrolines **2** and **5**. The latter **2** upon a further rearrangement leads to Scheme **3**. Further investigations are in progress to establish a possible mechanism as well as a possibility of extension of this rearrangement.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were obtained in $CDCl_3$ with tetramethylsilane as internal reference and recorded on a Bruker AM 400 X spectrometer. Merck Silica gel 60 (230-400 Mesh) was used for column chromatography. Iminophosphonates **2** were prepared according to previously reported method.[15]

Typical Procedure for Rearrangement of Iminophosphonate 2

Under an argon atmosphere 1 mmol iminophosphonate **2** was heated at 80°C for 6 h and the reaction was monitored by ^{1}H and ^{31}P NMR. The resulting crude product was further purified by column chromatography. (5-isopropyliden-2,3,3-trimethylpyrrolidin-2-yl)diethylphosphonate **3b** (90% yield), yellowish oil. ^{1}H NMR (400 MHz) δ (ppm): 0.094 (s, 3H); 1.31 and 1.33 (2t, 6H, J = 7.0 Hz); 1.34 (s, 3H); 1.40 and 1.48 (2s, 6H); 1.45 (d, 3H, J = 16.6 Hz); 2.33–3.12 (AB system d, 2H, J = 16.8 Hz and J = 5.0 Hz (2.33 ppm), J = 16.8 Hz and J = 6.8 Hz (3.12 ppm); 4.13 (M, 4H). ^{13}C NMR (100.61 MHz) δ (ppm): 16.37 and 16.50 (2d, 2C, J = 5.8 Hz, $OCH_2\underline{C}H_3$); 16.68 (1C, $\underline{C}H_3$—C—P); 22.23 and 22.78 (2C, $CH_3)_2C$=C); 23.78 (d, 1C, J = 4.1 Hz, ($\underline{C}H_3)_2$ C—C); 25.68 (d, 1C, J = 10.8 Hz, ($\underline{C}H_3)_2$C—C); 44.19 (d, 1C, J = 4.6 Hz, $\underline{C}$—$(CH_3)_2$); 50.31 (1C, C=C—$\underline{C}H_2$-); 61.68 and 63.40 (2d, 2C, J = 7.5 Hz, $O\underline{C}H_2CH_3$); 79.39 (d, 1C, J = 148.3 Hz, C—P); 82.43 (1C, $(CH_3)_2\underline{C}$=C); 185.15 (d, 1C, J = 11.0 Hz, C=$\underline{C}$—N). ^{31}P NMR (40.53 MHz) δ (ppm): 26.07. Analysis calcd for $C_{14}H_{28}NO_3P$,: C: 58.10, H: 9.76; N: 4.84; found: C: 57.53; H: 9.64; N: 4.66. (5-(1-methylpropyliden)-2,3,3-trimethylpyrrolidin-2-yl)diethylphosphonate **3c**. (88% yield), yellowish oil. ^{1}H NMR (200 MHz) δ (ppm): 0.91 and 0.93 (2s, 3H); 0.92 and 0.94 (2t, 3H, J = 7.4 Hz); 1.29 and 1.32 (2s, 3H); 1.31 (t, 6H, J = 7.0 Hz); 1.37 and 1.47 (2s, 3H); 1.43 and 1.44 (2d, 3H, J = 16.1 Hz); 1.55–2.00 (2M, 2H); 2.29 and 2.32 (2q., 1H, J = 17.0 Hz and J = 4.9 Hz); 2.98 and 3.06 (2q., 1H, J = 17.0 Hz and J = 6.8 Hz). ^{13}C NMR (100.61 MHz) δ (ppm): 7.51 and 7.53 (1C, —$CH_2\underline{C}H_3$); 16.38 and 16.61 (M, 2C, $OCH_2\underline{C}H_3$); 16.61 and

16.77 (1C, $\underline{C}H_3$—C—P); 19.27 and 19.84 (1C, $\underline{C}H_3$—C═C); 23.73 and 23.90 (2d, 1C, J = 3.5 Hz, $(\underline{C}H_3)_2$C—C); 25.48 and 25.90 (2d, 1C, J = 10.6 Hz, $(\underline{C}H_3)_2$C—C); 28.05 and 29.05 (1C, CH_3—$\underline{C}H_{2^-}$); 44.12 and 44.29 (2d, 1C, J = 4.5 Hz, $\underline{C}$—$(CH_3)_2$); 50.71 and 51.01 (1C, C═C—$\underline{C}H_{2^-}$); 61.66 and 61.84, 63.33 and 63.74 (4d, 2C, J = 7. Hz and J = 6 Hz, O$\underline{C}H_2CH_3$); 78.86 and 79.12 (2d, 1C, J = 149.0 Hz, $\underline{C}$—P); 84.78 and 85.25 (1C, $CH_3CH_2\underline{C}$═C); 184.82–185.15 (M, 1C, C═$\underline{C}$—N, J = 11.0 Hz). ^{31}P NMR (40.53 MHz) δ (ppm): 25.11 and 25.99.

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