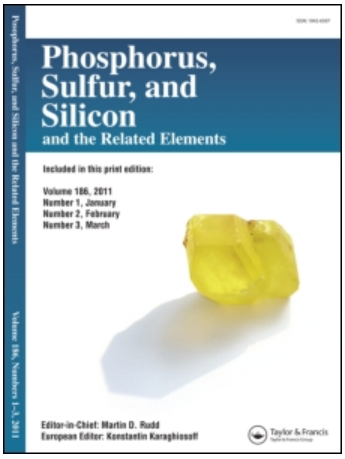


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# THE ISOMERIZATION/CHLORINATION OF O,O-DIALLYL THIOPHOSPHORO (-NO)THIONATES WITH PHOSPHORUS OXYCHLORIDE — A NEW CONVENIENT METHOD FOR SYNTHESIS OF S-ALLYL THIOPHOSPHORIC(-NIC) ACID DERIVATIVES

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# THE ISOMERIZATION/CHLORINATION OF O,O-DIALLYL THIOPHOSPHORO (-NO)THIONATES WITH PHOSPHORUS OXYCHLORIDE — A NEW CONVENIENT METHOD FOR SYNTHESIS OF S-ALLYL THIOPHOSPHORIC(-NIC) ACID DERIVATIVES

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The isomerization/chloriation of O,O-diallyl thiophosphoro(-no)thionates with phosphrus oxychloride gave S-allyl thiophosphoro(-no)chloride, which reacted with subsitituted phenol in chloroform in the presence of triethylamine to afford eighteen new S-allyl thiophosphoric(-nic) acid derivatives. Thus, a new convenient method has been provided for synthesis of the title compounds.

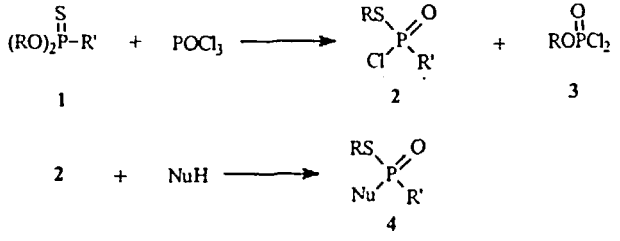
*Keywords:* Isomerization; Chlorination; Phosphoro(-no)thionate; Phosphoro(-no)thiolate; Phosphoro(-no)chlorothiolate; phosphorus oxychloride

## 1. INTRODUCTION

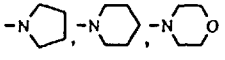
In 1991 we found that the isomerization/chlorination of O,O-dialkyl O-aryl thiophosphates 1 (R′=ArO) with phosphorus oxychloride can take place and gives S-alkyl O-aryl thiophosphorochloridates 2 (R′=ArO) and O-alkyl phosphorodichloridates 3[1]. In the reaction, when 1 is chlorinated with phosphorus oxychloride, the isomerization of the P=S to the P-S occurs simultaneously. Additionally, this isomerization/chlorination can

* Corresponding author

convert an achiral phosphorus atom into a chiral one to give **2**. Later investigations indicated that when R′ equals alkylthio[2], arylthio[2], dialkylamino[3], phenyl[4], methyl[5], and nitrogen heterocyclic group[6] in **1**, respectively, the isomerization/chlorination of **1** with phosphorus oxychloride also proceeds smoothly and gives the desired products **2** and **3**. The products **2** react further with various nucleophiles, NuH, to give a variety of compounds **4**. Thus, this constitutes a new convenient method for synthesis of S-alkyl thiophosphoric(-nic) acid derivatives probably possessing extensive biological activity.



R = $C_{1\sim6}$ Alkyl, 2-Chloroethyl
R′ = Alkoxy, Aryloxy, Alkylthio, Dialkylamino, Me, Ph,



In the previous papers[1~6], the isomerization/chlorination of **1** has been only investigated when R equals saturated alkyl such as $C_{1\sim6}$ alkyl or 2-chloroethyl. Here we report that when R equals unsaturated allyl in **1** the isomerization/Chlorination of **1** (R=allyl, **5**) with phosphorus oxychloride can also take place and gives the desired product **6** and **7** (Table I). Products **6** reacted further with substituted phenol in the presence of organic or inorganic base as acid acceptor to give the title compounds S-allyl O-substituted phenyl thiophosphric(-nic) acid esters **8** (Table II).

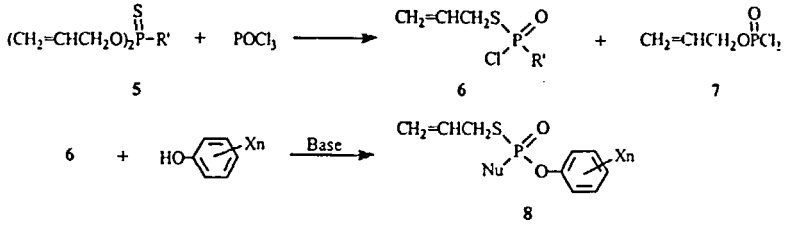


TABLE I The Isomerization/Chlorination of **5** with $POCl_3$ and Data of Products **6**

| *6* | *R'* | *Reaction temp.(°C)* | *Reaction time (h)* | $n_D^{25}$ | *Yield (%)* | *$^1H$ NMR ($CDCL_3$/TMS), δ, $J_{P-H}$(Hz)* |
|---|---|---|---|---|---|---|
| a | MeO | 70~80 | 3 | 1.5005 | 68.3 | 3.78(dd,2H,J=10.8), 3.92(d,3H,J =9.2), 5.40 (t,2H), 6.00(m,1H) |
| b | EtO | 70~80 | 6 | 1.4926 | 82.0 | 1.44(t,3H), 3.76(dd,2H,J=9.4), 4.40(dq,2H, J=10.8), 5.36(t,2H), 6.00(m,1H) |
| c | PrO | 80~90 | 8 | 1.4941 | 58.2 | 0.98(t,3H), 1.77(m,2H), 3.63(dd,2H,J=10.8), 4.19(dt,2H,J=10.6), 5.30(t,2H), 5.96(m,1H) |
| d | EtS | 60~70 | 8 | 1.5540 | 72.2 | 1.44(t,3H), 3.78(dq,2H,J=18.2), 3.76(dd,2H, J=18.0), 5.40(t,2H), 6.00(m,1H) |
| e | PrS | 60~70 | 12 | 1.5484 | 60.3 | 1.04(t,3H), 1.84(m,2H), 3.08(dt,2H,J=20.8), 3.72(dd,2H,J=17.6), 5.32(t,2H), 5.92(m,1H) |
| f | $Et_2N$ | 100 | 16 | 1.4826 | 45.0 | 1.24(t,6H), 3.68(dq,4H,), 3.81(dd,2H,J=9.2), 5.24(t,2H), 6.00(m,1H) |
| g | Me | 65 | 6 | 1.4476 | 77.8 | 1.98(d,3H,J=15.6), 3.56(dd,2H,J=14.4), 5.28 (t,2H), 5.88(m,1H) |

## 2. RESULTS AND DISCUSSION

Compounds **5** reacted with equivalent amounts of phosphorus oxychloride at 60~100°C. It took 3~20h until **5** disappeared from the reaction mixture (TLC control). When R′ group equals methyl, lower alkoxy or lower alkylthio in **5**, the isomerization/chlorination of **5** can be completed at a lower reaction temperature and within a shorter time; whereas when R′ is diethylamino, a relatively higher temperature and a longer time are required, and in the cases, the yields of products **6** are obviously lower, while viscous polymer increases. After removal of by-product **7** under reduced pressure, the crude product **6** was purified by column chromatography on silica gel, then **6** reacted with various substituted phenols in th presence of HCl acceptor respectively to give S-allyl O-substituted phenyl phosphoro(-no)thiolates **8**, which can be purified by column chromatography on silica gel or recrystallization. Thus, eighteen new compounds **8** have been prepared (Table II and III). The bioassay results on their fungicidal activity against five plant disease fungi (P. Zeae, A. Solani, R. Solani, P. Piricola, C. Arachidicala) show that **8** possess somewhat excellent fungicidal activity at 0.005% concentration.



The $^1$H NMR data of the reactants **5** and the isomerization/chlorination products **6** are shown in the table IV and I, respectively. These data indicated that the chemical shift value ($\delta$=4.56~4.72 ppm) of proton on the $\alpha$-carbon of allyl in **5** has changed into 3.56~3.78 in **6**. This result proved that allyloxy in **5** has been converted to allylthio in **6**. Additionally, in the final products **8**, a strong absorption peak at 1215~1262cm$^{-1}$ in IR spectra is identified with P=O group, and a characteristic double doublet peak at 3.32~3.72 ppm in $^1$H NMR spectra represents the presence of P-S-$\underline{CH_2}$. To be sure, the above results showed that the isomerization/chlorination of **5** has really occurred and give the products **6**.

Previously [1~6] we found that the isomerization/chlorination of **1** becomes more and more difficult as the number of carbon atoms of R group increases. Therefore O,O-dimethyl phosphorothionates, **1** (R = methyl), possess the relatively best reactivity in the isomerization/chlorination. In order to evaluate the reactivity of unsaturated O,O-diallyl phosphorothionates **5**, the isomerization/chlorination of O,O-diallyl O-methyl phosphorothionate **5a** was thoroughly investigated by the GC-MS technique. After the isomerization/chlorination of **5a** completed , the reaction mixture was analyzed by the GC-MS technique. The desired products **6a** and the by-product **7** were found in the mixture, and however the possible products **9** (One of allyloxy groups was leaved and methoxy was isomerized) and **10** (One allyloxy was isomerized and meth-

oxy was leaved) were not detected. This result preliminarily indicates that the unsaturated allyloxy possesses a better ability as isomerizing or leaving group in the isomerization/chlorination than saturated lower alkoxy, such as methoxy.

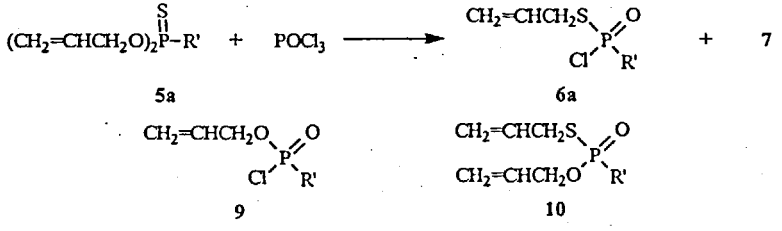




TABLE II Data of Compounds **8** Prepared

| *8* | *R'* | *Xn* | $n_D^{25}$ *or mp (°C)* | *Yield (%)* | *Elemental Analysis Found (Calc.)* | | |
|---|---|---|---|---|---|---|---|
| | | | | | *C%* | *H%* | *N%* |
| a | PrS | 4-Me | 1.5775 | 69.5 | 51.94(51.63) | 6.29(6.33) | |
| b | PrS | 2,4,5-$Cl_3$ | 1.5850 | 61.6 | 36.47(36.78) | 3.70(3.60) | |
| c | PrS | 2,4-$Cl_2$ | 1.5760 | 70.0 | 40.39(40.34) | 4.16(4.23) | |
| d | PrS | 2,6-$Cl_2$-4-Me | 1.5741 | 53.9 | 41.95(42.05) | 4.38(4.61) | |
| e | EtS | 2,4-$Cl_2$ | 1.5631 | 55.4 | 38.71(38.49) | 3.42(3.82) | |
| f | EtS | 2-Cl-4-Br | 1.5847 | 58.7 | 34.02(34.08) | 2.98(3.38) | |
| g | EtS | 2,6-$Cl_2$-4-Me | 1.5895 | 56.9 | 40.42(40.34) | 3.88(4.23) | |
| h | Me | 2,4,5-$Cl_3$ | 1.5718 | 69.4 | 36.13(36.22) | 3.19(3.04) | |
| i | Me | 2,4-$Cl_2$ | 1.5708 | 56.7 | 40.32(40.42) | 3.53(3.73) | |
| j | Me | 2,6-$Cl_2$-4-Me | 155~156 | 61.7 | 42.54(42.46) | 3.79(4.21) | |
| k | $Et_2N$ | 2,4,5-$Cl_3$ | 1.5569 | 47.2 | 40.12(40.17) | 4.38(4.41) | 3.67(3.60) |
| l | $Et_2N$ | 2,6-$Cl_2$-4-Me | 1.5500 | 57.0 | 45.28(45.66) | 5.50(5.47) | 3.87(3.80) |
| m | $Et_2N$ | 2-Cl-4-Br | 1.5421 | 62.7 | 39.45(39.16) | 4.74(4.55) | 3.47(3.51) |
| n | $Et_2N$ | 2,4-$Cl_2$ | 1.5450 | 42.4 | 44.39(44.08) | 5.30(5.12) | 4.01(3.95) |
| o | EtO | 2,4,5-$Cl_3$ | 1.5611 | 47.0 | 36.15(36.54) | 3.44(3.34) | |
| p | EtO | 2-Cl-4-Br | 1.5517 | 56.5 | 35.32(35.55) | 3.86(3.53) | |
| q | PrO | 2,4,5-$Cl_3$ | 1.5535 | 58.6 | 38.45(38.36) | 3.49(3.76) | |
| r | PrO | 2,6-$Cl_2$-4-Me | 1.5455 | 60.7 | 43.78(43.94) | 4.46(4.82) | |

TABLE III IR and $^1$H NMR Data of Compounds **8**

| 8 | IR (film or KBr), ν ($cm^{-1}$) | | | | $^1H$ NMR ($CDCl_3$/TMS), δ, $J_{p\text{-}H}$ (Hz) |
|---|---|---|---|---|---|
| | P-S-C | P-O-Ar | P=O | P-C/N | |
| a | 597 | 901,1185 | 1245 | | 1.00(t,3H), 1.76(m,2H), 2.32(s,3H), 2.96(dt,2H,J=15.1), 3.60(dd, 2H,J=14.8), 5.24(t,2H), 5.92(m,1H), 7.16(m,4H) |
| b | 595 | 947,1118 | 1229 | | 1.02(t,3H), 1.80(m,2H), 3,00(dt,2H,J=16.2), 3.68(dd,2H, J=15.2), 5.28(t,2H), 5.92(m,1H), 7.56(m,2H) |
| c | 594 | 914,1138 | 1215 | | 1.00(t,3H), 1.76(m,2H), 3.00(dt,2H,), 3.68(dd,2H,J=15.1). 5.24(t, 2H), 5.92(m, 1H), 7.40(m,3H) |
| d | 594 | 927,1199 | 1253 | | 1.00(t,3H), 1.76(m,2H), 2.08(s,3H), 3.00(dt,2H,J=15.2), 3.64(dd, 2H,J=15.1), 5.24(t,2H), 5.92(m,1H), 7.16(s,2H) |
| e | 572 | 949,1159 | 1218 | | 1.44(t,3H), 3.09(dq,2H,J=15.2), 3.72(dd,2H,J=16.2), 5.32(t,2H), 6.00(m,1H), 7.44(m,3H) |
| f | 563 | 949,1158 | 1216 | | 1.44(t,3H), 3.12(dq,2H,J=15.2), 3.72(dd,2H,J=15.6), 5.34(t,2H), 5.96(m,1H), 7.48(m,3H) |
| g | 595 | 880,1199 | 1257 | | 1.42(t,3H), 2.32(s,3H), 3.10(dq,2H,J=16.2), 3.2(dd,2H, J=15.5), 5.32(t,2H), 5.96(m,1H), 7.24(s,2H) |
| h | 561 | 956,1120 | 1237 | 1250 | 2.08(d,3H,J=15.5), 3.60(dd,2H,J=14.4), 5.28(t,2H), 5.88(m, 1H), 7.64(m,2H) |
| i | 562 | 924,1139 | 1219 | 1251 | 2.08(d,3H,J=15.5), 3.56(dd,2H,J=14.4), 5.28(t,2H), 5.88(m,1H), 7.48(m,3H) |
| j | 577 | 933,1201 | 1220 | 1278 | 2.09(d,3H,J=16.0), 2.26(s,3H), 3.57(m,2H), 5.18(q,2H), 5.88(m, 1H), 7.12(m,2H) |
| k | 575 | 948,1121 | 1251 | 948 | 1.20(t,6H), 3.36(dq,4H,J=13.0), 3.54(dd,2H,J=14.0). 5.20(t,2H), 5.84(m,1H), 7.55(s,1H) |
| l | 589 | 947,1166 | 1252 | 925 | 1.10(t,6H), 2.28(s,3H), 3.38(dq,4H,J=13.3), 3.50(dd,2H, J=13.7), 5.20(t,2H), 5.84(m,1H), 7.78(s,2H) |
| m | 556 | 948,1167 | 1252 | 948 | 1.20(t,6H), 3.30(dq,4H,J=13.3), 3.64(dd,2H,J=12.6), 5.20(m, 2H), 5.88(m,1H), 7.44(m,3H) |
| n | 565 | 949,1168 | 1251 | 945 | 1.20(t,6H), 3.32(dq,4H,J=12.3), 3.50(dd,2H,J=11.2), 5.20(m, 2H), 5.88(m,1H), 7.40(m,3H) |
| o | 583 | 954,1156 | 1262 | | 1.41(t,3H), 3.56(dd,2H,J=14.6), 4.32(dq,2H,J=11.0), 5.30(m, 2H), 5.81(m,1H), 7.51(m,2H) |
| p | 585 | 961,1157 | 1250 | | 1.40(t,3H), 3.53(dd,2H,J=14.6), 4.30(dq,2H,J=11.0), 5.16(m, 2H), 5.81(m,1H), 7.33(m,3H) |
| q | 591 | 948,1153 | 1249 | | 1.02(t,3H), 1.82(m,2H), 3.64(dd,2H,J=16.2), 4.28(dt,2H,J=9.4). 5.32(t,2H), 5.90(m,1H), 7.60(t,2H) |
| r | 589 | 947,1158 | 1246 | | 1.02(t,3H), 1.80(m,2H), 2.36(s,3H), 3.72(dd,2H,J=16.2), 4.30(dt, 2H,J=9.4), 5.36(t,2H), 6.00(m,1H), 7.25(s,4H) |

TABLE IV Data of Compounds 5 Prepared

| 5 | R' | $n_D^{25}$ | Yield (%) | $^1H$ NMR ($CDCl_3$ / TMS), δ, $J_{P\text{-}H}$(Hz) |
|---|---|---|---|---|
| a | MeO | 1.4704 | 74.3 | 3.80(d,3H,J=13.7), 4.56(dd,4H,J=9.8), 5.40(t,4H), 5.96(m,2H) |
| b | EtO | 1.4749 | 63.1 | 1.36(t,3H), 4.20(dq,2H,J=10.1), 4.56(dd,4H,J=10.1), 5.32(t,4H), 5.92(m,2H) |
| c | PrO | 1.4680 | 67.8 | 0.96(t,3H), 1.74(m,2H), 4.08(dt,2H,J=10.1), 4.62(dd,4H, J=10.0), 5.40(t,2H), 6.00(m,1H) |
| d | EtS | 1.5247 | 63.2 | 1.38(t,3H), 2.96(dq,2H,J=16.2), 4.70(dd,4H,J=10.1), 5.44(t,4H), 6.04(m,2H) |
| e | PrS | 1.5170 | 70.2 | 1.02(t,3H), 1.85(m,2H), 2.90(dt,2H,J=11.6), 4.72(dd,4H, J=10.1), 5.32(t,4H), 5.92(m,2H) |
| f | $Et_2N$ | 1.4922 | 82.5 | 1.20(t,6H), 3.36(dq,4H,J=12.8), 4.60(dd,4H,J=10.1), 5.40(m, 4H), 6.00(m,2H) |
| g | Me | 1.4878 | 87.0 | 1.88(d,3H,J=15.8), 4.60(dd,4H,J=10.8), 5.36(t,4H), 5.96(m,2H) |

## EXPERIMENTAL

All temperature are uncorrected. Melting points were determined with a Yanaco MP-500 apparatus. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer as thin film or KBr pellets. $^1$H NMR spectra were measured on a JEOL FX-90Q instrument at 90 MHz, using TMS as internal standard and $CDCl_3$ as solvent. Column chromatography was performed on silica gel (200~300mesh) using petroleum ether (bp 69~90°C)/EtOAc as eluent.

### O,O-diallyl phosphoro(-no)thionates 5

According to a general procedure, sodium allyl alcoholate reacted with O-mehtyl (ethyl or propyl) thiophosphorodichloridate, N,N-diethylamino thiophosphoramidodichloridate or thiomethylphosphonodichloride in toluene to give compound **5a**, **5b**, **5c**, **5f**, or **5g**, respectively. Compound **5e** or **5d** was prepared from the reaction of sodium O.O-diallyl phosphorodithioate with ethyl iodide or propyl bromide (Table IV).



### S-Allyl (di)thiophosphoro(-no)chloridates 6 (General procedure)

A mixture of O.O-diallyl phosphoro(-no)thionate **5** (0.01 mol) and $POCl_3$ (1.54 g, 0.01 mol) was heated with stirring at 60~100 °C for 3~20 h until **5** had disappeared from the reaction mixture (TLC control, solvent system petroleum ether (bp 60~90 °C) EtOAc 5:1). After removal of by-product O-allyl phosphorodichloridate **7**, the crude product **6** was purified by using silica gel column chromatography. Data of **6** prepared are listed in Table I.

### S-Allyl O-substituted phenyl phosphoro(-no)thionates 8 (General procedure)

To a mixture of substituted phenol (0.01 mol), triethylamine (0.011 mol) and $CHCl_3$ (20 mL) was added dropwise a solution of **6** (0.01 mol) in $CHCl_3$ (10 mL) at 20~25 °C. After completion of addition, the resulting mixture was stirred at room temperature for 1h, then heated at 55 °C for 5 h with stirring. After cooling to r.t., the reaction mixture was poured into cold water (30 mL) and shaked thoroughly. The organic layer was sepa-

rated and dried ($MgSO_4$). After removal of the solvent, the crude product **8** was purified by using silica gel column chromatography. Data of **8** prepared are listed in Table II and III.

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