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Stereoselective reduction and reductive dephosphonylation of β-iminophosphonates

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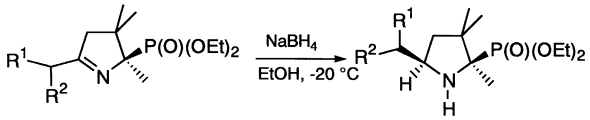
Abstract—Proline-like 2,4-dialkyl-5-phosphonylpyrrolidines **2** were obtained stereoselectively by reduction of the corresponding β-iminophosphonates **1** with $NaBH_4$. The detailed characterization of compounds **2** was accomplished by ^1H and ^{13}C NMR as well as by crystal structure analysis. When **1** was reduced with $LiAlH_4$ the reaction gave dephosphonylated pyrrolidines **3**. The latter method is suitable for providing substituted pyrrolidines regioselectively. A possible mechanism for the dephosphonylation is proposed. © 2002 Elsevier Science Ltd. All rights reserved.

Pyrrolidine derivatives are attractive synthetic targets[1] because they occur in numerous biological compounds[2] and some are pharmaceutically important.[3] Substituted pyrrolidines have been obtained by pyrrolidine construction, e.g. photocyclization of *N*-chloramines,[4] reductive amination of 1,4-diketones[5] and metal-catalyzed cyclizations.[6] In continuation of our concept of using stable free radicals, extensively developed in our laboratories, we became interested in pyrrolidine derived β-phosphonylated nitroxides. Nitroxide radicals are becoming more important due to the need of materials which enjoy new or improved physical and chemical properties. After being used in ESR as spin probes,[7] they have also been applied as contrast-enhancing agents for magnetic resonance imaging.[8] They also found a successful application in the field of living free radical polymerization.[9] In line with this project and taking aim at new pyrrolidines, we recently reported the synthesis of β-allenyl aminophosphonates and their cyclization into β-iminophosphonates **1**.[10]

On one hand, imine and iminium salts can be readily reduced by metallic hydrides such as $LiAlH_4$ or $NaBH_4$ and its derivatives.[11] Another consideration which must be addressed involves the control of stereochemistry. Indeed, reduction of substituted cyclic imines with hydrides displays varying stereoselectivity, depending both on the reagent and the substrate.[12] For instance, 2,5-dialkylpyrrolines gave the *cis*-pyrrolidines with DIBAL-H, while the *trans*-isomer is favored with LAH/Me_3Al. Hydrides such $NaBH_4$ or $NaBH_3CN$ afford less selectivity. Likewise, *cis*-pyrrolidines were obtained by treatment of 3- and 4-ethoxycarboxy-1-pyrrolines with $NaBH_4$.[13]

On the other hand, β-functionalized phosphonates undergo dephosphonylation upon reduction. Although various methods and reagents[14] have been used to reduce a C–P^V bond into a C–H bond, the known chemical methods for C–P^V cleavage are of limited generality. Moreover, there is only one literature[15] reference involving the C–P bond reduction of β-keto-1-phosphonato esters. It was pointed out that there is no general method for cleavage of the C–P bond in β-keto phosphonates.[16] Recently, dephosphonylation of β-keto phosphonates with $LiAlH_4$ has been reported.[17] The phosphonate was used as a temporary activating group.



1

1a $R^1 = CH_3$, $R^2 = H$
1b $R^1 = R^2 = CH_3$
1c $R^1 = CH_3$, $R^2 = CH_2CH_3$
1d R^1, $R^2 = -(CH_2)_5-$

cis-isomer **2**

2a
2b
2c
2d

Scheme 1.

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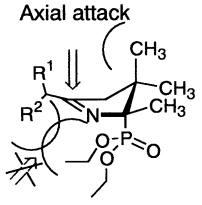
However β-iminophosphonates have not been investigated. In this paper we wish to report our preliminary results on the stereoselective reduction of β-iminophosphonates **1** with $NaBH_4$ and on their unprecedented reductive dephosphonylation (Scheme 1).

We first observed the dephosphonylation of β-iminophosphonate **1b** when reacted with $NaBH_4$ using the conditions described in the literature.[13,18] This led to complicated mixtures in which no product of type **2** could be detected. Although disappointing, the experiments were repeated and the reaction was monitored by ^{31}P NMR. It was gratifying to find that reduction had occured. The ^{31}P NMR chemical shift of the only product formed was at δ 27 ppm. However, this peak tended to disappear and another peak appear at δ 6.3 ppm, which corresponds to the diethylphosphite ^{31}P NMR chemical shift. The intermediate aminophosphonate **2b** appeared to be extremely sensitive under the reaction conditions. After several trials, under the mildest conditions, we were able to isolate **2b** which was crystallized from pentane. Its structure was unequivocally confirmed by spectroscopic and X-ray methods as the *cis*-isomer **2b**.[10b] Analysis of the mother solution did not show any *trans*-isomer.

Keeping in mind that $NaBH_4$ is a small reducing reagent, one could expect that coordination of the sodium of the $NaBH_4$ by the phosphonyl oxygen could direct hydride addition to the imine and give the *trans*-isomer. The stereoselectivity in the reduction of pyrrolines **1** can be rationalized by assuming a steric effect between the diethylphosphonyl and the methyl groups.

Indeed, this particular steric hindrance puts the diethylphosphonyl group in a pseudoaxial position, and therefore makes possible the attack from the less shielded face (Scheme 2).



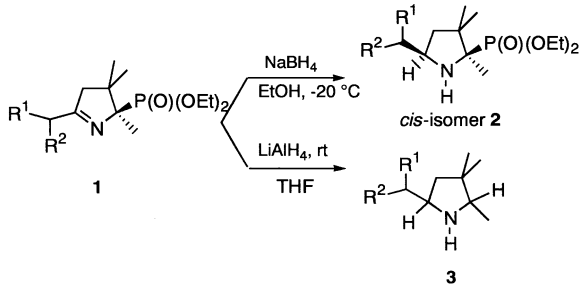
Scheme 2.

Nevertheless, the pyrroline **1c** needed 6 equiv. of $NaBH_4$ for reduction and a reaction at room temperature to afford 70% conversion as shown by ^{31}P NMR. This difference in reactivity could arise from the steric hindrance by the cyclohexyl group.

It is worth noting that the amount of $NaBH_4$ used and the temperature were both important. The highest conversion rate (80%) was reached by using 0.5 equiv. of $NaBH_4$ at −20°C over 4 h.[19] If the reaction was run for longer the pyrrolidine undergoes dephosphonylation, and with a larger amount of $NaBH_4$ this decomposition occurs much faster.

^{31}P NMR analysis showed that complete dephosphonylation is reached after 8 h leading to complicated mixtures. In contrast, after their crystallization, the aminophosphonates **2** are stable in nonpolar solvents as well as in crystalline form (Table 1).

In contrast to $NaBH_4$, reaction with $LiAlH_4$ did not afford compounds **2**. Although the starting materials were completely consumed on reaction of β-iminophosphonates **1** with $LiAlH_4$[20] in THF, complicated mixtures resulted. Purification by chromatography yielded pyrrolidines **3** as a mixture of stereoisomers in a 1:1 ratio (Table 1), along with side products which could not be identified. Thus, β-iminophosphonates **1** were dephosphonylated by reaction with 3 equiv. of $LiAlH_4$ in THF at 20°C for 1 h and then quenching with a 4N NaOH aqueous solution (Scheme 3). Additionally, the reaction with the nucleophilic L-Selectride (tri-*sec*-butylborohydride) produced **2a** as the sole product. In the case of the electrophilic 9-BBN, **2a** was obtained along with a small amount of **3a**. No significant change was noticed upon further addition of 9-BBN. It has

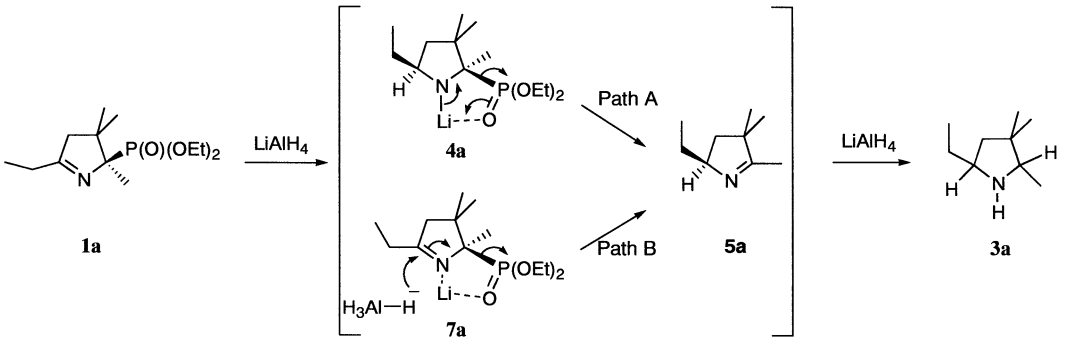


Scheme 3.

Table 1. Reduction of β-iminophosphonates **1**

Substrate	R^1	R^2	Reagent	Time (h)	Products	Yield (%)
1a	Me	H	$NaBH_4$	4	**2a**	72[a]
1b	Me	Me	$NaBH_4$	4	**2b**	64[a]
1c	Me	Et	$NaBH_4$	4	**2c**	61[a]
1d	$-(CH_2)_5-$	$-(CH_2)_5-$	$NaBH_4$	4	**2d**	52
1a	Me	H	$LiAlH_4$	0.5	**3a**	70[b]
1b	Me	Me	$LiAlH_4$	0.5	**3b**	57[b]
1c	Me	Et	$LiAlH_4$	0.5	**3c**	62[b]
1d	$-(CH_2)_5-$	$-(CH_2)_5-$	$LiAlH_4$	0.5	**3d**	47

[a] The yields are for isolated material after crystallization.
[b] The yields are for isolated material after preparative TLC.



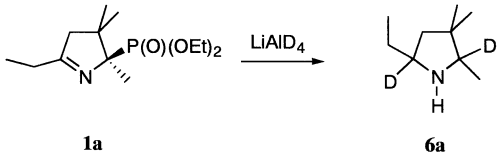
Scheme 4.

been reported that during C–P bond cleavage, the hydride does not attack the carbon atom bearing the phosphonyl group.[17]

The above results suggested that dephosphonylation might occur via a lithium amide intermediate which resulted from the hydride attack on the imino group as outlined in Scheme 4.

To gain insight into possible reaction pathways, we carried out the following experiments. Aminophosphonate **2a** was lithiated by reaction with LDA to generate the intermediate **4a**. The latter intermediate was expected to rearrange by dephosphonylation into **5a** and thus give diastereoisomers **3a** (path A, Scheme 4). However, this was not the case and no dephosphonylation was observed for **4a**. When the reduction of **1a** was performed with $LiAlD_4$ the reaction yielded a pyrrolidine **6a** containing two deuteriums, as shown in Scheme 5. This also shows that both hydrides were transferred from $LiAlH_4$ and not during the quenching step,[17] which is consistent with the 1:1 ratio of the diastereomers obtained. Although there is no evidence for a direct hydride attack on the carbon bearing the phosphorus atom, this cannot be excluded at this time. However, the formation of **5a** could be rationalized by assuming a concerted process according to path B (Scheme 4) in which a hydride attack on the imine carbon is followed immediately by the double bond migration within the intermediate **7a** and then dephosphonylation.

In summary, we have developed an effective methodology for hydride reduction of the 2,4-alkyl-5-phosphonyl pyrrolines **1** using $NaBH_4$. This reduction has been shown to occur stereoselectively and allowed us to isolate *cis*-isomers of the resulting pyrrolidines **2** after crystallization from pentane. A preliminary study has led to identification of dephosphonylated compounds **3** by reaction with $LiAlH_4$. Further studies are in progress including use of pyrrolidines **2** as nitroxide precursors and development of an asymmetric route to compounds **2**.



Scheme 5.

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19. Typical procedure for the reduction of β-iminophosphonate **1** with $NaBH_4$: To 1.5 g (5×10^{-3} moles) of pyrroline **1** in a solution of 10 ml of ethanol was added, in small portions over 30 min, 2.5×10^{-3} mol of sodium borohydride. The resulting mixture was stirred for 4 h then acidified with 5% HCl solution to pH 3, and the ethanol was evaporated under reduced pressure. The remaining aqueous layer was neutralized with a solution of 10% KOH and extracted three times with dichloromethane. After washing with brine, the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a colorless oil which was dissolved in 10 ml of pentane to afford white crystals of the pure pyrrolidine **2** in 52–72% yield. Data for a representative compound **2a** are given below.
Compound **2a**: (5-Ethyl-2,3,3-trimethylpyrrolidin-2-yl)diethylphosphonate. Yield 72%. Colorless crystalline prisms, mp: 71°C. ^{1}H NMR (200 MHz) δ (ppm): 0.90 (t, 3H, $J=7.4$ Hz); 1.01 (s, 3H); 1.23 (s, 3H); 1.25 (d, 3H, $J=15.4$ Hz); 1.33 and 1.34 (2t, 6H, $J=7.0$ Hz); 1.4–1.8 (m, 2H); 1.99 (dd, 1H, $J=9.3$ Hz, $J=12.1$ Hz); 3.20 (m, 1H, $J=8.4$ Hz); 4.12 (m, 2H); 4.23 (quin., 2H, $J=7.1$ Hz). ^{13}C NMR (100.61 MHz) δ (ppm): 11.59 ($\underline{C}H_3CH_2$-C); 16.29–16.62 (d, $OCH_2\underline{C}H_3$); 19.44 (d, $J=4.5$, $\underline{C}H_3$-C-P); 24.71 and 25.06 (d, $J=12.5$ Hz, $J=4.1$ Hz ($\underline{C}(CH_3)_2$C); 30.1 (s, $CH_3\underline{C}H_2$-C); 43.93 (d, $J=5.9$ Hz $(CH_3)_2\underline{C}$); 46.32 and 46.38 (-$\underline{C}H_2$-); 57.12 (d, $J=5.1$ Hz, CH_3CH_2-$\underline{C}$-N); 61.02 and 63.09 (d, $J=7.5$ Hz, $O\underline{C}H_2CH_3$); 65.91 (d, $J=155.9$ Hz, $\underline{C}$-P). ^{1}P NMR (40.53 MHz) δ (ppm): 27.67. Anal. calcd for $C_{13}H_{28}NO_3P$: C, 56.28; N, 5.05; H, 10.18; found: C, 56.23; N, 4.99; H, 10.10%.
20. Typical procedure for the reduction of β-iminophosphonate **1** with $LiAlH_4$: Compound **1** (275 mg, 1 mmol) in a solution of 2 ml dry THF was added, in small portions over 30 min, to 114 mg (3 mmol) of $LiAlH_4$ at room temperature. The resulting mixture was stirred for 1 h and then quenched with a solution of NaOH (4N) and then filtered. The remaining white cake was washed with THF (3×10 ml) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a colorless oil which was then purified by preparative TLC (dichloromethane). Pyrrolidines **3** were isolated in 47–70% yield as 1:1 mixtures of diastereomers. Data for a representative compound **3a** are given below.
Compound **3a**: 5-Ethyl-2,3,3-trimethylpyrrolidine. Yield 72%. Colorless oil. ^{1}H NMR (400 MHz) δ ppm: 0.83 (s, 3H, C$\underline{H}_3$-C-3); 0.91 (t, 3H, $J=7.6$ Hz, C$\underline{H}_3$-CH_2-); 0.98 (s, 3H, C$\underline{H}_3$-C-3); 0.99 (d, 3H, $J=6.6$ Hz, C$\underline{H}_3$-C-2); 1.45 (AB system, 2H, $J=12.8$ Hz, $\underline{H}_2$C-4); 1.33–1.55 (m, 2H, $J=7.2$ Hz, CH_3-C$\underline{H}_2$-); 2.73 and 2.79 (m, 1H, $J=6.8$ Hz, $\underline{H}$C-2); 2.94 and 3.08 (m, 1H, $J=7.2$ Hz, $\underline{H}$C-5); ^{13}C NMR (100.61 MHz) δ ppm: 62.70; 57.70; 48.00; 40.80; 30.50; 26.87; 22.51; 14.74; 11.67. EIMS m/z: 142 (M+1, 100%); 112 (42); 70 (30).