A Convenient Synthesis of S-Alkyl O-Aryl Thiophosphoric Acid Derivatives

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A new convenient synthesis of S-alkyl O-aryl thiophosphoric acid derivatives is reported. The chlorination of O-aryl O,O-dialkyl thiophosphates with phosphorus oxychloride proceeds with isomerization to give S-alkyl O-aryl thiophosphorochloridates, which react further with various nucleophiles in the presence of base to give the title compounds.

S-Alkyl O-aryl thiophosphoric acid derivatives possess extensive biological and especially insecticidal activity. In the synthetic methods reported for these compounds, mercaptans or their derivates were generally used as starting materials,1-7 or they were prepared by reacting salts of thiophosphoric acid with an alkyl halide.8-11

In 1983, a Japanese patent reported the reaction of O,O,O-trialkyl phosphorothionates 1 with phosphorus oxychloride resulting in the O,S-dialkyl thiophosphorochloridates 2 and O-alkyl phosphorodichloridates 3.12 We have now found that O-aryl O,O-dialkyl thiophosphates 4 can also react with phosphorus oxychloride giving the desired products, S-alkyl O-aryl thiophosphorochloridates 5. Treatment of compounds 5 react with nucleophiles 6 in the presence of a base affords S-alkyl O-aryl thiophosphoric acid derivatives 7. Obviously, the reaction of 4 with phosphorus oxychloride includes the isomerization of P=S bond into P-S bond and the substitution of a RO group by a chlorine atom. Thus, the reaction may be called an isomerization/chlorination. Since the isomerization/chlorination of 4 can convert an achiral phosphorus atom into S-alkyl O-aryl thiophosphorochloridate 5 possessing a chiral phosphorus atom, this constitutes a new convenient method for preparation of chiral S-alkyl O-aryl thiophosphoric acid derivatives 7.

Compounds 4 react with equivalent amounts of phosphorus oxychloride at 100 °C. It takes 1.5-38 h until 4 disappears (TLC control). The reaction time increases with increasing number of carbon atoms in the R¹ group and is related to the negativity of the R² group. After the removal of byproduct 3 under reduced pressure, the products 5, which are not purified, are reacted directly with various nucleophiles 6, e.g. methanol, phenols, mercaptans, in the presence of triethylamine. The crude products 5 can also be reacted with an excess of ammonia or an amine without another base. The crude products 7 can be purified by distillation at reduced pressure, recrystallization or chromatography on silica gel. By using the above reactions, 15 new compounds 7b–p have been prepared (Tables 1 and 2).

The main advantage of this synthetic method is that dialkyl arylthiophosphates 4 obtained by using cheap low molecular weight alcohols, are used as starting materials. It avoids the use of expensive and foul smelling mercaptans or alkyl bromides. Besides, the reaction conditions are mild, and the yield of the products 7 is over 50% based on 4. However, this method has some limitations. Firstly, S-long chain alkyl or branched compounds, e.g. S-isopropyl and isobutyl derivatives cannot be obtained. Secondly, when there is a large group or
### Table 1. Compounds 7a–p

<table>
<thead>
<tr>
<th>Product</th>
<th>Reaction Time (h)*</th>
<th>Yield (%)</th>
<th>mp (°C) or bp (°C)/Torr</th>
<th>Molecular Formula or Lit. Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>12</td>
<td>71</td>
<td>126–128/0.2</td>
<td>C₁₀H₂₂O₄P₂S (246.3)</td>
</tr>
<tr>
<td>7b</td>
<td>9</td>
<td>74</td>
<td>127–128/0.6</td>
<td>C₁₂H₂₄O₅P₃ (274.3)</td>
</tr>
<tr>
<td>7c</td>
<td>13</td>
<td>51</td>
<td>131–134/0.1</td>
<td>C₁₄H₁₈O₅P₃ (301.1)</td>
</tr>
<tr>
<td>7d</td>
<td>38</td>
<td>71</td>
<td>129–131/0.1</td>
<td>C₁₆H₂₀O₅ClP₂S (280.7)</td>
</tr>
<tr>
<td>7e</td>
<td>35</td>
<td>50</td>
<td>137–139/0.3</td>
<td>C₁₈H₂₂O₅P₃ (339.3)</td>
</tr>
<tr>
<td>7f</td>
<td>9</td>
<td>67</td>
<td>–</td>
<td>C₂₀H₂₄O₅P₃S (354.4)</td>
</tr>
<tr>
<td>7g</td>
<td>9.5</td>
<td>59</td>
<td>–</td>
<td>C₂₂H₂₆O₅P₃S (399.3)</td>
</tr>
<tr>
<td>7h</td>
<td>12</td>
<td>64</td>
<td>–</td>
<td>C₂₄H₂₆O₅P₃S₂ (290.4)</td>
</tr>
<tr>
<td>7i</td>
<td>1.5</td>
<td>61</td>
<td>42–44</td>
<td>C₂₆H₂₈O₅P₃S₂ (296.3)</td>
</tr>
<tr>
<td>7j</td>
<td>1.5</td>
<td>57</td>
<td>–</td>
<td>C₂₈H₃₀O₅P₃S₂ (276.3)</td>
</tr>
<tr>
<td>7k</td>
<td>9.5</td>
<td>65</td>
<td>–</td>
<td>C₃₀H₃₂O₅P₃S₂ (259.3)</td>
</tr>
<tr>
<td>7l</td>
<td>12</td>
<td>58</td>
<td>135–138</td>
<td>C₃₂H₃₄O₅P₃S₂ (237.6)</td>
</tr>
<tr>
<td>7m</td>
<td>2</td>
<td>53</td>
<td>125–127</td>
<td>C₃₄H₃₆O₅P₃S₂ (245.3)</td>
</tr>
<tr>
<td>7n</td>
<td>1.5</td>
<td>63</td>
<td>55–57</td>
<td>C₃₆H₃₈O₅P₃S₂ (273.3)</td>
</tr>
<tr>
<td>7o</td>
<td>9</td>
<td>63</td>
<td>86–88</td>
<td>C₃₈H₄₀O₅P₃S₂ (269.4)</td>
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<tr>
<td>7p</td>
<td>20</td>
<td>52</td>
<td>69–71</td>
<td>C₄₀H₄₂O₅P₃S₂ (265.3)</td>
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### Table 2. IR and ¹H-NMR Data of Compounds 7a–p

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<thead>
<tr>
<th>Product</th>
<th>IR (film or KBr) (cm⁻¹)</th>
<th>¹H-NMR (CDCl₃/TMS) δ, J (Hz)</th>
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<tr>
<td></td>
<td>δ</td>
<td>J (Hz)</td>
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<tr>
<td></td>
<td>P=O</td>
<td>P=O–Ar</td>
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<td></td>
<td>(C=C)</td>
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### Notes

- Reaction time of isomerization/chlorination (4 + POCl₃ → 5 + 3).
- Total yield of two-step reactions based on 4.
- Satisfactory microanalyses obtained: C = 0.32, H ± 0.26.
- No data are given in Ref. 13.
- Decomposed during distillation (oil bath: 150°C at 0.1–0.2 Torr), purified by column chromatography on silica gel.

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### Additional Notes

- Several substituents, especially strongly electron-withdrawing groups on the benzene ring, this isomerization/chlorination does not occur. For example, when R² equals 4-O₂N or 4-MeS, the desired products are not formed.
Melting points were determined with a model Yanaco MP-500 apparatus. IR spectra were recorded on a model Shimadzu IR-435 spectrophotometer. 1H-NMR spectra were measured on a JEOL FX-900 instrument at 90 MHz. Column chromatography was performed on silica gel (200–300 mesh) using petroleum ether (bp 60–90 °C)/EtOAc (5:1 or 3:1) as eluent.

O-Aryl O,O-dialkyl thiophosphates 4 were synthesized according to literature, by reacting O,O-dialkyl thiophosphorochloridate with a suitable phenol in the presence of K₂CO₃ in ethyl methyl ketone at 60–80 °C for 4–6 h.

O-Methyl O-Phenyl S-Propyl Thiophosphate (7a); Typical Procedure:

A mixture of O,O-dipropyl O-phenyl thiophosphate (4a; 11.0 g, 40 mmol) and POCl₃ (6.2 g, 40 mmol) is heated at 100 °C for 12 h with stirring until 4 has disappeared from the reaction mixture [TLC control, solvent system: petroleum ether (bp 60–90 °C)/Et₂O, 10:1]. After the removal of the byproduct, O-propyl phosphorodichloridate (3, R = Pr) under vacuum (1 Torr) at 100 °C (oil bath), the residue is dissolved in CHCl₃ (40 mL). To the chloroform solution is added dropwise a mixture of MeOH (10 mL) and Et₃N (6.5 g, 64 mmol) at 20 °C, the mixture is stirred at 35–40 °C for 4 h. The mixture is cooled to r.t. and poured into cold water (50 mL). The organic layer is separated, washed with water (40 mL), and dried (MgSO₄). After the removal of the solvent the crude product is distilled under reduced pressure; yield: 7.0 g (71%), bp 126–128 °C/0.2 Torr (Lit. 13 no data) (Tables 1 and 2).

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