A Novel Approach to the Transformation of Aldoximes to Nitriles Utilizing Spin-Labeled Phosphoryl Imidazolides

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The spin-labeled imidazolides of phosphorus 1 and 3 were utilized for the conversion of

\[ \text{O} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{O} \quad \text{P}< \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{C} \]

aldoximes to nitriles in high yield. It is hypothesized that this transformation under mild, neutral conditions might serve as a model reaction, mimicking the detoxification of phosphorus-inhibited acetyl cholinesterases.

Over the years there have been numerous reports concerning the transformation of aldoximes to nitriles. The limitation of space prevents one to even attempt to list all literature references pertinent to this topic. However, it was noted that there have been comparatively few such transformations achieved by using various phosphorus compounds. Thus, the reactions of diethyl phosphorochloridate, diphenyl hydrogen phosphonate, phosphonitrilic chloride, triphenyl phosphine and carbon tetrachloride with aldoximes gave the corresponding nitriles in moderate to good yields. In the case of a phosphorochloridate as the reagent, a condensing agent, such as triethylamine, had to be used. It was proposed that the reaction proceeds by way of a phosphorylated intermediate, which, however, has not been isolated.

In view of the role of certain phosphorus compounds, such as, diisopropyl phosphorofluoridate (DFP), tetraethyl pyrophosphate (TEPP), isopropyl methylphosphonofluoridate (SARIN), and O,O-diethyl O-(4-nitrophenyl) phosphorothioate (Parathion) as anticholinesterase agents in preventing synaptic transfer, and in view of the role of certain oximes, such as, pyridine-2-aldoxime methiodide (2-PAM) and pyridine-4-aldoxime methiodide (4-PAM), as reactivators of the inhibited enzyme, we hypothesized that a phosphorylated imidazole of histidine in the acetyl cholinesterase might be involved in the poisoning process of the enzyme. The phosphorylated enzyme can be reactivated, i.e., dephosphorylated, with certain oximes by the transfer of the phosphoryl moiety from imidazole to form a phosphorylated oxime. This phosphorylated intermediate might then undergo a decomposition, perhaps base catalyzed, to give less toxic compounds, i.e., a phosphorus acid derivative and a nitrile.

Now we wish to report that the reaction of spin-labeled imidazolides of phosphorus with aldoximes proceeds to give nitriles under mild, neutral conditions, and, therefore, the mechanism, as we hypothesized, for the detoxification of a poisoned cholinesterase via a dephosphorylation of imidazole by an oxime might indeed be feasible. Thus, the reaction of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl imidazole-1-phosphonate (1) with aldoximes proceeds at 50-55 °C within 2 h to give the nitriles in yields, in most cases, exceeding 90%.
The phosphorylated intermediate 2 could not be isolated for the oximes which were investigated in this study. However, work currently underway in our laboratory indicates that intermediates of the type 2 can be isolated in certain cases. The reaction is rapid, i.e., complete within 2 h at the slightly elevated temperatures of 50–55 °C (Table). The nitriles were obtained essentially in pure form following the workup.

Similarly, (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl) diimidazole-1,1'-phosphinate (3) was utilized for the conversion of 2 mols of aldoxime per mol of reagent to the corresponding nitrile. The yields, in most cases, exceeded 80%.

Twenty hours at room temperature are required for the completion of the reaction. Unlike in the preceding case, the extent of the reaction can be easily monitored visually. Thus, the completion of the reaction is indicated by the conversion of a red-colored, initially homogeneous, reaction mixture to a heterogeneous system consisting of an oil and a colorless supernatant liquid. Essentially pure nitriles were obtained after the workup (Table).

**Materials**

All reagents were of the finest quality commercially available. The dioxan used in the transphosphorylation reactions was distilled from and stored over sodium. The oximes were prepared by standard methods. The imidazole used to prepare compounds 1 and 3 was generously donated by BASF Corporation of Parsippany, New Jersey.

**Analytical procedures**

All IR analyses were performed on a Perkin-Elmer Infracord Spectrophotometer Model 137. Column chromatography was performed on basic aluminum oxide (20:1 w/w). One gram of the concentrated reaction mixture was dissolved in a minimal amount of chloroform, and then eluted from the column with chloroform. The 2-cyano-pyridine purified in this manner was isolated after removal of the solvent at 20–25 °C/12 torr.
Reaction of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl) phenyl imidazole-1-phosphonate (1) with aldoximes

A solution of 1\(^1\) (1.89 g, 5 mmol) and the aldoxime (5 mmol) in dioxan (35 ml) was stirred at 50-55 °C for 2 h. The solvent was removed on a rotating evaporator at 20-25 °C (12-15 torr). The crude oil was treated with diethyl ether (20 ml) and distilled water (5 ml). The aqueous layer was discarded. The organic layer was washed with 10% aqueous HCl solution (2 x 5 ml), 10% NaOH (2 x 5 ml), and distilled water (2 x 5 ml). The organic layer was dried (MgSO\(_4\)). After removal of the drying agent and the solvent, there were obtained the nitriles (Table). In the case of the reaction with pyridine-2-aldoxime, the washes were omitted. The pure nitrile was isolated after chromatography of the crude reaction mixture.

Reaction of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl) diimidazole-1,1'-phosphinate (3) with aldoximes

A solution of 3\(^3\) (1.76 g, 5 mmol) and the aldoxime (10 mmol) in dioxan (35 ml) was kept at 20-25 °C for 20 h. During this time, a red oil settled to the bottom of the flask. The solvent was removed on a rotating evaporator at 20-25 °C (12-15 torr). The crude oil was treated with diethyl ether (30 ml) and distilled water (5 ml). The aqueous layer was discarded. The organic layer was washed with 10% aqueous HCl solution (3 x 10 ml), 10% NaOH (2 x 5 ml), and distilled water (3 x 5 ml). The organic layer was dried (MgSO\(_4\)). After removal of the drying agent and the solvent, there were obtained the nitriles (Table). In the case of the reaction with pyridine-2-aldoxime, the washes were omitted. The pure nitrile was isolated after chromatography of the crude reaction mixture.

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