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The Isomerization/Chlorination of 0,0-Dialkyl Methylthiophosphonates with Phosphorus Oxychloride—A New Convenient Synthesis of S-Alkyl Methylthiophosphonic Acid Derivatives

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ABSTRACT

A new method for the synthesis of S-alkyl methylthiophosphonic acid derivatives is reported. The chlorination of 0,0-dialkyl methylthiophosphonates **8** *with phosphorus oxychloride proceeds with isomerization of the P=S to the P–S bond to give S-alkyl methylthiophosphonochloridates* **9**, *which react further with various nucleophiles in the presence of triethylamine to afford S-alkyl methylthiophosphonic acid derivatives* **10**. *Among them, several compounds* **10** *show excellent fungicidal or insecticidal activities.* © *1995 John Wiley & Sons, Inc.*

INTRODUCTION

In synthetic methods reported for S-alkyl thiophosphoric acid derivatives possessing extensive biological and especially insecticidal activity, mercaptans or their derivatives were generally used as starting materials [1–7], or they were prepared by reacting salts of thiophosphoric acid with an alkyl bromide [8–11].

In 1983, a Japanese patent reported the reaction of 0,0,0-trialkyl thiophosphates **1** with phosphorus oxychloride, resulting in the 0,S-dialkyl thiophosphorochloridates **2** and O-alkyl phosphorodichloridates **3** [12]. Later, we found that 0,0-dialkyl thiophosphoric acid derivatives **4** can also react with phosphorus oxychloride, giving S-alkyl thiophosphorochloridates **5** and **3** [13–17]. In this reaction, when compounds **4** are chlorinated with phosphorus oxychloride, the isomerization of the P=S to the P–S bond occurs at the same time. The isomerization/chlorination of **4** can convert an achiral phosphorus atom into a chiral phosphorus atom to give **5**, which reacts further with various nucleophiles, NuH **6**, in the presence of a base to afford varied S-alkyl thiophosphoric acid derivatives **7**. Thus, this constitutes a new, convenient method for the synthesis of this type of compound possessing extensive biological activity.

Recently, we have found that the isomerization/chlorination of 0,0-dialkyl methylthiophosphonates **8** with phosphorus oxychloride can also give the desired products, S-alkyl methylthiophosphonochloridates **9** and 0-alkyl phosphorodichloridates **3**. In this article, we report that the isomer-

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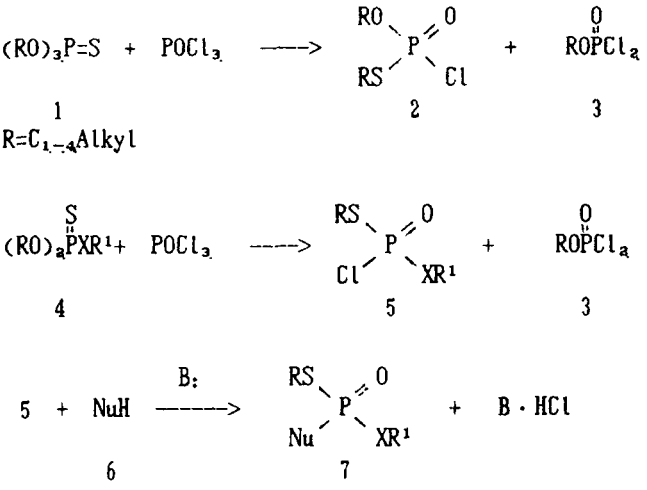
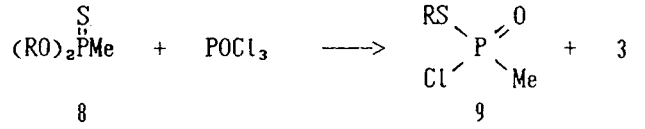
ization/chlorination can be used for the synthesis of S-alkyl methylthiophosphonic acid derivatives **10**.

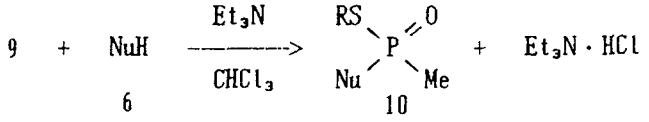


RESULTS AND DISCUSSION

Compounds **8** react with equivalent amounts of phosphorus oxychloride at 80–100°C. It takes 1.5–20 hours for **8** to disappear (TLC control). The reaction time and temperature increase with increasing number of carbon atoms in the R group. Compared with the related thiophosphate **4**, the reaction of the thiophosphonate **8** with phosphorus oxychloride occurs more easily. When the R group of the thiophosphonate **8** and thiophosphate **4** equals a long chain alkyl group (over four carbon atoms) or 2-chloroethyl, the desired product **9** can be obtained, but the product **5** cannot. Additionally, when the R group is a bulky group, e.g., isopropyl or *t*-butyl, the desired product **9** or **5** cannot always be formed.



8	*R*	*t* (°C)	*Time* (*h*)	*8*	*R*	*t* (°C)	*Time* (*h*)
a	Me	80	1.5	**e**	Amy	100	13
b	Et	100	13	**f**	Hexyl	100	20
c	Pr	100	5	**g**	$ClCH_2CH_2$	100	15
d	Bu	100	7				



10	*R*	*Nu*	*10*	*R*	*Nu*
a	Me	2, 4, 5-$Cl_3C_6H_2O$	**j**	Pr	2-Cl-4-BrC_6H_3O
b	Et	2, 4, 5-$Cl_3C_6H_2O$	**k**	Pr	4-$MeSC_6H_4O$
c	Me	4-$MeSC_6H_4O$	**l**	Pr	$PhCH_2S$
d	Et	4-$MeSC_6H_4O$	**m**	Pr	4-ClC_6H_4O
e	Et	2-Cl-4-BrC_6H_3O	**n**	Bu	EtO
f	Et	$PhCH_2S$	**o**	Bu	2, 4, 5-$Cl_3C_6H_3O$
g	Et	EtO	**p**	Amyl	2, 4, 5-$Cl_3C_6H_2O$
h	Pr	2-Cl-4-BrC_6H_3O	**q**	Hexyl	Et_2N
i	Pr	2, 4, 5-$Cl_3C_6H_2O$	**r**	$ClCH_2CH_2$	2, 4, 5-$Cl_3C_2H_2O$

In the thiophosphate case, separation of isomerization/chlorination products **5** (except X = NR^1 in **5**) by column chromatography on silica gel or by distillation under vacuum was attempted and was unsuccessful because of decomposition of **5**, but in the methylthiophosphonate case, the products **9** were successfully separated by distillation under reduced pressure and were identified (Table 1).

The products **9**, purified by distillation under vacuum, were reacted further with various nucleophiles **6**, e. g., alcohols, phenols, mercaptans, and amines, in the presence of triethylamine to give S-alkyl 0-alkyl(aryl) methyphosphonothiolates **10a–e, g–k, m–p, r,** S-alkyl S-alkyl methylphosphonodithiolates $\mathbf{10}_{f,l}$, and S-alkyl N,N-diethyl methylphosphonamidothiolate $\mathbf{10}_q$, respectively. Crude products **10** can be purified by column chromatography on silica gel. Using the preceding reactions, 18 compounds **10** have been prepared (Tables 2 and 3); only compounds **10g, n** have been previously reported in the literature [19]. The main advantage of this synthetic method is that 0,0-dialkyl methylthiophosphonates **8**, obtained by using cheap low molecular weight alcohols, are used as starting materials; this avoids the use of expensive and foul smelling mercaptans or alkyl bromides.

The results of the tests in biological activity showed that compounds **10a, b, l, o, p, r** and **10a, h, j, k, m** possess excellent fungicidal and insecticidal activity, respectively.

EXPERIMENTAL

All temperatures are uncorrected. Melting points were determined with a Yanaco MP-500 apparatus. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer as thin films or KBr pellets. ^1H NMR spectra were measured on a JEOL FX-90Q instrument at 90 MHZ, using TMS as an internal standard and CDCl, as the solvent. Column chromatography was performed on silica gel (200–300 mesh) using petroleum ether (bp 60–90°C)/EtOAc (5:1 or 3:1) as the eluent.

TABLE 1 Data of Compounds **9** Prepared

9	R	Bp (°C/mm)	n_D^{25}	Yield* (%)	^1H NMR ($CDCl_3$/TMS), δ (ppm) J_{PH} (Hz)
a**	Me	72–74/8	1.5135	73.9	2.18 (d, 3H, J = 15.1), 2.41 (d, 3H, J = 16.2)
b**	Et	73–75/6	1.5030	74.9	1.43 (t, 3H) 2.26 (d, 3H, J = 14.8), 3.12 (dq, 2H, J = 15.1)
c**	Pr	91–93/8	1.4960	77.3	1.06 (t, 3H), 1.84 (m, 2H), 2.32 (d, 3H, J = 14.8), 3.14 (dt, 2H, J = 14.5)
d**	Bu	90–92/0.7	1.4990	71.4	0.88 (t, 3H), 1.20–1.92 (m, 4H), 2.22 (d, 3H, J = 14.5), 3.05 (dt, 2H, J = 14.4)
e	Amyl	99–101/0.3	1.4990	45.9	0.88 (t, 3H), 1.00–2.00 (m, 6H), 2.23 (d, 3H, J = 14.8), 3.05 (dt, 2H, J = 14.5)
f	Hexyl	102–104/0.2	1.5095	37.6	0.90 (t, 3H), 1.36 (m, 6H), 1.80 (m, 2H), 2.22 (d, 3H, J = 14.5), 3.12 (dt, 2H, J = 14.8)
g***	$ClCH_2CH_2$	91–93/0.4	1.4959	51.6	2.23 (d, 3H, J = 16.2), 2.92 (dt, 2H, J = 14.8), 3.20 (t, 2H)

*Isolated yield
**Cf. [18]
***Cf. [21]

TABLE 2 Data of Compounds **10** Prepared

10	n_D^{25}	Yield (%)	Molecular Formula or Literature Data	Elemental Analyses C% Calcd	C% Found	H% Calcd	H% Found
a	1.5861	48.4	$C_8H_8Cl_3O_2PS$ (305.5)	31.45	31.28	2.64	2.98
b	1.5666	63.7	$C_9H_{10}Cl_3O_2PS$ (319.6)	33.83	33.56	3.15	3.24
c	1.5725	68.6	$C_9H_{13}O_2PS_2$ (248.3)	43.54	43.73	5.28	5.12
d	1.5809	61.0	$C_{10}H_{15}O_2PS_2$ (262.3)	45.96	45.70	5.79	5.84
e	1.5728	67.8	$C_9H_{11}BrClO_2PS$ (329.6)	32.80	32.50	3.36	3.29
f	1.5766	52.6	$C_{10}H_{15}OPS_2$ (246.3)	48.76	48.77	6.14	5.95
g	1.4703	60.3	bp 96–98°C/10 mm Ref. [19]				
h	1.5549	65.2	$C_{10}H_{13}Cl_2O_2PS$ (299.2)	40.15	39.86	4.38	4.40
i	1.5641	63.7	$C_{10}H_{12}Cl_3O_2PS$ (333.6)	36.01	36.22	3.63	3.56
j	1.5704	46.2	$C_{10}H_{13}BrClO_2PS$ (343.6)	34.96	34.93	3.81	3.94
k	1.5725	54.8	$C_{11}H_{17}O_2PS_2$ (276.3)	47.81	47.92	6.20	6.36
l	1.5811	53.3	$C_{11}H_{17}OPS_2$ (260.9)	50.64	50.69	6.57	6.82
m	1.5425	55.9	$C_{10}H_{14}ClO_2PS$ (264.7)	45.39	45.13	5.33	5.29
n	1.4886	63.7	bp 112–114°C/mm Ref. [19]				
o	1.5675	54.6	$C_{11}H_{14}Cl_3O_2PS$ (347.6)	38.01	37.98	4.06	4.20
p	1.5046	52.2	$C_{12}H_{16}Cl_3O_2PS$ (361.6)	39.85	40.13	4.46	4.58
q	1.5125	53.1	$C_{11}H_{26}NOPS$ (251.4)	52.56	52.59	10.43	10.36
r	1.5820	48.2	$C_9H_9Cl_4O_2PS$ (354.0)	30.54	30.51	2.56	2.54

0,0-Dialkyl Methylthiophosphonates **8**

Compounds **8** were prepared according to a general procedure, by reacting methylthiophosphonodichloride with a suitable alcohol in the presence of triethylamine at 20–60°C for 2–4 hours or with a sodium alkoxide at 15–40°C for 2–3 hours. The crude products **8** were purified by distillation at reduced pressure or by column chromatography on silica gel (Table 4).

S-Ethyl Methylthiophosphonochloridate **9b** *(Typical Procedure)*

A mixture of 0,0-diethyl methylthiophosphonate **8b** (3.95 g, 24 mmol) and $POCl_3$ (3.70 g, 24 mmol) was heated at 95–100°C for 3 hours with stirring until **8b** had disappeared from the reaction mixture (TLC control, solvent system: petroleum ether (bp 60–90°C)/EtOAc 5:1). After removal of the by-product, 0-ethyl phosphorodichloridate **3** (R = Et) under vacuum (10 mm) at 70°C (oil bath), the residue was

TABLE 3 IR and ^1H NMR Data of Compounds **10**

10	IR (film or KBr) (cm^{-1}) P–S–C	P=O	P–Me	^1H NMR ($CDCl_3$/TMS), δ (ppm), J_{PH} (Hz)
a	535	1200	1299	1.98 (d, 3H, J = 15.8), 2.26 (d, 3H, J = 14.8), 7.34 (m, 2H)
b	534	1197	1296	1.92 (d, 3H, J = 16.2), 2.22 (d, 3H, J = 13.7), 2.41 (s, 3H), 7.22 (m, 4H)
c	537	1193	1297	1.34 (t, 3H), 2.06 (d, 3H, J = 15.5), 2.92 (dq, 2H, J = 15.5), 7.40 (m, 2H)
d	534	1199	1298	1.20 (t, 3H), 1.90 (d, 3H, J = 16.2), 1.40 (s, 3H), 2.88 (dq, 2H, J = 15.8) 7.20 (m, 4H)
e	553	1218	1298	1.24 (t, 3H), 2.00 (d, 3H, J = 15.5), 2.84 (dq, 2H, J = 15.5), 7.44 (m, 3H)
f	531	1187	1287	1.32 (t, 3H), 1.80 (d, 3H, J = 14.4), 2.90 (dq, 2H, J = 13.5), 4.06 (d, 2H, J = 13.0) 7.30 (m, 5H)
g	528	1213	1298	1.26 (t, 3H), 1.38 (t, 3H), 1.88 (d, 3H, J = 15.0), 2.80 (dq, 2H, J = 13.8), 4.15 (dq, 2H, J = 11.6)
h	537	1216	1289	0.84 (t, 3H), 1.48 (m, 2H), 1.98 (d, 3H, J = 15.8), 2.78 (dt, 2H, J = 13.0), 7.30 (m, 3H)
i	538	1189	1296	0.86 (t, 3H), 1.52 (m, 2H), 1.98 (d, 3H, J = 15.8), 2.80 (dt, 2H, J = 15.0), 7.60 (m, 2H)
j	553	1220	1298	0.88 (t, 3H), 1.56 (m, 2H), 1.98 (d, 3H, J = 16.2), 2.80 (dt, 2H, J = 15.0), 7.48 (m, 3H)
k	534	1198	1295	0.86 (t, 3H), 1.52 (m, 2H), 1.90 (d, 3H, J = 16.2), 2.42 (s, 3H), 2.78 (dt, 2H, J = 13.7), 7.22 (m, 4H)
l	531	1186	1285	0.94 (t, 3H), 1.68 (m, 2H), 1.82 (d, 3H, J = 13.0), 2.84 (dt, 3H, J = 13.0), 4.08 (d, 3H, J = 13.7), 7.32 (m, 5H)
m	533	1196	1295	0.84 (t, 3H), 2.50 (m, 2H), 2.90 (d, 3H, J = 15.5), 2.72 (dt, 2H, J = 15.5), 7.24 (m, 4H)
n	527	1215	1296	0.86 (t, 3H), 1.28 (t, 3H), 1.12–1.64 (m, 4H), 2.72 (d, 3H, J = 15.8), 2.76 (dt, 2H, J = 14.0), 4.10 (m, 2H)
o	539	1196	1298	0.90 (t, 3H), 1.48 (m, 4H), 2.08 (d, 3H, J = 16.2), 2.94 (dt, 2H, J = 13.7), 7.40 (m, 2H)
p	539	1217	1310	0.80 (t, 3H), 1.20 (m, 4H), 1.54 (m, 2H), 2.04 (d, 3H, J = 16.2), 2.86 (dt, 2H, J = 13.7), 7.46 (m, 2H)
q	540	1233	1311	0.90 (t, 3H), 1.00–1.86 (m, 14H), 2.08 (d, 3H, J = 16.4) 2.80 (m, 2H), 3.30 (m, 4H)
r	530	1232	1312	1.96 (d, 3H, J = 18.4), 2.60 (m, 2H), 3.70 (m, 2H), 7.52 (m, 2H)

TABLE 4 Compounds **8** Prepared

8	R	B_p (°C/mm)	n_D^{25}	Yield* (%)	^1H NMR ($CDCl_3$/TMS) δ (ppm), J_{PH} (Hz)
a**	Me	52–54/2	1.4750	90.3	1.80 (d, 3H, J = 16.4), 3.75 (d, 3H, J = 13.3)
b**	Et	58–60/2	1.4615	92.2	1.50 (t, 6H), 1.80 (d, 3H, J = 16.7), 4.25 (dq, 4H, J = 12.0)
c	Pr	86–88/2	1.4606	84.2	0.95 (t, 6H), 1.64 (m, 4H), 1.83 (d, 3H, J = 16.2), 4.08 (dq, 4H, J = 11.8)
d	Bu	90–91/0.8	1.4600	65.2	0.86 (t, 6H), 1.10–1.65 (m, 12H), 1.72 (d, 3H, J = 15.3), 4.05 (dq, 4H, J = 11.6)
e	Amyl	118–120/0.8	1.4650	63.5	0.86 (t, 6H), 1.10–1.65 (m, 12H), 1.72 (d, 3H, J = 15.8), 4.08 (dq, 4H, J = 12.0)
f	Hexyl	106–108/0.5	1.4640	87.5	0.8 (t, 6H), 1.00–1.82 (m, 16H), 2.20 (d, 3H, J = 16.2), 4.02 (dq, 4H, J = 12.4)
g	$ClCH_2CH_2$	112–114/0.5	1.5020	54.0	1.82 (d, 3H, J = 16.2), 3.62 (t, 4H), 4.30 (dt, 4H, J = 12.8)

*Isolated yield
**See Ref. [20]

distilled under reduced pressure to give the product **9b**; yield: 2.85 g (74.9%), bp 73–75 °C/8 mm, n_D^{25} 1.5030 (Table 1).

S-Ethyl O-(4-methylthio)Phenyl Methylphosphonothiolate **10d** *(Typical Procedure)*

To a mixture of **9b** (2.70 g, 1 mmol) and $CHCl_3$ (15 mL) was added dropwise a solution of 4-methylthiophenol (2.38 g, 17 mmol), triethylamine (1.81 g, 18 mmol) and $CHCl_3$ (10 mL) at 20°C. The reaction mixture was stirred at 35–40 °C for 5 hours then cooled to r.t. and poured into cold water (15 mL). The organic layer was separated, washed with water (15 mL), and dried ($MgSO_4$). After removal of the solvent, the crude product **10d** was purified by using column chromatography on silica gel; yield: 2.72 g (61.0%), n_D^{25} 1.5809 (Tables 2 and 3).

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