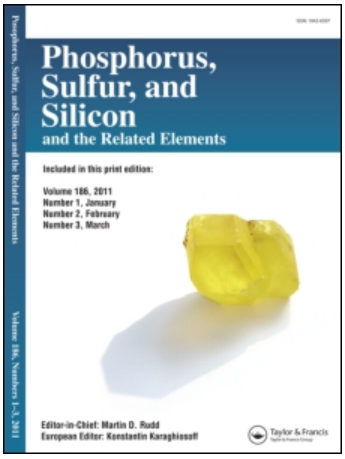

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

THE ISOMERIZATION/CHLORINATION OF O,O-DIALKYL N,N-DIALKYL THIOPHOSPHORAMIDATE WITH PHOSPHORUS OXYCHLORIDE—A NEW METHOD FOR SYNTHESIS OF S-ALKYL N,N-DIALKYL THIOPHOSPHORAMIDIC ACID DERIVATIVES

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To cite this Article Tang, Chu Chi , Wu, Gui Ping , He, Shui Ji and He, Zheng Jie(1995) 'THE ISOMERIZATION/CHLORINATION OF O,O-DIALKYL N,N-DIALKYL THIOPHOSPHORAMIDATE WITH PHOSPHORUS OXYCHLORIDE—A NEW METHOD FOR SYNTHESIS OF S-ALKYL N,N-DIALKYL THIOPHOSPHORAMIDIC ACID DERIVATIVES', Phosphorus, Sulfur, and Silicon and the Related Elements, 101: 1, 91 — 94
To link to this Article: DOI: 10.1080/10426509508042503
URL: http://dx.doi.org/10.1080/10426509508042503

Phosphorus, Sulfur, and Silicon, 1995, Vol. 101, pp. 91–94
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THE ISOMERIZATION/CHLORINATION OF O,O-DIALKYL N,N-DIALKYL THIOPHOSPHORAMIDATE WITH PHOSPHORUS OXYCHLORIDE—A NEW METHOD FOR SYNTHESIS OF S-ALKYL N,N-DIALKYL THIOPHOSPHORAMIDIC ACID DERIVATIVES

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(Received July 27, 1994; in final form October 16, 1994)

A new convenient method for synthesis of S-alkyl N,N-dialkyl thiophosphoramidic acid derivatives is reported. The chlorination of O,O-dialkyl N,N-dialkyl thiophosphoramidates with phosphorus oxychloride proceeds with isomerization to give S-alkyl N,N-dialkyl thiophosphoramidochloridates, which react further with various nucleophiles in the presence of base to give the title compounds. However, in the reaction of O,O-diethyl N,N-dimethyl thiophosphoramidate with phosphorus oxychloride, an unexpected exchange between chlorine atom and dimethylamino group is observed.

Key words: Thiophosphoramidate, thiophosphorochloridate, isomerization, chlorination.

In the previous paper,[1,2] we reported that when O-aryl O,O-dialkyl thiophosphates are chlorinated with phosphorus oxychloride, the isomerization of P=S to P—S bond occurs at the same time. This isomerization/chlorination can convert an achiral phosphorus atom into a chiral phosphorus atom to give S-alkyl O-aryl thiophosphorochloridates, which react further with various nucleophiles in the presence of a base to obtain biologically active S-alkyl O-aryl thiophosphoric acid derivatives. Thus, a new convenient method was provided for synthesis of chiral S-alkyl O-aryl thiophosphoric acid derivatives.

TABLE I

Compounds 2 and 5 prepared

Product	Yield (%)*	bp(°C)/Pa or mp(°C)	n_D^{25}	Elemental Analysis					
				C%		H%		N%	
				Calc.	Found	Calc.	Found	Calc.	Found
2c	51.8	86-88/40	1.4950	36.60	36.38	7.46	7.29	6.10	5.97
2e	54.8		1.4949	39.43	39.29	7.86	7.57	5.75	5.46
5a	46.3		1.5208	50.95	50.66	7.00	6.95	5.40	5.19
5b	54.5	75-77/27	1.4933	39.80	39.48	8.59	8.67	6.63	6.67
5c	54.9		1.5236	52.73	53.02	7.38	7.30	5.13	4.96
5d	56.1	37-39		36.72	36.38	8.73	8.44	14.27	14.07
5e	67.6	40-42		45.41	45.48	5.99	6.09	3.78	3.70
5f	67.5		1.5424	46.98	46.96	6.37	6.58	8.43	8.15
5g	71.4		1.5082	55.79	55.79	8.03	7.89	4.65	4.45
5h	73.0		1.5043	57.12	57.25	8.31	8.33	4.44	4.49

*Total yield of two-step reactions based on 1 except 2c and 2e.

TABLE II

IR and ^{1}H NMR data of compounds 2 and 5

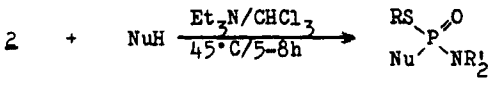
Product	IR(film or KBr), ν(cm^{-1}) P-S-C	P=O	P-O-Ar	^{1}H NMR($CDCl_3$/TMS), δ(ppm), J_{PH}(HZ)
2c	575	1240		0.95(t,3H,CH_3),1.10(t,6H,$2CH_3$),1.68(m,2H, CH_2),2.75(dt,2H,J=16.4,CH_2S),3.11(dq,4H, J=14.8,$2CH_2N$).
2e	571	1235		0.82(t,6H,$2CH_3$),1.32(t,3H,CH_3),1.50(m,2H, CH_2),2.75(dq,2H,J=14.4,CH_2S),2.97(dt,4H, J=12.4,$2CH_2N$).
5a	555	1240	1190 945	1.09(t,6H,$2CH_3$),2.18(d,3H,J=14.8,CH_3S), 3.18(dq,4H,J=12.8,$2CH_2N$),7.17(s,5H,Ar).
5b	590	1228		1.14(t,6H,$2CH_3$),1.35(t,3H,CH_3),2.82(dq, 2H,J=14.4,CH_2S),3.17(dq,4H,J=12.3,$2CH_2N$), 3.71(d,3H,J=12.2,CH_3S).
5c	595	1235	1190 925	1.15(t,6H,$2CH_3$),1.36(t,3H,CH_3),2.84(dq,2H, J=14.8,CH_2S),3.26(dq,4H,J=12.6,$2CH_2N$),7.29 (s,5H,Ar).
5d	550	1210		1.09(t,6H,$2CH_3$),1.29(t,3H,CH_3),2.78(m,2H, CH_2S),3.12(m,4H,$2CH_2N$),3.30(s,2H,NH_2).
5e	566	1231	1197 915	0.78(t,6H,$2CH_3$),1.15(t,3H,CH_3),1.40(m,2H, CH_2),2.66(dq,2H,J=14.8,CH_2S),2.97(dt,4H, J=13.0,$2CH_2N$),6.90-7.50(m,3H,Ar).
5f	578	1215	1195 949	0.93(t,3H,CH_3),1.05(t,6H,$2CH_3$),1.60(m,2H, CH_2),2.67(dt,2H,J=14.0,CH_2S),3.10(dq,2H, J=12.6,$2CH_2N$),7.60(m,4H,Ar).
5g	570	1215	1190 945	0.92(t,3H,CH_3),1.21(t,6H,$2CH_3$),1.48(m,4H, $2CH_2$),2.95(dt,2H,J=15.8,CH_2S),3.30(dq,4H, J=14.4,$2CH_2N$),7.01(m,5H,Ar).
5h	560	1242	1190 950	0.91(t,3H,CH_3),1.19(t,6H,$2CH_3$),1.44(m,4H, $2CH_2$),2.30(s,3H,CH_3),2.93(dt,2H,J=15.5, CH_2S),3.28(dq,4H,J=14.4,$2CH_2N$),7.09(m,4H, Ar).

Recently, we have found that the isomerization/chlorination of O,O-dialkyl N,N-dialkylthiophosphoramidates 1 with phosphorus oxychlorides can also give the desired products, S-alkyl N,N-dialkyl thiophosphoramidochloridates 2 and O-alkyl phosphorodichloridates 3. The products 2 can be purified by column chromatography on silica gel, e.g. 2c (2; R = Pr, R′ = Et), 2e (2; R = Et, R′ = Pr) (Tables I and II). Treatment of 2 with nucleophiles NuH(4) in the presence of triethylamine gives S-alkyl N,N-dialkyl thiophosphoramidates 5. The nucleophiles 4 are alcohols, phenols, ammonia and any other compounds with active hydrogen. The crude products 5 are purified by column chromatography on silica gel, distillation under reduced pressure or recrystallization. Thus, eight new compounds 5 have been prepared (Tables I and II).

It is worthy to note that in the reaction of O,O-dialkyl N,N-dimethyl thiophosphoramidate 1f (1; R = Et, R′ = Me) with phosphorus oxychloride the desired

1 2 3

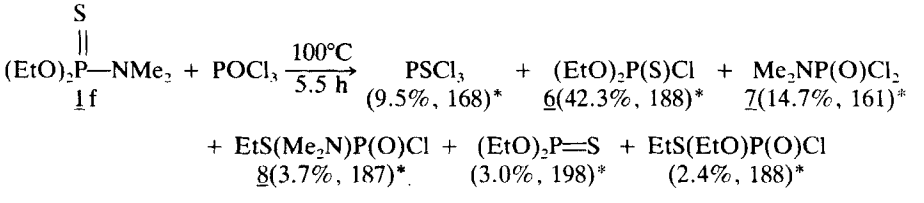
1	R	R'	t°C	Reaction Time(h)
a	Me	Et	60	4
b	Et	Et	100	6.5
c	Pr	Et	100	10
d	Bu	Et	100	15
e	Et	Pr	100	6



2 4 5

5	R	R'	Nu	5	R	R'	Nu
a	Me	Et	PhO	e	Et	Pr	$2,4\text{-}Cl_2C_6H_3O$
b	Et	Et	MeO	f	Pr	Et	$4\text{-}O_2NC_6H_4O$
c	Et	Et	PhO	g	Bu	Et	PhO
d	Et	Et	NH_2	h	Bu	Et	$4\text{-}MeC_6H_4O$

product 2 is not obtained, but the exchanged products between chlorine atom and dimethylamino group, namely, O,O-diethyl thiophosphorochloridate 6 and N,N-dimethyl phosphorochloride 7, are formed as the main products. Besides, there are some other by-products. The structures and amounts of seven main components of reaction mixture are determined through GC-MS technique. The amount of each of them is over 2% and their total amount is over 90% (by normalization). In the reaction mixture, material 1f is undetected, but the amount of phosphorus oxychloride reaches up to 15.3%. The amount of normal isomerization/chlorination product, S-ethyl N,N-dimethyl thiophosphoramidochloridate 8 is only 3.7% of all, but the percentage of the exchanged product 6 is 42%. Compound 6 is obtained by isolation on silica gel column. Thus, the reaction of 1f with phosphorus oxychloride is shown in the following equation:



In addition, treatment of compounds $(RO)_2P(S)NHR'$ or $(RO)_2P(S)NH_2$ (R,R' are same as that of compounds 1) with phosphorus oxychloride under similar con-

*In parentheses are percentages of content and M^+.

ditions has been investigated in our laboratory. Results show that these reactions are complicated and in some cases very rigorous. The desired isomerization/chlorination products have not been obtained by isolation.

EXPERIMENTAL

1. Apparatus and Reagents

Melting points were determined with a model Yanaco MP-500 apparatus. IR spectra were recorded on a model Shimadzu IR-435 spectrophotometer at film or KBr tablet. ^{1}HNMR spectra were measured on a JEOL FX-90Q instrument at 90 MHZ using TMS as internal standard. GC-MS spectra were recorded on a HP-5890A-GC/5988A-MS instrument. GC conditions are follows: capillary column—Ultra 2, 25 m × 0.32 mm × 0.17 mm film thickness; carrier gas—helium, velocity of flow 1.4 mL/min.; temperature-programmed, injection port temperature 240°C, transfer line temperature 270°C. MS conditions are follows: ion source EI, 200°C, 70 eV; target current 300 μA; scanning range 10–420 amu.

For column chromatography Qingdao silica gel (200–300 mesh) was used. O,O-Dialkyl N,N-dialkyl thiophosphoramidates 1 were prepared by the reaction of O,O-dialkyl thiophosphorochloridates with an excess of dialkylamines using chloroform or acetone as the solvent at 40–45°C for 5–8 h. Phosphorus oxychloride needs to be redistilled before using. Other reagents are commercial.

2. Synthesis of N,N-diethyl S-propyl Thiophosphoramidochloridate 2c

(Typical procedure): A mixture of 18.6 g (74 mmol) of 1c (1; R = Pr, R^1 = Et) and 11.3 g (74 mmol) of $POCl_3$ is heated at 100°C for 10 h with stirring until 1c disappears (TLC control, solvent system: petroleum ether/Et_2O, 10:1, V/V, iodine as detecting agent). After the removal of the by-product 3 (R = Pr) under vacuum (133 Pa) at 100°C (oil bath), the crude product 2c is purified by column chromatography on silica gel (200–300 mesh) using petroleum ether/EtOAc (10:1, V/V) as the eluent to give 8.8 g of 2c with a yield of 52%, bp 86–88°C/39.9 Pa, n_D^{25} 1.4950 (Tables I and II).

3. Synthesis of N,N-dipropyl S-ethyl O-2,4-dichlorophenyl Thiophosphoramidate 5e

(Typical procedure): A mixture of 2.5 g (10 mmol) of 1e (1; R = Et, R^1 = Pr) and 1.5 g (10 mmol) of $POCl_3$ is heated at 100°C for 6 h with stirring until 1 disappears (TLC control, solvent system: petroleum ether/Et_2O, 10:1, V/V, iodine as detecting agent). After the removal of the by-product 3 (R = Et) under vacuum (266 Pa) at 90°C (oil bath), the residue is dissolved in acetone (10 mL). To the acetone solution is added dropwise a mixture of 10 mL of acetone, 1.6 g (10 mmol) of 2,4-dichlorophenol and 1.5 g (15 mmol) of Et_3N at 20°C, and the mixture is stirred at 45–50°C for 8 h. After cooling to r.t. the reaction mixture is poured into cold water (30 mL). The organic layer is extracted with $CHCl_3$ (2 × 20 mL). The $CHCl_3$ layer is washed with water (20 mL), and dried ($MgSO_4$). After the removal of the solvent the crude product 5e is purified by column chromatography on silica gel (200–300 mesh) with petroleum ether/EtOAc (10:1, V/V) as the eluent to give 2.5 g of 5e with a yield of 68%, mp 40–42°C (Tables I and II).

4. The Reaction of O,O-diethyl N,N-dimethyl Thiophosphoramidate 1f *with Phosphorus Oxychloride*

A mixture of 7.9 g (40 mmol) of $POCl_3$ is heated at 100°C for 5.5 h with stirring until 1f disappears (TLC control, solvent system: petroleum ether/Et_2O, 10:1, V/V, iodine as detecting agent). After the reaction mixture is cooled to r.t., a sample for GC-MS is taken out. To remove a small amount of substance with low boiling point the remainder is distillated at 60°C (oil bath) under reduced pressure (266 Pa) to give 10 g of the crude product, which is purified by using column chromatography on silica gel (200–300 mesh) with petroleum ether/EtOAc (10:1, V/V) as the eluent yielding three fractions. Fraction 1, weighed 4.5 g, n_D^{25} 1.4670, bp 48–49°C/26.6 Pa, ^{1}HNMR δ (ppm): 1.38 (t, 6H), 4.15 (dq, 4H, J_{PH} = 10.6 HZ) (Compound 6 in lit.[3]: bp 60°C/266 Pa, n_D^{20} 1.4685), Fraction 2, weighed 1.5 g; Fraction 3, weighed 0.5 g. Fractions 2 and 3 are a complicated mixture.

REFERENCES

1. C. C. Tang, G. P. Wu and G. Z. Zhang, *Synthesis*, 454 (1991).
2. C. C. Tang, G. P. Wu, G. Z. Zhang, X. R. Chen, F. C. Bi, W. L. Wang and L. H. Zhu, *Chem. J. Chinese Univs.*, **12**, 1478 (1991).
3. R. S. Edmundson (Ed.), "Dictionary of Organophosphorus Compounds," (Chapman and Hall, London, 1988), p. 250.