Stereoselective Synthesis, Molecular Geometry, and Oxidation of (5-Isopropyl-2-methylpyrrolidin-2-yl)phosphonates

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Received May 10, 1993 (Revised Manuscript Received April 12, 1994•)

Intramolecular aminomercuration of (1-amino-1,5-dimethylhex-4-enyl)phosphonates was shown to be regio- and stereoselective and to lead to (5-isopropyl-2-methylpyrrolidin-2-yl)phosphonates. The stereoselectivity was shown to be controlled by the experimental conditions. The configurations of the chiral carbons for the diastereomers were determined by X-ray and NMR analysis. Oxidation of the pyrrolidin-2-ylphosphonates with *m*-CPBA led to diastereomeric nitroxides exhibiting different phosphorus splitting and different half-lives.

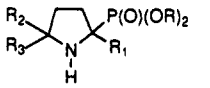
Introduction

As a part of our program of research on the characterization of new stable nitroxides exhibiting a large hyperfine coupling with a one-half spin nucleus,[1,4k] we were interested in the synthesis of pyrrolidin-2-ylphosphonates with no hydrogens on the carbons bound to the nitrogen. These cyclic α-amino phosphonates could be readily oxidized to yield the desired nitroxides.

A great number of acyclic α-amino phosphonates and their corresponding acids have been prepared in the past fifteen years,[2] and many phosphorus analogs of natural α-amino acids were found to exhibit useful biological activity.[3] In the course of this research a few limited methods have been developed to prepare pyrrolidin-2-ylphosphonates, and these methods were devoted mainly to synthesizing the phosphorus analogs of proline[4] (Scheme 1).

To the best of our knowledge, however, these methods cannot be extended to prepare pyrrolidin-2-ylphosphonates bearing quaternary carbons adjacent to the nitrogen atom. We looked therefore for a new synthetic approach to these phosphonates which could permit varying the degree of substitution at the carbons adjacent to the nitrogen atom. We found that intramolecular aminomercuration of δ- or ϵ-ethylenic α-amino phosphonates

Scheme 1

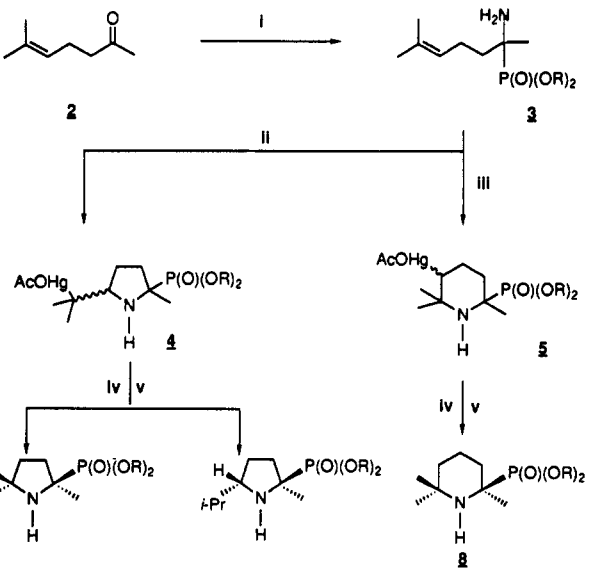


Phosphorus analog of proline: R = R_1 = R_2 = R_3 = H

6: R = R_1 = Me; R_2 = *i*-Pr; R_3 = H

7: R = Et; R_1 = Me; R_2 = *i*-Pr; R_3 = H

Scheme 2[a]



[a] (i) $HP(O)(OR)_2$, NH_3; (ii) $Hg(OAc)_2$, MeC(O)Me; (iii) $Hg(OAc)_2$, THF/H_2O (1/1); (iv) $NaBH_4$, NaOH, $(Et_3NCH_2Ph)^+Cl^-$, CH_2Cl_2; (v) $NaBH_4$, NaOH, THF/H_2O (1/1).

led to reasonable yields of these compounds (45–65%), and we recently described the preparation of pyrrolidin-2-yl- and piperidin-2-ylphosphonates with $R_1 = R_2 = R_3$ = Me, R = Et (Scheme 1) and their oxidation to the corresponding stable nitroxides.[4k]

We now describe the aminomercuration of **3** (Scheme 2), which yielded the corresponding (5-isopropyl-2-methylpyrrolidin-2-yl)phosphonates and was shown to be highly

• Abstract published in *Advance ACS Abstracts*, May 15, 1994.

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regioselective and stereoselective. Pure diastereomers were isolated and their structures were determined by X-ray and NMR analysis. The (5-isopropyl-2-methylpyrrolidin-2-yl)phosphonates were oxidized with *m*-CPBA and the resulting pyrrolidinoxyl radicals were studied by ESR. The half-lives of the diastereomeric nitroxides were shown to be significantly different and to depend on the nature of the solvent.

Results and Discussion

Synthesis of 6a,b and 7a,b. Bubbling ammonia into a solution of 6-methyl-5-hepten-2-one (**2**) (Scheme 2) in a dialkyl phosphite afforded the δ-alkenyl amino phosphonates **3** (R = Me or Et), in about 70% yield.[4k,5] Cyclization of these α-amino phosphonates was carried out by treatment with mercuric acetate in either acetone or THF/water (1/1). Cyclization in acetone was followed by removal of the solvent and then reduction of the organomercury compound in methylene chloride, using a phase-transfer catalysis procedure[6] (KBH_4, NaOH, $(Et_3NCH_2Ph)^+Cl^-$). This sequence yielded, with a high stereoselectivity, a mixture of diastereoisomers **6a/6b** (12/88) for the dimethyl phosphonate and **7a/7b** (10/83) for the diethyl phosphonate. The intramolecular aminomercuration of **3** (R = Me) is regiospecific, and only 7% of piperidin-2-ylphosphonate **8** (identified by comparing its NMR data with those of an authentic sample[4k]) were obtained when R = Et.

Tokuda et al.[7] have already stressed the influence of the experimental conditions on the stereoselectivity of mercury(II) intramolecular aminomercurations leading to 2,5-disubstituted pyrrolidines. For example, the stereoselectivity observed in organic solvents ($CHCl_3$, THF) is changed when the reaction is carried out in presence of water (THF/H2O, 1/1). When the cyclization of **3** was performed in THF/H_2O and followed by reduction of the organomercury compound in the same solvent, using the classic procedure of Perié et al.[8] ($NaBH_4$, NaOH), the stereoselectivity changed. The ratios of **6a/6b** and **7a/7b** were, respectively, 88/12 and 80/17. Moreover, using these experimental conditions, the cyclization remained regiospecific for R = Me, while only 3% of **8** was formed for R = Et. The cyclization of **3** (R = Et) to form **4** was monitored by NMR and was shown to take about 5 min to complete (absence of ethylenic hydrogens). It is worth noting, however, that a significant amount of **4** was always converted back to **3** upon reduction. Borohydride reductions of organomercurials involve free radical chains, and the conversion of **4** to **3** upon reduction could be explained as shown on Scheme 3.

Molecular Geometry. A pure sample of **7a** was obtained by successive recrystallizations of a mixture of **7a/7b** (80/17) and **8** in pentane at −20 °C. Then slow crystallization in heptane at 20 °C afforded triclinic crystals, which were acceptable for an X-ray structure analysis.[9a] The molecular structure of **7a** is shown in Figure 1. The two chiral centers (C1 and C5) have the same configuration, the isopropyl and diethoxyphosphoryl groups being in a cis position. The torsional angle $NC_1C_2C_{11}$ is small (7.18°), and the ring has an envelope form, with the carbon C_5 at the flap of the envelope bearing a pseudoequatorial isopropyl group.

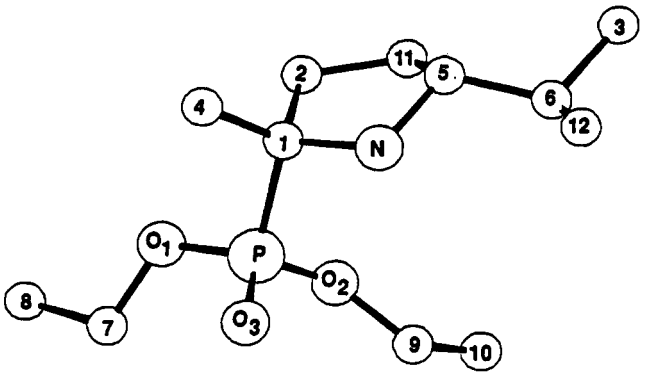

Figure 1. X-ray structure of diastereomer **7a**.

Scheme 3

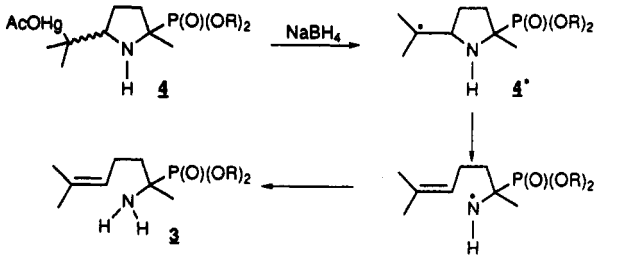

Table 1. Characteristic Coupling Constants *J* (Hz) and Chemical Shifts (C_6H_6, ppm) for Diastereomers 7a,b and 6a,b

	7a[a]	6a	7b	6b
$^3J_{P-C_5}$	10.36	10.46	2.11	2.41
$^3J_{P-C_{11}}$	5.73	5.53	2.72	2.72
$^1J_{P-C_1}$	170.8	171.50	156.50	157.80
δ ^1H (C_5)	2.63	2.69	2.90	3.01
δ ^{31}P	30.40	28.60	32.40	30.60

[a] For the atom numbering, see Figure 1.

Pure samples of **6a** and **6b** were likewise obtained by successive recrystallizations of the crude mixture obtained by intramolecular aminomercuration of **3** (R = Me). The relative configuration at C_1 and C_5 in diastereoisomers **6a** and **6b** was assigned through the comparison of their ^1H, ^{13}C, and ^{31}P NMR spectra with those of **7a** and **7b** (Table 1). On the basis of the similarity of their NMR data, it is reasonable to assume that the relative configuration at C_1 and C_5 is the same in **7a** and **6a** or in **7b** and **6b**.

Oxidation. ESR Study. Pure samples of **6a**, **6b**, **7a**, and **7b** were oxidized with 2 equiv of *m*-CPBA in deoxygenated pentane or methylene chloride, and the resulting nitroxides were studied by ESR. The ESR features of these nitroxides are listed in Table 2.

The a_H and a_P coupling (Table 2) in **6a** (O•) and **7a** (O•), or **6b** (O•) and **7b** (O•), are very similar, thus providing evidence that the C_1 and C_5 configurations are the same

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Table 2. ESR Features[a] (25 °C) of Nitroxides Derived from 6a, 6b, 7a, and 7b

nitroxide	a_N(G)	a_P(G)	a_H(G)	solvent
6a (O•)	14.0	46.1	20.6	*n*-pentane
7a (O•)	14.0	46.0	20.5	*n*-pentane
6b (O•)	13.5	51.2	20.7	*n*-pentane
	14.0	49.5	22.0	CH_2Cl_2
7b (O•)	13.5	51.2	21.0	*n*-pentane
	13.8	49.4	21.9	CH_2Cl_2

[a] $g = 2.0060 \pm 0.0002$.

in **6a** and **7a**, or **6b** and **7b**. It is noteworthy that **6a** (O•) and **7a** (O•) are much less persistent than **6b** (O•) or **7b** (O•), and in methylene chloride we never succeeded to obtain clear spectra of the former. Force field calculations on **6a** (O•) and **7a** (O•) have shown that these nitroxides could adopt many conformations very close in energy and exhibiting different a_H and a_P couplings.[9b] On the other hand, in **6a** (O•) and **7a** (O•) the C_5 hydrogen atom is less hindered than in **6b** (O•) and **7b** (O•) and thus disproportionation of the former nitroxides should be faster. Finally, we oxidized the diastereomeric mixture of mercuric compounds **4** obtained by cyclizing the amino phosphonates **3** (R = Et) in acetone (Scheme 2). The ESR spectrum obtained was simulated assuming the presence of only one diastereomeric nitroxide and the existence of a γ-coupling with the ^{199}Hg ($I = 1/2$) nucleus (a_N = 14.2 G, a_H = 22.6 G, a_P = 50.5 G, a_{Hg} = 10.0 G (18%)).

Experimental Section

Instrumentation. ^{31}P NMR spectra were recorded at 100 MHz with 85% H_3PO_4 as external reference. ^1H and ^{13}C NMR spectra were recorded at 200 or 400 MHz. ESR spectra were recorded at X-band (9.79 GHz).

Dialkyl (1-Amino-1,5-dimethyl-4-enyl)phosphonates 3. Gaseous ammonia was bubbled through a stirred mixture of hept-5-en-2-one (0.10 mol) and dialkyl phosphite (0.11 mol) at 60 °C. The progress of the reaction was monitored by TLC. The reaction was generally complete within 4 h. The reaction mixture was then treated with 1 M aqueous HCl and extracted with ether. Aqueous NaOH was then added to pH 10 and the mixture was then extracted with ether. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the α-amino phosphonate as a yellow oil in 70% yield.

Dimethyl (1-amino-1,5-dimethyl-hex-4-enyl)phosphonate: bp 118–120 °C at 10^{-2} mm; IR (neat) 3300–3380, 1230; ^1H NMR (C_6D_6) δ 1.26 (3H, d, J_{P-H} = 16 Hz), 1.59 (3H, s), 1.66 (3H, s), 1.70–2.20 (6H, m), 3.51 (3H, d, J_{P-H} = 10 Hz), 3.54 (3H, d, J_{P-H} = 10 Hz), 5.14 (1H, m); ^{31}P NMR (C_6D_6) δ 33.1; ^{13}C NMR (C_6D_6) δ 17.59, 21.94 (d, J_{P-C} = 7.65 Hz), 22.50, 25.75, 38.09 (d, J_{P-C} = 4.02 Hz), 52.37 (d, J_{P-C} = 146.10 Hz), 62.04 (d, J_{P-C} = 7.24 Hz), 62.25 (d, J_{P-C} = 7.65 Hz), 124.95, 131.43. Anal. Calcd for $C_{10}H_{22}NO_3P$: C, 51.05; H, 9.43; N 5.95. Found: C, 51.11; H, 9.49; N, 5.94%.

Diethyl (1-amino-1,5-dimethyl-hex-4-enyl)phosphonate: bp 130 °C at 10^{-2} mm; IR (neat) 3300–3380, 1230; ^1H NMR (C_6D_6) δ 1.06 (3H, t, J = 7 Hz), 1.07 (3H, t, J = 7 Hz), 1.29 (3H, d, J_{P-H} = 16.5 Hz), 1.58 (3H, s), 1.64 (3H, s), 1.77–2.3 (6H, m), 4 (4H, m), 5.2 (1H, m); ^{31}P NMR (C_6D_6) δ 31; ^{13}C NMR (C_6D_6) δ 16.62, 17.61, 22.03 (d, J_{P-C} = 7.75 Hz), 22.50, 25.75, 38.07 (d, J_{P-C} = 3.82 Hz), 52.01 (d, J_{P-C} = 146.10 Hz), 62.04 (d, J_{P-C} = 7.24 Hz), 62.25 (d, J_{P-C} = 7.65 Hz), 125.09, 131.33. Anal. Calcd for $C_{12}H_{26}NO_3P$: C, 54.74; H, 9.95; N, 5.32. Found: C, 54.97; H, 9.99; N, 5.32%.

Dimethyl (5-Isopropyl-2-methylpyrrolidin-2-yl)phosphonate (6a). Compound **3** (R = Me, 2.35 g, 10^{-2} mol) was added dropwise to a suspension of mercuric acetate (10^{-2} mol) in 20 mL of THF/water (1:1). The mixture was stirred for 12 h and then treated with 4.5 mL of a 2.5 M aqueous NaOH solution containing 10^{-2} mol of $NaBH_4$. The mixture was stirred for 1 h and then saturated with NaCl and extracted with ether. The organic phase was dried over Na_2SO_4 and then evaporated under reduced pressure to afford 1.70 g of a mixture of cyclic products **6a**/**6b** (88/12) and starting compound (according to NMR the ratio (**6a** + **6b**)/**3** = 3/2). After several crystallizations from pentane at −20 °C the diastereomer **6a** was obtained: mp 74 °C; ^1H NMR (C_6D_6) δ 0.79 (3H, d, J = 6.5 Hz), 0.88 (3H, d, J = 6.5 Hz), 1.3 (3H, d, J_{P-H} = 16 Hz), 1.51–2.36 (6H, m), 2.67 (1H, m), 3.54 (3H, J_{P-H} = 10 Hz), 3.6 (3H, J_{P-H} = 10 Hz); ^{31}P (C_6D_6) δ 30.4; ^{13}C NMR (C_6D_6) δ 19.7, 20.4, 24.4 (d, J_{P-C} = 7.9 Hz), 29.8 (d, J_{P-C} = 5.5 Hz), 34.2, 35.2; 60.1 (d, J_{P-C} = 171.5 Hz), 64.4 (d, J_{P-C} = 10.5 Hz). Anal. Calcd for $C_{10}H_{22}NO_3P$: C, 51.05; H, 9.43; N, 5.95. Found: C, 51.07; H, 9.43; N, 5.89%.

Dimethyl (5-Isopropyl-2-methylpyrrolidin-2-yl)phosphonate (6b). Compound **3** (R = Me, 2.35 g, 10^{-2} mol) was added dropwise to a suspension of mercuric acetate (10^{-2} mol) in 20 mL of acetone. After stirring for 12 h, the solution was concentrated under reduced pressure. The solid residue was dissolved in 25 mL of CH_2Cl_2 and added to an aqueous solution of benzyltriethylammonium chloride (5 g in 50 mL). To the vigorously stirred mixture was added an aqueous solution of NaOH (2 g in 10 mL) and 10^{-2} mol of $NaBH_4$. The mixture was stirred for 1 h and then extracted with CH_2Cl_2. The organic phase was washed with water (3 × 20 mL) and then dried with Na_2SO_4. After evaporation of solvent, 1.80 g of a mixture containing the cyclic products **6a**/**6b** (12/88) and the starting compound was obtained (according to NMR the ratio (**6a** + **6b**)/**3** = 5). Several crystallizations from pentane at −20 °C afforded the diastereomer **6b**: mp 53 °C; ^1H NMR (C_6D_6) δ 0.77 (3H, d, J = 6.5 Hz), 0.88 (3H, d, J = 6.5 Hz), 1.34 (3H, d, J_{P-H} = 16 Hz), 1.47–2.3 (6H, m), 2.98 (1H, m), 3.53 (6H, J_{P-H} = 10 Hz); ^{31}P (C_6D_6) δ 32.5; ^{13}C NMR (C_6D_6) δ 19.7, 20.3, 25.7 (d, J_{P-C} = 7.6 Hz), 29.7 (d, J_{P-C} = 2.7 Hz), 34.3, 34.8, 60.0 (d, J_{P-C} = 157.8 Hz), 66.5 (d, J_{P-C} = 2.4 Hz). Anal. Calcd for $C_{10}H_{22}NO_3P$: C, 51.05; H, 9.43; N, 5.95. Found: C, 51.08; H, 9.35; N, 5.92%.

Diethyl (5-Isopropyl-2-methylpyrrolidin-2-yl)phosphonates 7a and 7b. Stereoisomers **7a** and **7b** were likewise obtained with comparable stereoselectivities and yields. **7a**: mp 65 °C; ^1H NMR (C_6D_6) δ 0.81 (3H, d, J = 6.5 Hz), 0.89 (3H, d, J = 6.5 Hz), 1.12 (3H, d, J = 6.8 Hz), 1.14 (3H, t, J = 6.8 Hz), 1.33 (3H, d, JP_{-H} = 16 Hz), 1.49–2.4 (6H, m), 2.69 (1H, m), 4.09 (4H, m); ^{31}P NMR (C_6D_6) δ 28.6; IR (neat) 3275 (N–H); 1250 (P=O); ^{13}C NMR (C_6D_6) δ 19.7, 20.5, 24.6 (d, J_{P-C} = 7.8 Hz), 30.0 (d, J_{P-C} = 5.7 Hz), 34.3, 35.3, 59.8 (d, J_{P-C} = 170.8 Hz), 64.5 (d, J_{P-C} = 10.4 Hz). Anal. Calcd for $C_{12}H_{26}NO_3P$: C, 54.74; H, 9.45; N, 5.32. Found: C, 54.6; H, 9.63; N, 5.24%.

7b: mp 58 °C; ^1H NMR (C_6D_6) δ 0.77 (3H, d, J = 6.5 Hz), 0.87 (3H, d, J = 6.5 Hz), 1.09 (6H, t, J = 6.8 Hz), 1.34 (3H, d, J_{P-H} = 16 Hz), 1.4–2.3 (6H, m), 3.01 (1H, m), 4.01 (4H, m); ^{31}P NMR (C_6D_6) δ 30.5. IR (neat) 3275 (N–H), 1250 (P=O); ^{13}C NMR (C_6D_6) δ 19.7, 20.3, 25.8 (d, J_{P-C} = 7.9 Hz), 29.7 (d, J_{P-C} = 2.7 Hz), 34.4, 34.7, 59.8 (d, J_{P-C} = 156.5 Hz), 66.5 (d, J_{P-C} = 2.1 Hz). Anal. Calcd for $C_{12}H_{26}NO_3P$: C, 54.74; H, 9.95; N, 5.32. Found: C, 54.69; H, 9.91; N, 5.26%.