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1,3-Phosphorotropic Rearrangement of Pyridyl Phosphates to Hydroxypyridyl Phosphonates

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ABSTRACT

The lithium diisopropylamide (LDA) induced regioselective 1,3-rearrangement of 3- and 2- pyridyl phosphates into the corresponding 3-hydroxy-4-pyridyl- and 2-hydroxy-3-pyridylphosphonates has been observed and investigated. The rearrangement is proposed as a useful method for a directed introduction of a phosphoryl group into a hydroxypyridine nucleus.

INTRODUCTION

Hydroxy and phosphoryl derivatives of pyridine exhibit a wide spectrum of biological activity. In particular, a 3-hydroxypyridine structural fragment is a constituent of several biologically important molecules, such as vitamin B_6, pyridoxal enzymes, etc. There have been a number of publications on biological activity and chemistry of substituted 3-hydroxypyridines [1] and phosphorylated pyridines [2,3] possessing practical and useful properties. However, the development of new methods for their functionalization and, in particular, for the introduction of a phosphoryl group remains as an important synthetic problem.

The synthesis of C-phosphorylated hydroxypyridines through the metallation induced phosphorotropic 1,3-O-C-rearrangement of pyridyl phosphates seems to be attractive as a practical synthetic route. Such a rearrangement has been reported for some aryl phosphates [4]. For heterocyclic analogs, it is unknown, although a similar migration of a carbamoyl group in O-pyridyl carbamates has recently been described [5,6]. The most important prerequisite to the rearrangements is the generation of a nucleophilic center in a heterocyclic ring by a regioselective ortho-metallation [6].

RESULTS AND DISCUSSION

We have realized the approach outlined above using, as an example, diethyl 3-pyridyl phosphate **1**, readily available from 3-hydroxypyridine (Scheme 1). It was found that lithium diisopropylamide (LDA) smoothly induces the 1,3-O-C-rearrangement wherein a phosphoryl group migrates predominantly to the C(4) atom of the heterocycle.

In the ^{31}P NMR spectrum of the raw reaction mixture, in place of a signal of the starting phosphate **1** ($\delta = -4.7$), a new signal ($\delta = 24.4$) appears in a phosphonate resonance region which most likely corresponds to the lithium salt **2**. Acidification of the mixture results in formation of the hydroxypyridyl phosphonate **3** ($\delta = 18.9$), isolated as a viscous oil in 40% yield. The product was also characterized as a crystalline picrate.

The structure of the phosphonate **3** has been proven additionally by ^1H and ^{13}C NMR spectral data. Very significant for the structural identification are the two signals corresponding to a pair of pyridine α-protons ($\delta_H = 8.46$ and 8.22) and the multiplicity of an H-5 PMR signal ($\delta = 7.26$, dd, $^3J_{PH}$ 14 Hz, $^3J_{HH}$ 4.6 Hz) for which J_{PH} appreciably

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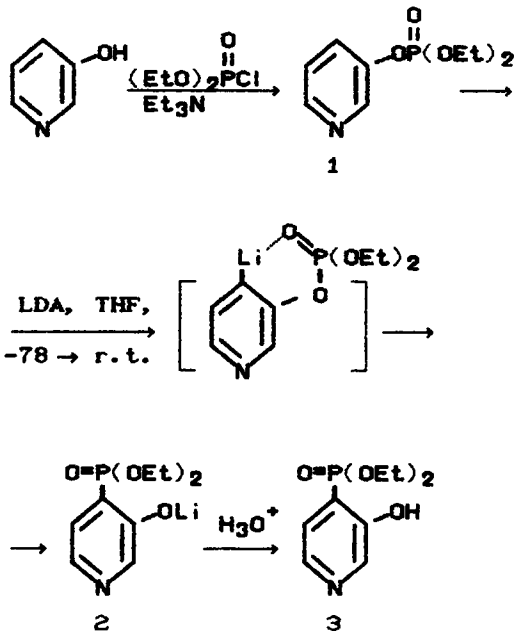
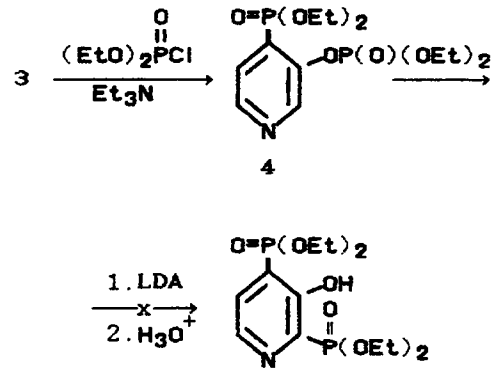


SCHEME 1

exceeds the H-5,H-4 vicinal coupling constant in C-4,C-5-unsubstituted pyridines. In full agreement with these data, the ^{13}C NMR signal of a C-4 (δ = 118.9, $^{1}J_{CP}$ 180 Hz) is split with a coupling constant characteristic of the one-bond interaction of a γ-carbon atom with the phosphonate phosphorus atom in pyridines [7].

The high regioselectivity of the phosphorotropic 1,3-rearrangement in **1** is likely due to the fact that the ortho-metallation proceeds predominantly at the C(4) atom. This is consistent with the rates for methoxide-anion catalyzed H-D exchange in the different positions of pyridine (C-2,6: C-3,5: C-4 1:9, 3:12) [8] which presumably reflect a thermodynamic stability of the corresponding substrate anions [9]. The enthalpies of deprotonation to give 3- and 4-pyridyl carbanions are about 5–7 kcal/mol lower than that yielding a 2-pyridyl carbanion, demonstrating that the former are more stable [11]. The low C–H acidity of 2,6-positions was attributed to repulsion between a nitrogen lone electron pair and a negative charge at a neighboring carbon atom. It seems reasonable that, in our case, with the use of LDA as a metallating agent, its approach to the C(2) center would be additionally hindered by steric crowding. In line with this, for phosphate **4**, prepared from hydroxypyridylphosphonate **3** and having an occupied position C(4), the O-C-migration, under the same conditions as in Scheme 1, was not detected.

Thus, the phosphorotropic O-C-rearrangement of pyridyl phosphates may serve as a useful tool for a regioselective P–C bond formation. It is known that, among phosphorus-substituted pyridines, 3(5)-



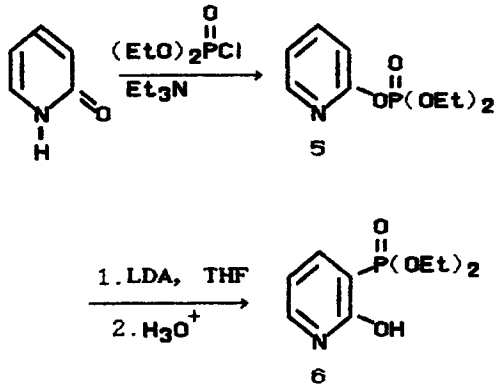
SCHEME 2

phosphoryl derivatives are the most difficult to access [3,12]. Bearing this in mind, we employed the approach proposed above for introduction of a phosphoryl group at a pyridine C-3 atom. It was found that the rearrangement of the 2-pyridyl phosphate **5** readily proceeds under conditions similar to those used for the isomer **1** and gives the 3-pyridylphosphonate **6** in 68% yield [13] (Scheme 3).

The P–C bond formation during the rearrangement manifests itself by the emergence of a new ^{31}P signal in the region of δ = 16. Very indicative in this respect are also the coupling constants for H-4,P ($^{3}J_{HP}$ 16.6 Hz) and C-3,P ($^{1}J_{CP}$ 197 Hz) nuclear interactions in the ^{1}H and ^{13}C spectra of the product **6** (see the following section).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Gemini 200 Bruker spectrometer (operating frequencies 200.12 and 50.23 MHz, respectively) in $CDCL_3$, unless otherwise stated, with TMS as the internal standard, while the ^{31}P NMR spectra were recorded on a Bruker WP-200 instrument (81.03 MHz) in benzene solutions with 85% H_3PO_4 as the



SCHEME 3

external standard. Chemical shift values are given in parts per million.

Diethyl 3-Hydroxy-4-pyridylphosphonate (**3**)

A solution of diethyl 3-pyridyl phosphate **1** [15] (22 mmol) in anhydrous THF (20 mL) was added dropwise to a freshly prepared and cooled (to −78°C) solution of LDA (from 44 mmol of iso-Pr_2NH in 20 mL of THF and 44 mmol of BuLi in 60 mL of hexane). The mixture was maintained at −10°C overnight, then warmed to room temperature, and poured over crushed ice. The aqueous layer was separated, washed with diethyl ether (3 × 30 mL), neutralized with 5% HCl to pH 7, and extracted with chloroform (3 × 50 mL). The extract was dried over $MgSO_4$, and the solvent was evaporated. After purification by chromatography on a silica gel column with ethyl acetate as the eluent, the product **3** was obtained in 40% yield as a viscous oil. ^{1}H NMR δ: 1.36 (6H, t, CH_3), 4.2 (4H, m, CH_2), 7.26 (1H, dd, $^3J_{HP}$ 14.6 Hz, $^3J_{56}$ 4.6 Hz, 5-H), 8.22 (1H, t, $^3J_{65} \approx {}^4J_{HP}$ 4.6 Hz, 6-H), 8.46 (1H, d, $^4J_{HP}$ 7.6 Hz, 2-H), 9.7 (1H, br.s, OH). ^{13}C NMR δ: 16.10 (d, $^3J_{CP}$ 6.3 Hz, CH_3), 63.22 (d, $^2J_{CP}$ 5.7 Hz, CH_2), 118.89 (d, $^1J_{CP}$ 180 Hz, 4-C), 125.19 (5-C), 139.92, 156.52 (2-C, 3-C). ^{31}P NMR δ: 18.9. Anal. calcd for $C_9H_{14}NO_4P$: N, 6.06; P, 13.39. Found: N, 6.04; P, 13.16%.

Picrate: mp 141–143°C (EtOH). ^{1}H NMR (acetone-d_6) δ: 1.36 (6H, dt, J_{HH} 7.0 Hz, $^4J_{HP}$ 0.6 Hz, CH_3), 4.3 (4H, m, CH_2), 7.96 (1H, dd, $^3J_{HP}$ 14.2 Hz, $^3J_{56}$ 5.4 Hz, 5-H), 8.49 (1H, dd, $^3J_{65}$ 5.4 Hz, $^4J_{HP}$ 3.4 Hz, 6-H), 8.64 (1H, d, $^4J_{HP}$ 6.2 Hz, 2-H), 8.94 (2H, s, picryl). Anal. calcd for $C_{15}H_{17}N_4O_{11}P$: N, 12.17; P, 6.72. Found: N, 12.07; P, 6.72%.

Diethyl 4-Diethoxyphosphoryl-3-pyridyl Phosphate (**4**)

Diethyl chlorophosphate (4 mmol) was added to a solution of phosphonate 3 (4 mmol) and triethylamine (4 mmol) in 10 mL of benzene. The mixture was left at room temperature for 48 hours, and the precipitate that had formed was filtered off. The filtrate was evaporated, and the residue was reprecipitated from a benzene solution by addition of petroleum ether to give the oily product **4** in 54% yield. ^{1}H NMR δ: 1.4 (12H, m, CH_3), 4.3 (8H, m, CH_2), 7.76 (1H, m, $^3J_{HP}$ 14.5 Hz, $^3J_{56}$ 4.7 Hz, 5-H), 8.56 (1H, dd, $^4J_{HP} \approx {}^3J_{65}$ 4.5 Hz, 6-H), 8.90 (1H, d, $^4J_{HP}$ 6.8 Hz, 2-H). ^{31}P NMR δ: −6.5 (P-O-Py), 11.3 (P-Py). Anal. calcd for $C_{13}H_{23}NO_7P_2$: N, 3.81; P, 16.86. Found: N, 3.92; P, 17.49%.

Diethyl 2-Pyridyl Phosphate (**5**)

Diethyl chlorophosphate (42 mmol) was added dropwise with stirring to a mixture of 2-hydroxypyridine (42 mmol) and triethylamine (44 mmol) in 120 mL of dry benzene. The reaction mixture was left at room temperature for 48 hours. A precipitate that had formed was filtered off, and the solvent was evaporated. The residue was distilled in vacuum to give the product **5** [16]: yield 67%, bp 105–108°C/0.02 torr. ^{1}H NMR δ: 1.39 (6H, dt, $^3J_{HH}$ 7.0 Hz, $^4J_{HP}$ 1.2 Hz, CH_3), 4.34 (4H, quintet, $^3J_{HH} \approx {}^3J_{HP}$ 7 Hz, CH_2), 7.05 (1H, dm, $^3J_{34}$ 8.2 Hz, 3-H), 7.14 (1H, m, $^3J_{56}$ 5.2 Hz, $^3J_{54}$ 6.8 Hz, 5-H), 7.74 (1H, m, $^3J_{43}$ 8.2 Hz, $^3J_{45}$ 7 Hz, 4-H), 8.31 (1H, m, $^3J_{65}$ Hz, $^4J_{64}$ 2 Hz, 6-H). ^{31}P NMR δ: −5.9. Anal. calcd for $C_9H_{14}NO_4P$: N, 6.06; P, 13.39. Found: N, 5.57; P, 13.19%.

Diethyl (2-Hydroxy-3-pyridyl)phosphonate (**6**)

was prepared as described for **3**, yield 68%. ^{1}H NMR δ: 1.36 (6H, t, $^3J_{HH}$ 7 Hz, CH_3), 4.2 (4H, m, CH_2), 6.39 (1H, ddd, $^3J_{54}$ 7 Hz, $^3J_{56}$ 6.5 Hz, $^4J_{HP}$ 3.4 Hz, 5-H), 7.75 (1H, d, $^3J_{65}$ 6.5 Hz, 6-H), 8.15 (1H, dd, $^3J_{HP}$ 16.6 Hz, $^3J_{45}$ 7 Hz, 4-H), 13.2 (br s, NH or OH). ^{13}C NMR δ: 16.4 (d, $^3J_{CP}$ 6.4 Hz, CH_3), 62.59 (d, $^2J_{CP}$ 5.6 Hz, CH_2), 106.08, 140.43, 149.77 (4-C, 5-C, 6-C), 118.98 (d, $^1J_{CP}$ 197 Hz, 3-C), 163.39 (d, $^2J_{CP}$ 13.2 Hz, 2-C). ^{31}P NMR δ: 16.0. Anal. calcd for $C_9H_{14}NO_4P$: N, 6.06; P, 13.39. Found: N, 5.57; P, 13.19%.

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