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

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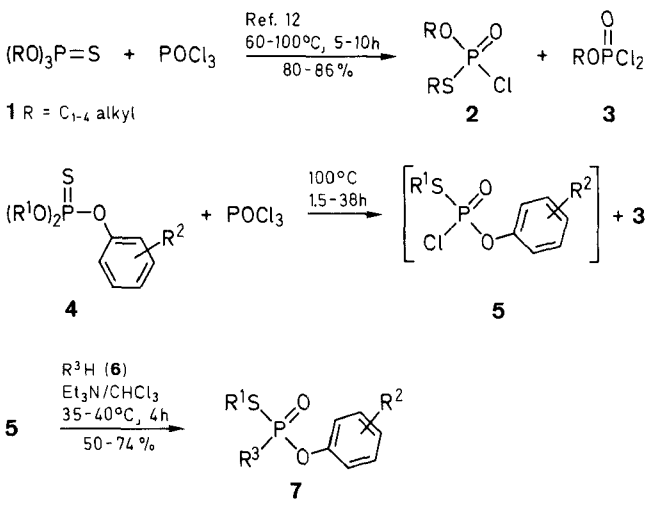
A new convenient synthesis of *S*-alkyl *O*-aryl thiophosphoric acid derivatives is reported. The chlorination of *O*-aryl *O,O*-dialkyl thiophosphates with phosphorus oxychloride proceeds with isomerization to give *S*-alkyl *O*-aryl thiophosphorochloridates, which react further with various nucleophiles 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 derivatives were generally used as starting material,[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 R^1 group and is related to the negativity of the R^2 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).



3–7	R^1	R^2	R^3	3–7	R^1	R^2	R^3
a	Pr	H	MeO	**i**	Me	H	PhS
b	Et	4-Me	MeO	**j**	Me	H	BuS
c	Bu	4-Me	MeO	**k**	Et	H	BuS
d	Pr	4-Cl	MeO	**l**	Bu	4-Me	NH_2
e	Et	2,4-Cl_2	MeO	**m**	Me	4-Cl	NH_2
f	Et	4-Me	2,4,5-$Cl_3C_6H_2O$	**n**	Me	H	*i*-PrNH
g	Et	H	4-$O_2NC_6H_4O$	**o**	Et	4-Me	*i*-PrNH
h	Pr	H	4-$MeSC_6H_4O$	**p**	Et	4-Cl	*i*-PrNH

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 **7** Prepared

Product	Reaction Time (h)[a]	Yield[b] (%)	mp (°C) or bp (°C)/Torr	n_D^{25}	Molecular Formula[c] or Lit. Data
7a	12	71	126–128/0.2	1.5165	–[d]
7b	9	74	127–128/0.6	1.5232	$C_{10}H_{15}O_3PS$ (246.3)
7c	13	51	131–134/0.1	1.5164	$C_{12}H_{19}O_3PS$ (274.3)
7d	38	71	129–131/0.1	1.5346	$C_{10}H_{14}ClO_3PS$ (280.7)
7e	35	50	137–139/0.3	1.5490	$C_9H_{11}Cl_2O_3PS$ (301.1)
7f	9	67	–[e]	1.5760	$C_{15}H_{14}Cl_3O_3PS$ (411.6)
7g	9.5	59	–[e]	1.5809	$C_{14}H_{14}NO_5PS$ (339.3)
7h	12	64	–[e]	1.5838	$C_{16}H_{19}O_3PS_2$ (354.4)
7i	1.5	61	42–44	–	$C_{13}H_{13}O_2PS_2$ (296.3)
7j	1.5	57	–[e]	1.5589	$C_{11}H_{17}O_2PS_2$ (276.3)
7k	9.5	65	–[e]	1.5472	$C_{12}H_{19}O_2PS_2$ (290.4)
7l	12	58	135–138	–	$C_{11}H_{18}NO_2PS$ (259.3)
7m	2	53	125–127	–	$C_7H_9ClNO_2PS$ (237.6)
7n	1.5	63	55–57	–	$C_{10}H_{16}NO_2PS$ (245.3)
7o	9	63	86–88	–	$C_{12}H_{20}NO_2PS$ (273.3)
7p	20	52	69–71	–	$C_{11}H_{17}ClNO_2PS$ (293.7)

[a] Reaction time of isomerization/chlorination (**4** + $POCl_3$ → **5** + **3**).
[b] Total yield of two-step reactions based on **4**.
[c] Satisfactory microanalyses obtained: C ±0.32, H ±0.26.
[d] No data are given in Ref. 13.
[e] Decomposed during distillation (oil bath: 150 °C at 0.1–0.2 Torr), purified by column chromatography on silica gel.

Table 2. IR and ^{1}H-NMR Data of Compounds **7a–p**

Product	IR (film or KBr) ν (cm^{-1})			^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
	arom (C=C)	P=O	P–O–Ar	
7a	1590, 1485	1255	1195, 925	0.88 (t, 3H, J = 7.1, CH_3), 1.55 (m, 2H, CH_2), 2.67 (dt, 2H, $J_{P,H}$ = 15.2, CH_2S), 3.72 (d, 3H, $J_{P,H}$ = 13.0, CH_3O), 7.09 (m, 5H_{arom})
7b	1604, 1499	1250	1195, 925	1.27 (t, 3H, J = 7.2, CH_3), 2.27 (s, 3H, CH_3), 2.78 (m, 2H, $J_{P,H}$ = 15.8, CH_2S), 3.74 (d, 3H, $J_{P,H}$ = 12.3, CH_3O), 6.96 (s, 4H_{arom})
7c	1605, 1500	1260	1195, 925	0.89 (t, 3H, J = 7.0, CH_3), 1.52 (m, 4H, $2CH_2$), 2.32 (s, 3H, CH_3), 2.88 (dt, 2H, $J_{P,H}$ = 15.1, CH_2S), 3.88 (d, 3H, $J_{P,H}$ = 13.7, CH_3O), 7.12 (m, 4H_{arom})
7d	1590, 1482	1260	1195, 920	0.95 (t, 3H, J = 7.1, CH_3), 1.66 (m, 2H, CH_2), 2.85 (m, 2H, CH_2S), 3.89 (d, 3H, $J_{P,H}$ = 13.0, CH_3O), 7.20 (m, 4H_{arom})
7e	1578, 1475	1250	1223, 926	1.24 (t, 3H, J = 7.3, CH_3), 2.80 (m, 2H, $J_{P,H}$ = 1.60, CH_2S), 3.78 (d, 3H, $J_{P,H}$ = 12.6, CH_3O), 7.32 (m, 3H_{arom})
7f	1580, 1495, 1445	1235	1190, 925	1.18 (t, 3H, J = 7.2, CH_3), 2.55 (s, 3H, CH_3), 2.88 (dq, 2H, $J_{P,H}$ = 16.2, CH_2S), 6.89–7.49 (m, 6H_{arom})
7g	1586, 1484	1265	1183, 920	1.21 (t, 3H, J = 7.3, CH_3), 2.87 (m, 2H, $J_{P,H}$ = 16.2, CH_2S), 7.15–8.17 (m, 9H_{arom})
7h	1587, 1482	1264	1182, 922	0.91 (t, 3H, J = 7.2, CH_3), 1.64 (m, 2H, CH_2), 2.44 (s, 3H, CH_3S), 2.90 (dt, 2H, $J_{P,H}$ = 15.8, CH_2S), 7.10–7.45 (m, 9H_{arom})
7i	1584, 1480	1235	1186, 910	2.13 (d, 3H, $J_{P,H}$ = 16.4, CH_3S), 7.01–7.46 (m, 10H_{arom})
7j	1584, 1483	1231	1185, 910	0.92 (t, 3H, J = 6.9, CH_3), 1.54 (m, 4H, $2CH_2$), 2.42 (d, 3H, $J_{P,H}$ = 16.6, CH_3S), 2.98 (m, 2H, $J_{P,H}$ = 15.5, CH_2S), 7.30 (m, 5H_{arom})
7k	1585, 1485	1232	1185, 910	0.84 (t, 3H, J = 6.7, CH_3), 1.33 (t, 3H, J = 7.4, CH_3), 1.50 (m, 4H, $2CH_2$), 2.83 (m, 4H, $2CH_2S$), 7.08 (m, 5H_{arom})
7l	1605, 1505	1255	1210, 915	0.86 (t, 3H, J = 6.9, CH_3), 1.42 (m, 4H, $2CH_2$), 2.29 (s, 3H, CH_3), 2.82 (m, 2H, CH_2S), 3.68 (br, 2H, NH_2), 7.09 (m, 4H_{arom})
7m	1555, 1485	1225	1200, 910	2.30 (d, 3H, $J_{P,H}$ = 15.5, CH_3S), 4.19 (s, 2H, NH_2), 7.24 (m, 4H_{arom})
7n	1585, 1485	1220	1190, 930	1.08 (dd, 6H, J = 6.6, $2CH_3$), 2.12 (d, 3H, $J_{P,H}$ = 14.4, CH_3S), 3.35 (br, 1H, CH), 5.04 (brt, 1H, NH), 7.08 (m, 5H_{arom})
7o	1590, 1500	1225	1200, 922	1.10 (dd, 6H, J = 6.5, $2CH_3$), 1.24 (t, 3H, J = 7.2, CH_3), 2.23 (s, 3H, CH_3), 2.70 (m, 2H, $J_{P,H}$ = 14.4, CH_2S), 3.37 (br, 1H, CH), 4.69 (brt, 1H, NH), 6.91 (m, 4H_{arom})
7p	1585, 1482	1230	1215, 915	1.08 (dd, 6H, J = 6.5, $2CH_3$), 1.18 (t, 3H, J = 7.3, CH_3), 2.69 (dq, 2H, $J_{P,H}$ = 14.4, CH_2S), 3.31 (br, 1H, CH), 4.98 (brt, 1H, NH), 7.07 (m, 5H_{arom})

several substituents, especially, strongly electron-withdrawing groups on the benzene ring, this isomerization/chlorination does not occur. For example, when R^2 equals 4-O_2N 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. ^{1}H-NMR spectra were measured on a JEOL FX-900 instrument at 90 MHz. Column chromatography were 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,[14] by reacting *O,O*-dialkyl thiophosphorochloridate with a suitable phenol in the presence of K_2CO_3 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 $POCl_3$ (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)/Et_2O, 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 $CHCl_3$ (40 mL). To the chloroform solution is added dropwise a mixture of MeOH (10 mL) and Et_3N (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 ($MgSO_4$). 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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