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The Isomerization/Chlorination of Nitrogen Heterocyclic O,O-Dialkyl Thiophosphoramidates with Phosphorus Oxychloride—A Convenient Synthesis of Nitrogen Heterocyclic S-Alkyl Thiophosphoramidic Acid Derivatives

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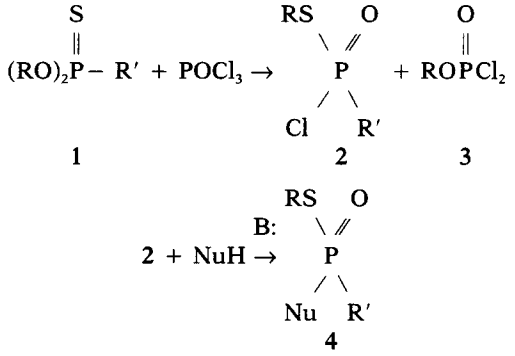
ABSTRACT

In this article, it is reported that the isomerization/chlorination reactions of nitrogen heterocyclic O,O-dialkyl thiophosphoramidates 5 with equivalent amounts of phosphorus oxychloride give nitrogen heterocyclic S-alkyl thiophosphorochloridates 6 and O-alkyl phosphorodichloridates 3. After removal of the by-products 3 under reduced pressure, the crude products 6 are directly reacted with various nucleophiles, NuH, in the presence of triethylamine to give nitrogen heterocyclic S-alkyl thiophosphoramidic acid derivatives 7. Thus, a new convenient method has been provided for the synthesis of the title compounds. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

In 1991, we found that the isomerization/chlorination of O,O-dialkyl O-aryl thiophosphate 1 (R′ = ArO) with phosphorus oxychloride can take place and gives S-alkyl O-aryl thiophosphorochloridate 2 (R′ = ArO) and O-alkyl phosphorochloridates 3 [1]. In this reaction, when 1 is chlorinated with phosphorus oxychloride, the isomerization of the P = S to the P–S bond occurs at the same time. This isomerization/chlorination can convert an achiral phosphorus atom into a chiral phosphorus atom to give 2, which reacts further with nucleophiles, NuH, in the presence of a base to give S-alkyl O-aryl thiophosphoric acid derivatives 4 (R′ = ArO) [2].



R = $C_{1\text{-}6}$ Alkyl, CH_2CH_2Cl
R′ = Alkoxy, Aroxy, Alkylthio, Arylthio, Dialkylamino, Me, Ph

Later investigations indicated that, when R′ equals alkylthio [3], arylthio [3], dialkylamino [4], phenyl [5], and methyl [6] in 1, respectively, the isomerization/chlorination of 1 with phosphorus oxychloride also proceeds smoothly and gives the desired prod-

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TABLE 1 Data of Compounds **7** Prepared

7	n_D^{25} or mp (°C)	Yield (%)[a]	Molecular Formula	Elemental Analysis C (%) Calc.	C (%) Found	H (%) Calc.	H (%) Found	N (%) Calc.	N (%) Found
a	1.5468	59.0	$C_{12}H_{18}NO_2PS$ (271.3)	53.12	53.02	6.69	7.00	5.16	4.86
b	1.5742	41.3	$C_{12}H_{15}Cl_3NO_2PS$ (374.6)	38.47	38.24	4.04	3.97	3.74	3.76
c	1.5582	30.8	$C_{13}H_{18}Cl_3NO_2PS$ (354.2)	44.08	44.00	5.12	5.42	3.95	3.80
d	1.5879	26.1	$C_{13}H_{20}NOPS_2$ (301.4)	51.81	52.03	6.69	6.77	4.65	4.31
e	1.5722	17.1	$C_{13}H_{19}ClNO_2PS$ (319.8)	48.83	49.02	6.00	6.04	4.38	4.29
f	1.5812	25.9	$C_{11}H_{14}BrClNO_3PS$ (386.6)	34.17	34.41	3.65	3.63	3.62	3.55
g	1.5391	69.3	$C_{12}H_{18}NO_3PS$ (287.3)	50.16	50.07	6.31	6.29	4.88	4.68
h	1.5614	37.9	$C_{12}H_{16}Cl_2NO_3PS$ (356.2)	40.46	40.18	4.53	4.82	3.93	3.97
i	1.5774	24.2	$C_{11}H_{13}Cl_3NO_3PS$ (376.6)	35.08	34.94	3.48	3.31	3.72	3.87
j	1.5740	36.9	$C_{11}H_{13}Cl_3NO_3PS$ (376.6)	35.08	35.30	3.48	3.78	3.72	3.90
k	1.5230	39.4	$C_7H_{15}N_2O_2PS$ (222.2)	37.83	38.07	6.80	6.55	12.60	12.61
l	1.5741	58.1	$C_{11}H_{13}Cl_3NO_2PS$ (360.6)	36.64	36.77	3.63	3.64	3.88	3.65
m	51-53	75.9	$C_{11}H_{13}Cl_3NO_2PS$ (360.6)	36.64	36.80	3.63	3.69	3.88	3.60
n	1.5720	25.4	$C_{11}H_{14}BrClNO_2PS$ (370.6)	35.65	35.88	3.81	3.87	3.78	3.67

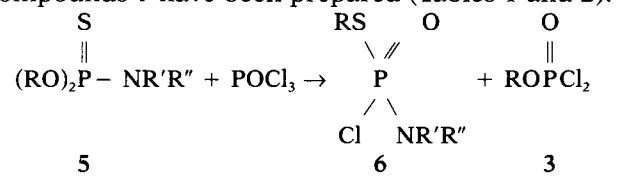
[a]Total yield of two-step reactions based on compounds **5**.

ucts **2** and **3**. The product **2** reacts further with various nucleophiles, NuH, to give varied compounds **4**. Thus, this constitutes a new convenient method for synthesis of S-alkyl thio(dithio)phosphoric and thio(dithio)phosphonic acid derivatives probably possessing extensive biological activity. The main advantage of this synthetic method is that compounds **1** obtained by using cheap low molecular weight alcohols are used as starting materials and avoids the use of expensive and foul smelling mercaptans or alkyl bromides.

In this article, we will report some new results in the isomerization/chlorination of nitrogen heterocyclic O,O-dialkyl thiophosphoramidate **5** with phosphorus oxychloride.

RESULTS AND DISCUSSION

Nitrogen heterocyclic O,O-dialkyl thiophosphoramidates **5** react with equivalent amounts of phosphorus oxychloride at 60–100°C to give nitrogen heterocyclic S-alkyl thiophosphorochloridates **6** and **3**. It takes 6.5–60 hours for **5** to disappear (TLC control). After removal of the by-products **3** under reduced pressure, the crude products **6** are directly reacted with various nucleophiles, NuH, e.g., phenols, mercaptans, and amines, in the presence of triethylamine to give nitrogen heterocyclic S-alkyl O-aryl thiophosphoramidates $\mathbf{7}_{a\text{-}c,e\text{-}j,l\text{-}n}$, S,S-dialkyl dithiophosphoramidates $\mathbf{7}_c$ and S-alkyl aziridinyl thiophosphorodiamidates $\mathbf{7}_k$, respectively. Crude products **7** can be purified by column chromatography on silica gel. By use of the above reactions, 14 new compounds **7** have been prepared (Tables 1 and 2).

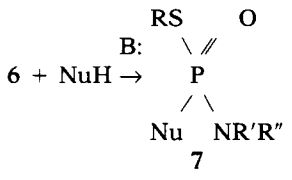


5 **6** **3**

5	R	R′R″	React. Temp. (°C)	React. Time (h)
a	Me		60–65	12.5
b	Me		60–65	18
c	Me		60–65	6.5
d	Et		100	60

TABLE 2 IR and ^{1}H NMR Data of Compounds **7**

7	IR, ν (cm^{-1}) (film or KBr) P=O	P–S	P–O–Ar	P–N	^{1}H NMR, δ (ppm), J_{PH} (HZ) ($CDCl_3$/TMS)
a	1235	546	1192, 909	954	1.54 (m, 6H), 2.28 (ds, 3H, J = 14.4), 3.26 (m, 4H), 7.27 (m, 5H)
b	1243	592	1206, 894	956	1.52 (m, 6H), 2.27 (ds, 3H, J = 16.2), 3.28 (m, 4H), 7.32 (s, 2H)
c	1235	559	1200, 913	954	1.52 (m, 6H), 2.23 (ds, 3H, J = 16.2), 2.24 (s, 3H), 3.28 (m, 4H), 7.20 (m, 2H)
d	1208	557		945	1.56 (m, 6H), 2.38 (ds, 3H, J = 14.4), 3.24 (m, 4H), 4.16 (d, 2H, J = 12.6), 7.42 (m, 5H)
e	1233	592	1186, 930	986	1.24 (t, 3H), 1.56 (m, 6H), 2.90 (dq, 2H, J = 18.0), 3.20 (m, 4H), 7.28 (m, 4H)
f	1228	559	1153, 911	968	2.32 (ds, 3H, J = 14.4), 3.38 (m, 4H), 3.70 (m, 4H), 7.48 (m, 3H)
g	1234	547	1193, 906	964	2.23 (ds, 3H, J = 16.7), 2.28 (s, 3H), 3.28 (m, 4H), 3.58 (m, 4H), 7.08 (m, 4H)
h	1238	557	1201,	962	2.23 (ds, 3H, J = 16.2), 2.26 (s, 3H), 3.30 (m, 4H), 3.60 (m, 4H), 7.20 (m, 2H)
i	1241	584	1205, 900	969	2.27 (ds, 3H, J = 16.2), 3.36 (m, 4H), 3.60 (m, 4H), 7.26 (s, 2H)
j	1238	572	1150, 878	963	2.29 (ds, 3H, J = 16.2), 3.32 (m, 4H), 3.64 (m, 4H), 7.58 (m, 2H)
k	1255	556		962	2.22 (ds, 3H, J = 12.5), 2.24 (m, 4H), 3.26 (m, 4H), 3.63 (m, 4H)
l	1249	566	1190, 877	945	1.92 (m, 4H), 2.31 (ds, 3H, J = 16.2), 3.40 (m, 4H), 7.52 (m, 2H)
m	1230	574	1155, 900	956	1.92 (m, 4H), 2.29 (ds, 3H, J = 16.2), 3.42 (m, 4H), 7.30 (s, 2H)
n	1254	557	1196, 910	968	1.92 (m, 4H), 2.28 (ds, 3H, J = 14.4), 3.40 (m, 4H), 7.46 (m, 3H)



7

7	R	R'R"	Nu	7	R	R'R"	Nu
a	Me		PhO	h	Me		2,6-Cl_2-4-MeC_6H_2O
b	Me	"	2,4,6-$Cl_3C_6H_2O$	i	Me	"	2,4,6-$Cl_3C_6H_2O$
c	Me	"	2,6-Cl_2-4-MeC_6H_2O	j	Me	"	2,4,5-$Cl_3C_6H_2O$
d	Me	"	$PhCH_2S$	k	Me	"	N◁
e	Et	"	4-ClC_6H_4O	l	Me		2,4,5-$Cl_3C_6H_2O$
f	Me		2-Cl-4-BrC_6H_3O	m	Me	"	2,4,6-$Cl_3C_6H_2O$
g	Me	"	4-MeC_6H_4O	n	Me	"	2-Cl-4-BrC_6H_3O

Separation of products **6** by column chromatography on silica gel or by distillation at reduced pressure was attempted and was unsuccessful because of decomposition of **6** on silica gel or at temperatures above 120°C. In comparison with **1**, the isomerization/chlorination of **5** is more difficult to effect. When the R group equals ethyl in **5**, e.g., 5_d, the reaction becomes very sluggish, and the yield is very low, but if the R group is an alkyl group with C_{1-4} **1**, the reaction can also proceed smoothly. The distinction between **1** and **5** might be due to the steric hindrance of the nitrogen heterocyclic ring in **5** and the reduction of effective positive charge at phosphorus atom owing to the formation of a p_π–d_π bond between electron-rich nitrogen and the phosphorus atom.

In view of the experimental results, we concluded that the isomerization/chlorination of **5** containing a five-membered nitrogen heterocyclic ring is more liable to take place than that of the compounds containing a six-membered ring. The isomerization/chlorination of the three-ring nitrogen heterocyclic (aziridinyl) thiophosphoramidate 5_e with phosphorus oxychloride did not afford the desired product.

EXPERIMENTAL

All temperatures are uncorrected. Melting points were determined with a Yanaco MP-500 apparatus. The IR spectra were recorded on a Shimadzu IR-435 spectrophotometer as thin films or as a KBr tablet. ^{1}H NMR spectra were measured on a JEOL FX-90Q instrument at 90 MHz, using TMS as an internal standard and $CDCl_3$ as the solvent. Column chromatography was performed on silica gel (200–300 mesh), using petroleum ether (bp 60–90°C)/EtOAc as the eluent.

Nitrogen heterocyclic O,O-dialkyl thiophosphoramidates **5**

Compounds **5** were prepared according to a general procedure, i.e., by a reaction of O,O-dialkyl thiophosphorochloridates with a suitable nitrogen heterocyclic compound in the presence of triethylamine in $CHCl_3$ at 30–40°C. The crude products **5** were purified by column chromatography on silica gel (Table 3).

TABLE 3 Data of compounds **5** prepared

5	R	R′R″	n_D^{25}	Yield (%)
a	Me		1.4959	84.5
b	Me		1.4998	63.5
c	Me		1.4986	68.4
d	Et		1.4862	79.3
e	Me		1.4941	49.9

S-Methyl 1-hexahydropyridyl thiophosphoramidochloridate 6_a

Typical procedure: A mixture of 5_a (8.90 g, 40 mmol) and $POCl_3$ (6.54 g, 40 mmol) was heated at 60–65°C for 12.5 hours with stirring until 5_a had disappeared from the reaction mixture (TLC control, solvent system: petroleum ether/EtOAc, 10:1). After removal of the by-product **3** (R = Me) under vacuum (1–2 mm) at 65°C (oil bath), the crude product 6_a (5.50 g) was directly used in the following preparation of 7_b.

S-Methyl O-(2,4,5-trichlorophenyl) 1-hexahydropyridyl thiophosphoramidate 7_b

Typical procedure: To a solution of the crude product 6_a (2.00 g, 14.5 mmol) prepared as described above, 2,4,5-trichlorophenol (2.86 g, 14.5 mmol) and $CHCl_3$ (30 mL) and a mixture of triethylamine (1.50 g, 14.9 mmol) and $CHCl_3$ (10 mL) were added dropwise at room temperature (r.t.). The reaction mixture was stirred at 40–45°C for 6 hours, then cooled to r.t. and poured into cold water (30 mL). The organic layer was separated, washed with water (20 mL), and dried ($MgSO_4$). After removal of the solvent, the crude product 7_b is purified by using column chromatography on silica gel, yield: 2.23 g (41.3%, based on 5_a).

S-Methyl aziridinyl morpholinyl thiophosphorodiamidate 7_k

To a mixture of crude product 6_b (1.80 g, 8 mmol) obtained from the isomerization/chlorination of 5_b and ether (20 mL), a solution of aziridine (0.40 g, 9 mmol), triethylamine (1.00 g, 10 mmol), and ether (20 mL) was added dropwise at 0–5°C, and the reaction mixture was stirred at 20–25°C for 4 hours. The forming hydrochloric acid salt of triethylamine was filtered off. After removal of ether from the filtrate, the crude product 7_k was purified by column chromatography on silica gel; yield: 0.70 g (39.3%, based on 5_b).

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