Preparation of Spin-Labeled Phosphoroamidates in High Yield
Using Imidazole as the Transfer Agent

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Spin-Labeled Phosphoroamidates, Amines, Nitroxyl Moiety, Transphosphorylation

The spin-labeled (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)-phenyl imidazole-1-phosphonate (4) was used to prepare (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl N-alkyl and N-aryl phosphoroamidates (8) in yields generally exceeding 70%.

\[
\begin{align*}
\text{(4)} & \quad \text{(8)} \\
\end{align*}
\]

Amidates 8 were also prepared from the corresponding chloridate 10. However, in the latter case, a basic condensing agent, such as, triethylamine was essential. The chloridate 10 was converted to the spin-labeled pyrophosphate 11 and the acid 12.

\[
\begin{align*}
\text{(11)} & \quad \text{(12)} \\
\end{align*}
\]

The pyrophosphate 11 can be employed to phosphorylatively spin-label amines.

There have been various reports in the last twenty-five years on the preparation and reactions of imidazolides 2 of diaryl and dialkyl esters of phosphoric acids1-18. Imidazolides 2 can be easily prepared in high yields from the corresponding acid chloride (1) and excess imidazole1,2.

\[
\begin{align*}
\text{(1)} & \quad \text{(2)} \\
\end{align*}
\]

The preparation of the reactive intermediate chloridate 1 can be avoided if a dialkyl or diaryl phosphite 3 is used in the presence of carbon tetrachloride and triethyl amine5,6.

\[
\begin{align*}
\text{(3)} & \quad \text{(1)} \quad \text{(2)} \\
\end{align*}
\]

Similarly, diimidazolides of monoesters of phosphoric acid7,8 and the trimidazolide of phosphoric acid7,8,18 (trimidazolyl-oxophosphorane) have been prepared from monoesters of alkyl phosphoric acid dichloridates and phosphorus oxychloride, respectively.

The lability of the imidazolyl moiety has been utilized in the synthesis of various esters of phosphoric acid. Nucleophiles, such as, N-blocked serine4, phosphoric and carboxylic acids10,17, alcohols and phenols2,7,9,12,14,16, and steroids13 have been reacted with a host of imidazolides. In most of the cases the yields were above 70%.

Analogous results have also been obtained with amines. Thus, the preparation of phosphoro mono, 2,9,10,13,17, di-11, and triamidates11 utilizing the lability of imidazole in effecting the transfer of the phosphorus group to the amino moiety has been achieved.

Recently, we reported the synthesis of spin-labeled steroids13 (5) and other hydroxy derivatives14, and phosphonates of esterified amino acids13 (6) in high yields employing (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenylimidazole-1-phosphonate (4) as the reactive intermediate.

Requests for reprints should be sent to Professor Dr. G. SOSNOVSKY, The University of Wisconsin-Milwaukee, Department of Chemistry, Milwaukee, Wisconsin 53201, USA.
Now we wish to report that imidazolide 4 is the reagent of choice for the preparation of phosphoroamidates containing the stable nitroxyl moiety.

The reaction of phosphonate 4 with various aliphatic primary amines, aniline, and secondary amines in dioxan gave the (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphoroamidates (8) in yields ranging, in most cases, from 70-94% (Table I).

In two of the cases, with R' = H, R'' = i-C₃H₇ and R' = H, R'' = c-C₆H₁₄, also formed were the corresponding alkyl ammonium salts of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphate (9) in 13-14% yields.

In order to verify the identity of the salt 9, the preparation of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphate (12) was attempted by the hydrolysis of the corresponding phosphorochloridate 10. It was found that, depending on the base used to neutralize the hydrogen chloride, either the anhydride 11 or the acid 12 were formed. Thus, hydrolysis of chloridate 10 in the presence of triethylamine produced only bis(1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)diphenyl pyrophosphate (11) in 93% yield, whereas the hydrolysis of chloridate 10 in the presence of aqueous sodium hydroxide produced the acid 12 in 95% yield.

The pyrophosphate 11 and the acid 12 both possess characteristic infrared absorption frequencies. Thus, in the infrared spectrum of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphate (12), the broad, weak P-O-H absorption centering at approximately 2800 cm⁻¹ is observed, while in the spectrum of bis(1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)diphenyl pyrophosphate (11), that P-O-H absorption is completely absent, and instead, a strong absorption band, characteristic of the P-O-P vibration is present at approximately 940 cm⁻¹.

Reactions of pyrophosphates with amines were reported to give the corresponding acids and salts. We have also found that the reaction of the spin-labeled pyrophosphate 11 with i-propyl and s-butyl amine results in a mixture of products.

The salt 9 was obtained in 39-40% yield, and the amide 8 in 45-47% yield. For verification, the amine salts 9 were prepared from the acid 12 and the amine 7 in 70-74% yields.

The transphosphorylation reaction of 4 can be also achieved in benzene as solvent, though in lower yields, ranging from 51 to 60%. This decrease in yield may be attributed to the fact that benzene, a conjugated aromatic, lacks the lone-pair electrons of the oxygens in dioxan, and, therefore, is a poorer solvating agent than dioxan. These results are listed in Table II.
Table I. Reaction of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl imidazole-1-phosphonate (4) with primary and secondary amines (7) in dioxan. Preparation of 1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl N-alkyl or N-aryl phosphoroamides (8, R = alkyl, aryl).

<table>
<thead>
<tr>
<th>Amine 7</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Microanalysis</th>
<th>EPR No. $\alpha_N$ [G] of lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Propylamine 75</td>
<td>softens 68, melts 76</td>
<td>m.p. 58.2</td>
<td>Caled C 58.52 H 8.19 N 7.58 3</td>
<td>15.0</td>
</tr>
<tr>
<td>n-Butylamine 70</td>
<td>softens 61-64, melts 76 [s 62; m 75]</td>
<td>m.p. 58.72</td>
<td>Caled C 59.51 H 8.41 N 7.31 3</td>
<td>15.0</td>
</tr>
<tr>
<td>s-Butylamine 74</td>
<td>softens 95, melts 107 [s 94; m 107]</td>
<td>m.p. 59.31</td>
<td>Caled C 59.47 H 8.30 N 7.13 3</td>
<td>15.3</td>
</tr>
<tr>
<td>i-Pentylamine 89</td>
<td>softens 55, melts 89 [s 55; m 89]</td>
<td>m.p. 60.44</td>
<td>Caled C 59.64 H 8.28 N 6.97 3</td>
<td>15.1</td>
</tr>
<tr>
<td>Cyclohexylamine 71</td>
<td>Oil</td>
<td>m.p. 60.74</td>
<td>Caled C 58.74 H 8.16 N 7.08 3</td>
<td>15.1</td>
</tr>
<tr>
<td>N.N-Dimethyl-1,3-propanediamine 93</td>
<td>Oil</td>
<td>m.p. 58.58</td>
<td>Caled C 58.58 H 8.22 N 10.02 3</td>
<td>15.2</td>
</tr>
<tr>
<td>Cyclohexylamine 86</td>
<td>softens 69, melts 84 [s 69; m 85]</td>
<td>m.p. 61.60</td>
<td>Caled C 61.60 H 8.42 N 6.84 3</td>
<td>15.1</td>
</tr>
<tr>
<td>Methylcyclohexylamine 68</td>
<td>Oil</td>
<td>m.p. 61.62</td>
<td>Caled C 61.62 H 8.27 N 6.99 3</td>
<td>15.1</td>
</tr>
<tr>
<td>n-Decylamine 76</td>
<td>softens 39, melts 50 [s 39; m 49]</td>
<td>m.p. 62.39</td>
<td>Caled C 62.39 H 8.57 N 6.61 3</td>
<td>15.3</td>
</tr>
<tr>
<td>Aniline 78</td>
<td>softens 101, melts 115 [s 101; m 115]</td>
<td>m.p. 62.52</td>
<td>Caled C 64.22 H 9.49 N 5.99 3</td>
<td>15.1</td>
</tr>
<tr>
<td>Benzylamine 94</td>
<td>softens 80, melts 85 [s 80; m 85]</td>
<td>m.p. 63.29</td>
<td>Caled C 63.56 H 7.36 N 6.77 3</td>
<td>15.1</td>
</tr>
<tr>
<td>Phenethylamine 70</td>
<td>softens 39, melts 50 [s 39; m 49]</td>
<td>m.p. 63.56</td>
<td>Caled C 64.02 H 7.48 N 6.49 3</td>
<td>15.2</td>
</tr>
<tr>
<td>Allylamine 69</td>
<td>Oil</td>
<td>m.p. 63.89</td>
<td>Caled C 59.84 H 7.68 N 7.62 3</td>
<td>15.2</td>
</tr>
<tr>
<td>di-n-Butylamine 51</td>
<td>Oil</td>
<td>m.p. 64.29</td>
<td>Caled C 58.66 H 7.82 N 7.43 3</td>
<td>15.2</td>
</tr>
<tr>
<td>Aziridine 77</td>
<td>Oil</td>
<td>m.p. 62.85</td>
<td>Caled C 57.78 H 7.41 N 7.93 3</td>
<td>15.0</td>
</tr>
<tr>
<td>Morpholine 85</td>
<td>Oil</td>
<td>m.p. 57.78</td>
<td>Caled C 57.42 H 7.61 N 7.05 3</td>
<td>15.2</td>
</tr>
</tbody>
</table>

* Also obtained was 14% of the i-propylammonium salt of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphonate (9, R' = H, R'' = i-C$_3$H$_7$); m.p. 151-153 °C (dec). b Also obtained was 13% of the cyclohexylammonium salt of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphate (9, R' = H, R'' = C$_6$H$_5$); m.p. 197-198 °C (dec). c Mol. Wt. obtained. d Compound is unstable, even at — 20 °C.
Table II. Reaction of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl imidazole-1-phosphonate (4) with amines in benzene.

<table>
<thead>
<tr>
<th>Amine 7</th>
<th>Yield [%]</th>
<th>m.p. [°C] [dec]</th>
<th>m.m.p. [°C] [dec]</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Propylamine</td>
<td>60</td>
<td>softens 68</td>
<td>softens 68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>melts 76</td>
<td>m.p. 77</td>
</tr>
<tr>
<td>s-Butylamine</td>
<td>60</td>
<td>softens 95</td>
<td>softens 95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>melts 107</td>
<td>m.p. 107</td>
</tr>
<tr>
<td>Cyclohexylaminea</td>
<td>53</td>
<td>softens 69</td>
<td>softens 69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>melts 84</td>
<td>m.p. 83</td>
</tr>
<tr>
<td>Benzylamine</td>
<td>51</td>
<td>softens 80</td>
<td>softens 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>melts 85</td>
<td>m.p. 85</td>
</tr>
</tbody>
</table>

*a* Also isolated was 25% of the cyclohexylammonium salt of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphate (9, R' = H, R'' = C₆H₄); m.p. 197-198 °C (dec); m.m.p. 196-197 °C (dec).

Phosphoroamidates 8 also were prepared from (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphorochloridate (10) and amines 7. Unlike the yields of the reactions of alcohols with chloridate 10, the yields of 8 from amines 7 and chloridate 10 are comparable to those obtained via the imidazole phosphonate 4 (see Table III). The advantage of utilizing the phosphonate 4 to prepare phosphoroamidates 8 lies in the fact that during the transphosphorylation reaction, a virtually neutral molecule, imidazole (pKₐ 6.95), is liberated, while during the preparation of amidates 8 from chloridate 10, hydrogen chloride might be released, which is potentially capable of destroying the nitroxyl moiety, or undergoing other side reactions. Therefore, an additional basic condensing agent, such as triethylamine, must be used, and as a result, its hydrogen chloride salt is obtained as a byproduct.

#### Experimental

**Materials:** All reagents were of the best quality commercially available and were used without further purification. (1-Oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphorochloridate (10) and its corresponding imidazole derivative 4 were prepared as described previously. The amines used as nucleophiles were dried over sodium hydroxide. The benzene and dioxan used in all reactions had been distilled from and stored over sodium. The imidazole used to prepare phosphate 4 was supplied by BASF Corporation of Parsippany, New Jersey.

**Analytical procedures:** All melting points are uncorrected. Molecular weights were determined isopiestically on a Hitachi Perkin-Elmer Model 115 Molecular Weight apparatus. The EPR spectra were obtained on a Varian E3 spectrometer. If the sample was soluble in benzene, an approximately 10⁻⁴ M solution in that solvent was purged with nitrogen for about five minutes, then analyzed. Benzene-insoluble salts 9 were analyzed as aqueous (~10⁻⁴ M) solutions with appropriate accessories. The infrared analyses were performed on a Perkin-Elmer Infrared Spectrophotometer Model 137. Micro analyses were performed on a F & M Scientific Corporation Carbon, Hydrogen, Nitrogen Analyzer Model 185.

The column chromatography for all compounds was performed on aluminium oxide (basic, Brockman, activity IV; 80-200 mesh). In each case, a ratio of 20:1 (w/w) of Al₂O₃ to crude sample was used, with chloroform as the eluant. The first fraction eluting was analyzed and found to contain the desired product. The solvent was removed on a rotating evaporator at 23 °C (12-15 torr).

**Preparation of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphate (12)**

Chloridate 10 was prepared and used without isolation. To an aqueous sodium hydroxide solution (5.1 ml of a 0.99 M solution) at room temperature was added as rapidly as possible the filtrate containing chloridate 10 (0.005 mol in 60 ml benzene). Following the addition the reaction mixture was stirred at ambient temperature for 20 h. Then, diethyl ether (50 ml) was added. The aqueous layer was drawn off. The organic layer was washed with distilled water (2 × 5 ml), then dried over...
anhydrous sodium sulfate. The drying agent was removed by filtration. The filtrate was concentrated on a rotating evaporator at 25 °C (12–15 torr), then kept at 0.2 torr for several hours. In this manner was obtained 1.6 g (95%) of 12, a red solid, softening at 67 °C, melting at 75 °C (dec). EPR: 3 lines; aN G. v(P–O–H): 2500–3000 cm⁻¹ (weak, broad).

Analysis

C₅H₉N₂O₅P
Caled C 54.87 H 7.06 N 4.27,
Found C 54.84 H 7.36 N 4.00.

Preparation of bis(1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphorochloridate (11)

(1-Oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl phosphorochloridate (10) was prepared and used without isolation. To a gently stirred mixture of water (5 ml) and triethylamine (0.5 g, 0.005 mol) was added all at once the filtrate containing 0.005 mol chloridate 10 in 80 ml benzene. Following the addition, the reaction mixture was stirred at ambient temperature for 20 h. The aqueous layer was drawn off. The organic layer was dried over sodium sulfate. The drying agent was filtered off. The filtrate was concentrated on a rotating evaporator at 25 °C (12–15 torr), then 1.6 g (95%) of 12, a red solid, softening at 67 °C, melting at 75 °C (dec). EPR: 3 lines; aN G. v(P–O–H): 2500–3000 cm⁻¹ (weak, broad).

Table III. Preparation of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)phenyl N-alkyl and N-aryl phosphoroamidates (8) via chloridate 10.

<table>
<thead>
<tr>
<th>Amine</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Microanalysis</th>
<th>EPR No. aN [G] of lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Propylamine</td>
<td>95</td>
<td>softens 68</td>
<td>C₁₈H₃₈N₂O₅P 369.442 (370)b</td>
<td>Caled C 58.52 H 8.19 N 7.58 3 14.9</td>
</tr>
<tr>
<td>n-Butylamine</td>
<td>99</td>
<td>m.p. 61–64</td>
<td>C₁₈H₃₂N₂O₅P 383.352 (388)b</td>
<td>Caled C 59.51 H 8.41 N 7.31 3 15.3</td>
</tr>
<tr>
<td>s-Butylamine</td>
<td>96</td>
<td>softens 95</td>
<td>C₁₈H₃₂N₂O₅P 383.452 (390)b</td>
<td>Caled C 59.51 H 8.41 N 7.31 3 15.1</td>
</tr>
<tr>
<td>Cyclopentylamine</td>
<td>65a</td>
<td>Oil</td>
<td>C₂₀H₄₂N₂O₅P 395.463 (390)b</td>
<td>Caled C 60.74 H 8.16 N 7.08 3 15.1</td>
</tr>
<tr>
<td>Cyclohexylamine</td>
<td>94</td>
<td>softens 69</td>
<td>C₂₁H₃₄N₂O₅P 409.490 (411)b</td>
<td>Caled C 61.60 H 8.37 N 6.84 3 15.2</td>
</tr>
<tr>
<td>n-Decylamine</td>
<td>92</td>
<td>softens 39</td>
<td>C₂₃H₄₄N₂O₅P 467.615 (470)b</td>
<td>Caled C 64.22 H 9.49 N 5.99 3 15.1</td>
</tr>
<tr>
<td>Allylamine</td>
<td>74</td>
<td>Oil</td>
<td>C₁₈H₂₇N₂O₅P 367.409 (355)b</td>
<td>Caled C 58.84 H 7.68 N 7.62 3 14.9</td>
</tr>
<tr>
<td>Aniline</td>
<td>43</td>
<td>softens 101</td>
<td>C₂₁H₂₈N₂O₅P 403.442 (410)b</td>
<td>Caled C 62.52 H 7.00 N 6.94 3 15.2</td>
</tr>
<tr>
<td>Benzylamine</td>
<td>77</td>
<td>softens 80</td>
<td>C₂₂H₂₉N₂O₅P 417.469 (419)b</td>
<td>Caled C 63.29 H 7.24 N 6.71 3 15.3</td>
</tr>
<tr>
<td>Phenethylamine</td>
<td>76</td>
<td>softens 39</td>
<td>C₂₃H₃₂N₂O₅P 431.496 (429)b</td>
<td>Caled C 64.02 H 7.48 N 6.49 3 15.3</td>
</tr>
<tr>
<td>Aziridine</td>
<td>82</td>
<td>Oil</td>
<td>C₁₇H₂₆N₂O₅P 353.382 (348)b</td>
<td>Caled C 57.78 H 7.41 N 7.93 3 15.0</td>
</tr>
<tr>
<td>Morpholine</td>
<td>98</td>
<td>Oil</td>
<td>C₁₉H₃₈N₂O₅P 397.435 (399)b</td>
<td>Caled C 57.42 H 7.61 N 7.65 3 15.0</td>
</tr>
</tbody>
</table>

a Compound is unstable, even at —20 °C. b Mol. Wt. obtained.
rator at 20 °C (12 torr) to give 3.0 g (93%) of 11, a red oil. EPR: 5 lines; $\alpha_N = 7.6 \text{ G}$. $\nu(P-O-P) = 940 \text{ cm}^{-1}$ (strong).

**Analysis**

$\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_3\text{P}_2$

Caled C 56.42 H 6.94 N 4.39 Mol. wt. 688,

Found C 56.58 H 7.20 N 4.50 Mol. wt. 600.

**Reaction of bis(1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)diphenyl pyrophosphate (11) with amines**

1. **Reaction with i-propyl amine:** A solution of 11 (1.3 g, 0.002 mol) and i-propylamine (0.5 g, 0.005 mol) in chloroform (30 ml) was stirred at ambient temperature for 20 h. The solvent was removed by rotation at 25 °C (12–15 torr). The solid cake was treated with 25 ml diethyl ether. The residue was slurried in 15 ml diethyl ether. The insoluble salt 9 ($R' = H$, $R'' = i-C_3\text{H}_7$) was filtered off as a pale pink solid in a yield of 1.4 g (74%), m. p. 151–157 °C (dec), m. m. p. 151–155 °C (dec).

2. **Reaction with cyclohexylamine:** As described in the preceding experiment, the reaction of 12 (1.6 g, 0.005 mol) with cyclohexylamine (0.8 g, 0.008 mol) in chloroform (20 ml) gave 1.5 g (70%) of the salt 9 ($R' = H$, $R'' = c-C_6\text{H}_{11}$), a pale pink solid, m. p. 197–198 °C (dec). EPR: 3 lines; $\alpha_N$ (aqueous) = 17.0 G.

**Analysis**

$\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_3\text{P}$

Caled C 59.00 H 8.49 N 6.55,

Found C 58.88 H 8.80 N 6.82.

**Reaction of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)-phenyl imidazole-1-phosphonate (4) with primary and secondary amines**

1. **In dioxan:** A solution of 4 (1.9 g, 0.005 mol) and the appropriate primary and secondary amine (0.006 mol) in dioxan (25 ml) was stirred at 20–25 °C for 20 h. The reaction mixture was then filtered, if necessary, to remove the byproduct salt 9. The filtrate was concentrated on a rotating evaporator at 25 °C (12–15 torr) to give the crude product which was purified by column chromatography on Al$_2$O$_3$. Crystallization of the solid derivatives was induced by trituration of the concentrated eluate with pentane and storing at −20 °C for 12 h. The amidates 8 thus prepared are listed in Table I.

2. **In benzene:** A solution of 4 (1.9 g, 0.005 mol) and the appropriate primary amine (0.006 mol) in benzene (20 ml) was stirred at 20–25 °C for 20 h. The reaction mixture was then filtered, if necessary, and treated further in a manner identical to that described in the preceding experiment. Identification of products 8 was made by mixture melting points. The results of these experiments are listed in Table II.

**Preparation of (1-oxyl-2,2,6,6-tetramethyl-4-piperidyl)-phenyl N-alkyl and N-aryl phosphoroamidates (8) via the chloridate 10**

The chloridate 10 was prepared$^{13}$ and used without isolation. To a solution of 10 (0.01 mol) in benzene (80 ml) was added dropwise at 8–10 °C a solution of the appropriate amine (0.01 mol) and triethylamine (1.1 g, 0.01 mol) in 100 ml benzene. Following the addition, the reaction mixture was stirred at 8–10 °C for 1 h, at ambient temperature for 20 h, then filtered. The filtrate was concentrated on a rotating evaporator at 25 °C (12–15 torr) to a red oil which was purified by chromatography on Al$_2$O$_3$ to give the amidates 8 listed in Table III.

This investigation was supported by a grant from the Public Health Service, U. S. Department of Health, Education, and Welfare (GM 16741) and the Graduate School of the University of Wisconsin–Milwaukee.
17. H. A. Staab, H. Schaller, and F. Cramer, Angew. Chem. 71, 736 [1959].