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THE CHLORINATION REACTION OF O-ALKYL S-ALKYL(ARYL) THIOPHOSPHORIC(-NIC) ACID DERIVATIVES WITH PHOSPHORUS OXYCHLORIDE

ZHENG-JIE HE, WEN-BING CHEN, FU-PENG MA, ZHENG-HONG ZHOU and CHU-CHI TANG*

Institute of Elemento-Organic Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P.R. China

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It is reported that a variety of O-alkyl S-alkyl(aryl) thiophosphoric(-nic) acid derivatives **4** can be readily chlorinated with phosphorus oxychloride giving S-alkyl(aryl) thiophosphoro(-no)chloridates **2** and O-alkyl phosphorodichloridates **3**.

Keywords: Chlorination; Phosphoro(-no)thiolate; Thiophosphoro(-no)chloridate; Phosphorus oxychloride

1. INTRODUCTION

In our laboratory, the isomerization/chlorination of a variety of O,O-dialkyl phosphoro(-no) thionates **1** with phosphorus oxychloride have been systematically studied. It was found that when R′ equals aryloxy[1], alkylthio[2], arylthio[2], dialkylamino[3], phenyl[4], methyl[5], and nitrogen heterocyclic group[6] in **1**, respectively, this reaction can proceed smoothly and gives the desired products **2** and **3**. Hence, it provides a general synthetic method for S-alkyl thiophosphoro(-no)chloridates, especially for the asymmetric ones.

During the course of investigating the isomerization/chlorination mechanism[7], it was found that the isomerization product of **1**, O,S-dialkyl phosphorothiolate **4**, can be readily chlorinated with phosphorus oxychloride leading its one alkoxy to be replaced by a chlorine atom to give S-alkyl

* Correspondence author.

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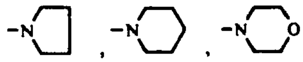
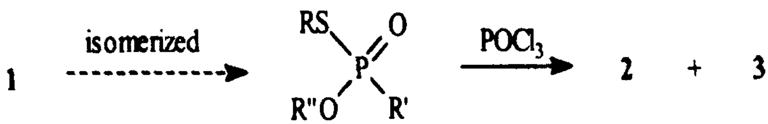
R = R'' = C_{1-4} Alkyl, 2-Chloroethyl
R' = Alkoxy, Aryloxy, Alkylthio, Dialkylamino, Me, Ph,



thiophosphorochloridate **2** and O-alkyl phosphorodichloridate **3**. In this paper, we hope that the chlorination of **4** with phosphorus oxychloride can be developed a new convenient method for synthesis of S-alkyl thiophosphoro(-no)chloridate **2**, which is a key intermediate for preparation unsymmetric S-alkyl phosphoro(-no)thiolate possessing extensive biological activity. Because compound **4** is easily prepared from some cheap material, such as dialkoxy phosphite, this reaction is of some value to the synthesis.



4

2. RESULTS AND DISCUSSION

Phosphoro(-no)thiolate **4** reacted with equivalent amount of phosphorus oxychloride at 65~100°C until **4** disappeared from the reaction mixture (TLC control). After removal of by-product **3** under reduced pressure, the crude product **2** was purified by column chromatography on silica gel or by distillation under vacuum. The structures of product **2** were confirmed by IR, ^{1}H NMR spectra and elementary analyses (Table II). When R equals alkyl or phenyl, R' is alkoxy, aryloxy, alkylthio, dialkylamino, nitrogen-containing heterocyclic group, methyl and phenyl, and R″ is C_{1-4} alkyl in compounds **4**, respectively, the chlorination of **4** can proceed smoothly giving the corresponding chlorinated products **2** in fair yields (Table I). Results show that the presence of alkylthio or arylthio RS group in **4** plays a critical role in the occurrence of this chlorination reaction. When trialkyl orthophosphoric acid ester, e.g. O,O,O-trimethyl phosphate, was treated with equivalent phosphorus oxychloride under a similar condition as **4**a, the desired product, O,O-dimethyl phosphorochloridate, was not obtained in a certain amount. In the previous literature[8,9], it was reported that O-alkyl phosphoramidates or trialkyl phosphates give only pyrophosphoric acid derivatives by treatment of phosphorus oxychloride.

TABLE I The Chlorination Reaction of 4 with $POCl_3$ and Products 2

Reactants						*Products*		
4	*R*	*R′*	*R″*	*Reaction temp. (°C)*	*Reaction time (h)*	*2*	n_D^{25}	*Yield (%)**
a	Me	MeO	Me	75	2.5	a	1.4899	72.0
b	Pr	EtO	Et	80	5	b	1.4791	77.4
c	allyl	EtO	Et	65	10	c	1.4978	63.2
d	$PhCH_2$	EtO	Et	85	5	d	1.5451	66.7
e	Ph	EtO	Et	100	5	e	1.5492	71.4
f	Et	PhO	Et	100	5	f	1.5508	42.3
g	Et	PhO	Pr	100	5	g	1.5590	71.5
h	Pr	PhO	Me	95	5	h	1.5436	85.5
i	Pr	PhO	Et	100	4	i	1.5440	55.9
j	Et	PhO	Bu	100	11	j	1.5580	74.7
k	Pr	2,4-$ClBrC_6H_3O$	Et	100	4	k	1.4770	43.9
l	Pr	MeS	Et	85	4	l	1.5490	42.8
m	Et	PrS	Et	75	5	m	1.5382	62.0
n	Et	Et_2N	Pr	100	6	n	1.4995	58.6
o	Ph	Et_2N	Et	100	5	o	1.5549	75.5
p	Pr	1-Piperidyl	Et	80	5	p	1.5189	66.7
q	Et	Me	Et	90	5	q	1.5042	75.7
r	Bu	Ph	Et	100	5	r	1.5120	62.5

* The isolated yields by column chromatography

TABLE II Data of 2 Prepared

2	IR(film), $\nu(cm^{-1})$ P=O	IR(film), $\nu(cm^{-1})$ P-Cl	^1H NMR ($CDCl_3$/TMS) δ, J_{PH} (Hz)	Elementary Analyses C% Cacl.	Elementary Analyses C% Found	Elementary Analyses H% Cacl.	Elementary Analyses H% Found
a	1223	591	2.50(d,3H,J=18.4), 3.90(d,3H,J=19.3)	14.95	14.52	3.91	3.74
b	1263	594	1.00(t,3H), 1.40(t,3H), 1.82(m,2H), 2.92(dt,2H,J=16.8), 4.20(dq,2H,J=14.1)	29.63	29.74	5.93	6.00
c	1267	587	1.35(t,3H), 3.64(dd,2H,J=18.1), 4.29(dq,2H, J=10.4), 5.22(d,2H), 5.88(m,1H)	29.92	29.79	4.98	5.13
d	1262	588	1.30(t,3H),4.11(dq,2H,J=14.2), 4.31(d,2H,J=16.2), 7.30(m,5H)	43.10	42.84	4.79	4.82
e	1266	596	1.35(t,3H), 4.29(dq,2H,J=14.3), 7.40(m,5H)	40.59	40.30	4.23	4.53
f	1264	592	1.45(t,3H), 3.00(dq,2H,J=16.1), 7.26(m,5H)	40.59	40.68	4.23	4.52
g	1265	592	1.44(t,3H), 2.96(dq,2H,J=16.2), 7.28(m,5H)	40.59	40.85	4.23	4.48
h	1260	587	0.98(t,3H), 1.78(m,2H), 3.08(dt,2H,J=18.7), 7.30(m,5H)	43.1 1	43.19	4.79	4.85
i	1261	586	0.98(t,3H), 1.88(m,2H), 3.09(dt,2H,J=18.5), 7.30(m,5H)	43.11	43.25	4.79	4.54
j	1265	593	1.44(t,3H), 2.95(dq,2H,J=16.2), 7.28(m,5H)	40.59	40.76	4.23	4.36
k	1267	590	1.02(t,3H), 1.80(m,2H), 3.18(dt,2H,J=18.7), 7.40(m,3H)	29.75	30.08	2.75	2.73
l	1226	587	1.00(t,3H), 1.74(m,2H), 2.48(d,3H,J=18.7), 2.98(dt,2H,J=18.7)	23.47	23.73	4.89	4.80
m	1249	579	1.02(t,3H), 1.44(t,3H), 1.80(m,2H), 3.05(m,4H)	27.46	27.52	5.49	5.48
n	1240	564	1.18(t,6H), 1.40(t,3H), 2.92(dq,2H,J=17.3), 3.24(dq,4H,J=14.4)	33.41	33.72	6.96	6.75
o	1249	559	0.97(t,3H), 3.17~3.30(m,4H), 7.36(m,3H), 7.58(m,2H)	45.54	45.39	5.69	5.47
p	1249	576	1.00(t,3H), 1.60(m,6H), 1.75(m,2H), 3.22(dt,2H,J=16.7), 3.26(m,4H)	39.75	39.38	7.04	6.90
q	1232	593	1.44(t,3H), 2.36(d,3H,J=16.2), 3.12(dq,2H,J=21.6)	22.71	22.89	5.04	5.45
r	1222	589	1.00(t,3H), 1.20~1.60(m,4H), 2.64(dt,2H,J=15.1), 7.48(m,5H)	48.29	48.01	5.63	5.75

TABLE III Data of Compounds 4 Prepared

4	*bp(°C/Pa)*	n_D^{25}	*Yield(%)*	*1H NMR ($CDCl_3$/TMS) δ, J_{PH} (Hz)*
a	78~80/266	1.4650	81.5	2.20(d,3H,J=15.1), 3.73(d,6H,J=12.6)
b	76~80/267	1.4560	76.4	0.93(t,3H), 1.27(t,2×3H), 1.65(m,2H), 2.76(m,2H), 4.08(m,2×2H)
c		1.4724	85.7	1.36(t,2×3H), 3.48(dd,2H,J=14.4), 4.18(dq,2×2H,J=8.6), 5.20(d,2H), 5.79(m,1H)
d	140~142/400	1.5216	67.4	1.25(t,2×3H), 4.00(d,2H,J=14.4), 4.04(dq,2x2H,J=12.8), 7.28(m,5H)
e	134~138/27	1.5136	93.5	1.28(t,2×3H), 4.18(dq,2×2H,J=8.3), 7.28~7.60(m,5H)
f	113~115/13.3	1.5165	69.9	1.28(t,3H), 1.32(t,3H), 2.85(dq,2H,J=15.8), 4.21(dq,2H, J=9.8), 7.38(m,5H)
g		1.5310	83.1	0.98(t,3H), 1.31(t,3H), 1.70(m,2H), 2.80(dq,2H,J=15.0), 4.10(dt,2H,J=9.8), 7.18(m,5H)
h	155~156/400	1.5235	39.5	1.02(t,3H), 1.72(m,2H), 2.89(dt,2H,J=13.5), 3.90(d,3H, J=10.7), 7.29(m,5H)
i	111~112/27	1.5165	49.7	0.90(t,3H), 1.33(t,3H), 1.63(m,2H), 2.83(m,2H), 4.25(m, 2H), 7.35(m,5H)
j		1.5305	79.2	0.82(t,3H), 1.10~1.90(m,4H), 1.32(t,3H), 2.82(dq,2H, J=14.8), 4.18(dt,2H,J=9.7), 7.18(m,5H)
k	110/0.13	1.5511	48.6	1.00(t,3H), 1.36(t,3H), 1.72(m,2H), 2.88(dt,2H,J=15.9), 4.25(dq,2H,J=9.8), 7.43(m,3H)
l	111~112/13.3	1.5036	60.0	1.01(t,3H), 1.37(t,3H), 1.73(m,2H), 2.33(d,3H,J=16.9), 2.87(dt,2H,J=16.2), 4.21(dq,2H,J=9.4)
m	128~130/267	1.4964	87.7	0.99(t,3H), 1.35(t,3H), 1.37(t,3H), 1.73(m,2H), 2.88(m, 4H), 4.19(dq,2H,J=9.8)
n		1.4705	75.3	0.90~1.18(m.9H), 1.30(t,3H), 1.68(m,2H), 2.70(dq,2H, J=14.8), 3.10(m,4H), 3.98(dt,2H,J=10.2)
o		1.5221	57.1	0.96(t,2×3H), 1.32(t,3H), 3.04(m,2×2H), 4.19(m,2H), 7.46(m,5H)
p	107~109/5.3	1.4916	66.4	1.00(t,3H), 1.32(t,3H), 1.56~1.84(m,8H), 2.80(dt,2H, J=14.0), 3.16(m,4H), 4.06(dq,2H,J= 11.9)
q	71~74/267	1.4726	78.7	1.32(t,3H), 1.40(t,3H), 1.78(d,3H,J=18.0), 2.90(dq,2H, J=12.2), 4.12(dq,2H,J=10.8)
r		1.5239	41.7	0.76(t,3H), 1.32(t,3H), 1.04~1.64(m,4H), 2.68(dt,2H, J=15.1), 4.19(dq,2H,J=9.2), 7.68(m,5H)

The chlorination reaction of phosphoro(-no)thiolates **4** can be performed under mild conditions. It also provides a new synthetic pathway for various S-alkyl(aryl) thiophosphoro(no)chloridates, particularly for chiral ones, which are often those important intermediates for synthesis of S-alkyl(aryl) thiophosphoric(-nic) acids derivatives probably possessing extensive biological activity. For example, the achiral S-propyl thiophosphate **4b**, $(EtO)_2P(O)SPr$, can be converted into the chiral S-propyl thiophosphorochloridate **2b**, (EtO)(PrS)P(O)Cl, in a good yield (Table I), **2b** is a key synthetic intermediate for several excellent S-propyl O-ethyl O-aryl thiophosphates insecticides, such as Profenofos, Diphenprofos, Heterophos, and Pyraclofos.

EXPERIMENTAL

All temperatures are uncorrected. IR spectra were recorded on a NICOLET 5DX spectrophotometer as thin film. ^{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. Elementary microanalysis data were determined with a Yanaco MT-3 instrument. For column chromatography, Qingdao silica gel (200~300 mesh) was used as a stationary phase. Phosphorus oxychloride was used after redistilled. Other reagents are commercial.

O-Alkyl S-alkyl(aryl) thiophosphoric(-nic) acid derivatives 4

According to a general procedure described in a previous literature[10], **4a** was prepared from the reaction of O,O-dimethyl ammonium thiophosphate with methyl iodide. Similarly, **4b~d**, **4f** and **4i** were prepared from reactions of their corresponding ammonium or sodium thiophosphates with appropriate alkyl halides RX (R is the same as in **4**, X is Cl, Br), respectively. O-Ethyl S-propyl ammonium phosphorodithioate and O-ethyl sodium phenylphosphonothioate reacted separately with butyl bromide giving **4m** and **4r**. According to an ordinary method, S-ethyl thiophosphoryl dichloride reacted with diethylamine or phenol to produce the corresponding thiophosphorochloridate, which in turn condensed with propanol or butanol giving **4g**, **4j** and **4n**. **4h**, **4k** and **4l** were prepared as described in the literatures[2,11,12], Using a known procedure[13], triethyl phosphorous acid ester reacted with phenylsulfur chloride to afford **4**e, which further reacted with phosphorus oxychloride followed by condensation with diethylamine to give **4**o. Compounds **4**prepared above were purified by distillation under reduced pressure or by column chromatography on silica gel. Their data are listed in Table III.

The chlorination reaction of thiophosphoric(-nic) acids deriveratives 4 with phosphorus oxychloride (General procedure)

A mixture of **4** and phosphorus oxychloride (equiv.) was heated with stirring at 65~100°C for 2.5~11 h until **4** disappeared from the reaction mixture (TLC control, petroleum ether / ethyl acetate 5 : 1 as eluent, iodine as detecting reagent). After the reaction was complete, by-product **3** was removed by distillation under reduced pressure. The crude product **2**was purified by vacuum liquid chromatography on silica gel (petroleum ether / ethyl acetate, gradient elution) to give pure **2** (Table I, II).

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