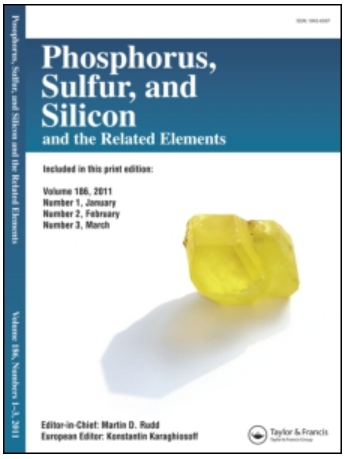

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GENERAL ROUTE TO UNSYMMETRICAL PHOSPHORODITHIOATES

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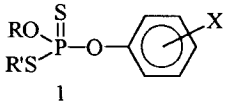
A general procedure for the synthesis of unsymmetrical phosphorodithioates has been developed. The method involves the reaction of O,O-diethyl S-alkylthiomethyl phosphorodithioates with dimethylamine to give O-ethyl S-alkylthiomethyl ethyldimethylammonium phosphorodithioates that were chlorinated using phosphorus pentachloride to furnish the intermediate phosphorochloridodithioates, reaction of which with a variety of nucleophiles in the presence of triethylamine furnished the desired unsymmetrical phosphorodithioates.

Key words: Phosphorodithioates, dealkylation, chlorination, insecticides, phosphorochloridodithioates.

INTRODUCTION

Unsymmetrical phosphorodithioates **1**, particularly O-ethyl S-*n*-propyl O-substituted phenols analogs, have recently been exploited as insecticides.[1] Sulprofos and prothiofos which have commercially been prepared are excellent products in this family of compounds **1**.



1

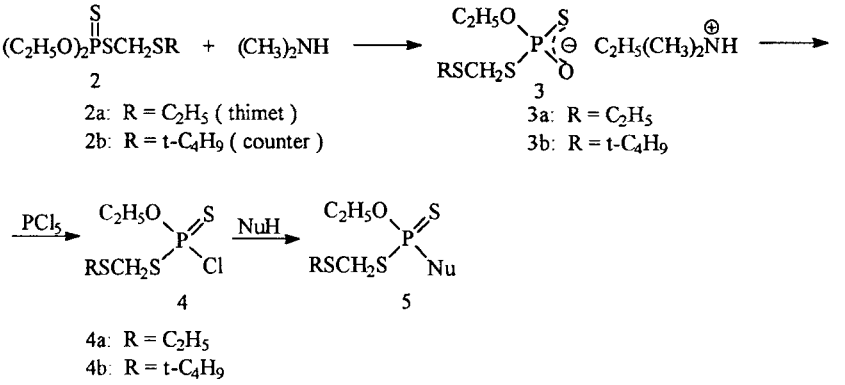
Sulprofos: $R = C_2H_5$, $R' = n\text{-}C_3H_7$, $X = 4\text{-}SCH_3$

Prothiofos: $R = C_2H_5$, $R' = n\text{-}C_3H_7$, $X = 2,4\text{-}Cl_2$

The study of such compounds is interesting for at least two reasons: (1) they have a chiral phosphorus which is usually quite different from an achiral one in biochemical and biological actions, (2) they exhibit generally potential insecticidal activity and low mammalian toxicity.

Although many papers exist on preparation of a variety of unsymmetrical phosphorodithioate derivatives,[2] the modification of structure is frequently focused on substituted groups in the benzene ring, whereas the S-alkyl is only restricted in propyl or butyl groups. We reasoned that using the biologically active thioether as a replacement for S-alkyl could provide access to a greater diversity of phosphorodithioate analogues. Toward this end, we selected thimet (O,O-diethyl S-ethylthiomethyl phosphorodithioate) and counter O,O-diethyl S-tert-butylthiomethyl phosphorodithioate) which have been produced commercially as starting materials, and discovered a novel route for converting them to unsymmetrical structure.

Scheme 1



compd	5a	5b	5c	5d
R	C_2H_5	C_2H_5	C_2H_5	C_2H_5
Nu	NH_2	$NHCH_3$	$(CH_3)_2N$	C_6H_5O

compd	5e	5f	5g	5h
R	C_2H_5	C_2H_5	C_2H_5	C_2H_5
Nu	2,4-$Cl_2C_6H_3O$	2,4-$ClBrC_6H_3O$	4-$NO_2C_6H_4O$	4-$CH_3SC_6H_4O$

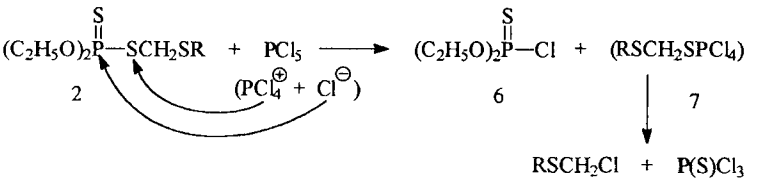
compd	5i	5j	5k	5l
R	t-C_4H_9	t-C_4H_9	t-C_4H_9	t-C_4H_9
Nu	NH_2	$NHCH_3$	$(CH_3)_2N$	C_6H_5O

compd	5m	5n	5o	5p
R	t-C_4H_9	t-C_4H_9	t-C_4H_9	t-C_4H_9
Nu	2,4-$Cl_2C_6H_3O$	2,4-$ClBrC_6H_3O$	4-$NO_2C_6H_4O$	4-$CH_3SC_6H_4O$

RESULTS AND DISCUSSION

Thimet and counter were treated with dimethylamine via dealkylation to furnish O-ethyl S-alkylthiomethyl ethyldimethylammonium phosphorodithioates **3**, which were chlorinated in situ using phosphorus pentachloride to provide the corresponding phosphorochloridodithioates **4**. The subsequent reaction of **4** with a variety of nucleophiles in the presence of triethylamine led to a series of the desired unsymmetrical phosphorodithioates **5** (Scheme 1).

The crucial step in this process is the synthesis of compounds **4**. According to the principle of hard and soft acids and bases (HSAB),[3] dimethylamine is a hard base, but aqueous dimethylamine can be considered as a borderline case between hard and soft bases because of water association. In the compounds **2**, the pentavalent phos-



Scheme 2

phorus is hard acid, α-carbon atom of methylthio group is a soft acid, whereas α-carbon atom of ethoxy is a bordeline. The HSAB principle states that hard acids prefer coordinating to hard bases and soft acids prefer coordinating to soft bases. When the compounds **2** react with aqueous dimethylamine, dimethylamine chooses to attack the α-carbon atom of the ethoxy group resulting in C—O cleavage. The unpurified compounds **3** are of sufficient purity to afford the subsequent reaction. Since the compounds **3** are ambident anions, tetrachlorophosphorus cation as a hard acid, which was dissociated from phosphorus pentachloride in a polar solvent, thus attacks the hard basic center of the ambident anion, i.e. the oxygen, leading to formation of compound **4** accompanied by the elimination of phosphorus oxychloride and ethyldimethylammonium chloride. Moreover, we also attempted a one step process to prepare compounds **4** by the reaction of compounds **2** with phosphorus pentachloride. Unfortunately, only O,O-diethyl phosphorochloridothioate **6** was isolated. Its formation is more reasonably understood in terms of Scheme 2.

On the other hand, the compounds **4** underwent facile reaction with a variety of nucleophiles to give compounds **5** in 46–71% yields. The compounds **5** were purified by silica gel chromatography and fully characterized by NMR spectra and elemental analyses (Tables I and II). The infrared spectra of compounds **5** show the absence of a strong intensity band $\nu p = o$ in the region 1200 cm^{-1} and the presence of two spectral regions $\nu p = s$ at 663 cm^{-1} and 628 cm^{-1}.

The preliminary bioassay shows that compounds **5** exhibited potent activity against mosquito, army worm, bean aphid, flour beetle and spider mite at 2–200 ppm. It seems that coupling of an unsymmetrical phosphorodithioate containing thioether group with the moiety of a biologically active molecular appears to be a reasonable strategy for the design of novel organophosphorus insecticides.

EXPERIMENTAL

The ^1H and ^{31}P NMR spectra were run on a JEOL FX-90Q spectrometer. The ^1H chemical shifts are reported in parts per million relative to internal tetramethylsilane. All ^{31}P chemical shifts are reported in parts per million relative to 85% phosphoric acid (external). In all cases, the nuclei which are deshielded relative to their respective standards are assigned a positive chemical shift. The ^{31}P NMR spectra were obtained by broadband proton decoupling. Quantitative elemental analyses were run on a Yana MT-3.

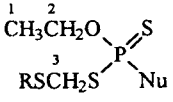
Thimet and counter were obtained from commercial sources and used without purification.

General Procedure for Preparation of **4**

The mixture of the compounds **2** (0.1 mol) and 33% aqueous dimethylamine (0.4 mol) was refluxed vigorously at 50–60°C for 7 hours. The excess aqueous dimethylamine was removed by rotary evaporation to give a viscous residue. The residue was added dropwise to a suspension of phosphorus pentachloride (20.9 g, 0.1 mol) in phosphorus oxychloride (20 ml) at 0–15°C. After addition, the reaction mixture was allowed to warm to room temperature, and stirred for three additional hours. The mixture

TABLE 1

^1H and ^{31}P NMR data of compounds 5



compd	^1H NMR($CDCl_3$)						^{31}P NMR ($CDCl_3$)
	1-H (t, $^3J_{HH}$ 7.2,)	2-H (dq, $^3J_{HH}$ 7.2, $^3J_{HP}$ 10.8)	3-H (d, $^3J_{HP}$ 12.6)	R = CH_2CH_3 (q, $^3J_{HH}$ 7.2, CH_2) (t, $^3J_{HH}$ 7.2, CH_3)	R = $(CH_3)_3C$	Nu*	
5a	1.24	4.16	4.02	2.68 1.30		3.48-3.00(broad, NH_2)	86.55
5b	1.22	4.08	3.98	2.60 1.32		3.08-2.88(broad, NH) 2.61(d, $^3J_{HH}$ 14.4, NCH_3)	88.57
5c	1.28	4.12	4.05	2.70 1.40		2.74(s, NCH_3) 2.90(s, NCH_3)	95.04
5d	1.28	4.38	4.20	2.70 1.44		7.62-7.20(m, OC_6H_5)	91.67
5e	1.28	4.38	4.20	2.70 1.44		7.68-7.20 (m, 2,4-$Cl_2C_6H_3O$)	91.80
5f	1.30	4.38	4.21	2.70 1.44		7.70-7.28 (m, 2,4-$ClBrC_6H_3O$)	91.13

5g	1.28	4.36	4.18	2.70 1.46		8.42-7.30 (m, 4-$NO_2C_6H_4O$)	90.73
5h	1.28	4.32	4.13	2.68 1.42		7.40-7.20(m, C_6H_4O) 2.48(s, CH_3S)	91.00
5i	1.40	4.24	4.14		1.42	3.52-3.20(broad, NH_2)	85.88
5j	1.42	4.29	4.23		1.40	3.08-2.92(broad, NH) 2.71(d, $^3J_{HH}$ 14.4, NCH_3)	91.54
5k	1.38	4.16	4.08		1.36	2.90(s, NCH_3) 2.76(s, NCH_3)	95.17
5l	1.44	4.28	4.11		1.36	7.52-7.20(m, C_6H_5O)	90.59
5m	1.46	4.40	4.22		1.40	7.68-7.20 (m, 2,4-$Cl_2C_6H_3O$)	90.06
5n	1.44	4.36	4.21		1.40	7.68-7.24 (m, 2,4-$ClBrC_6H_3O$)	89.92
5o	1.38	4.28	4.09		1.30	8.32-7.20 (m, 4-$NO_2C_6H_4O$)	90.73
5p	1.44	4.34	4.15		1.38	7.40-7.24(m, C_6H_4O) 2.50(s, CH_3S)	90.86

* unresolved multiplets

TABLE II

Quantitative elemental analyses data of compounds **5**

compd	yield* (%)	elemental analyses (%)					
		calcd			found		
		C	H	N	C	H	N
5a	50	25.97	6.06	6.06	25.77	5.94	6.03
5b	65	29.39	6.53	5.71	29.26	6.34	5.60
5c	50	32.43	6.95	5.41	32.26	6.80	5.61
5d	67	42.86	5.52		42.68	5.33	
5e	68	35.01	3.98		34.98	3.79	
5f	75	31.32	3.56		31.17	3.68	
5g	59	37.39	4.53	3.97	37.47	4.58	3.92
5h	66	40.68	5.37		40.46	5.50	
5i	70	32.43	6.94	5.4	32.46	6.78	5.35
5j	70	35.16	7.33	5.13	35.05	7.19	5.01
5k	68	37.63	7.67	4.88	37.52	7.69	4.83
5l	70	46.43	6.25		46.34	6.44	
5m	65	38.52	4.69		38.31	4.75	
5n	72	34.71	4.23		34.61	4.39	
5o	71	40.94	5.25	3.67	40.83	5.09	3.52
5p	46	43.98	6.02		43.82	5.89	

* yield determined by isolation

was concentrated in vacuo, then poured into ice-water (100 g), and extracted with petroleum ether until further extracts were colorless. The combined organic extracts were washed with water to PH 7. The solvent was removed and the remaining orange oil was purified through vacuum liquid chromatographic technique using petroleum ether-ethyl acetate (150:1) as the eluent to furnish the pure compounds **4**.

4a. 70% yield. ^{31}P NMR ($CDCl_3$): 89.65. ^{1}H NMR ($CDCl_3$): 4.28 (dq, $^3J_{HH}$ 7.2, $^3J_{HP}$ 10.8, 2H, CH_2O), 4.22 (d, $^3J_{HP}$ 12.6, 2H, SCH_2S), 2.76 (q, $^3J_{HH}$ 7.2, 2H, CH_2S), 1.40 (t, $^3J_{HH}$ 7.2, 3H, CH_3CH_2O), 1.30 (t, $^3J_{HH}$ 7.2, 3H, CH_3CH_2S). Anal. Calcd. for $C_5H_{12}ClOPS_3$: C, 23.95; H, 4.79. Found: C, 23.86; H, 4.86.

4b. 76% yield. ^{31}P NMR ($CDCl_3$): 89.12. ^{1}H NMR ($CDCl_3$): 4.33 (dq, $^3J_{HH}$ 7.2, $^3J_{HP}$ 10.8, 2H, CH_2O), 4.23 (d, $^3J_{HP}$ 12.6, 2H, CH_2S), 1.42 (t, $^3J_{HH}$ 7.2, 3H, CH_3), 1.40 (s, 9H, t-C_4H_9). Anal. Calcd. for $C_7H_{16}ClOPS_3$: C, 30.16; H, 5.75. Found: C, 30.21, H, 5.88.

General Procedure for Preparation of **5**

To a solution of triethylamine (0.01 mol) and nucleophile (0.01 mol) in benzene (20 ml) was added dropwise the compound **4** (0.01 mol) at room temperature with rapid stirring. After addition, the resulting mixture was stirred at 50°C for 5–7 hours, then washed with water to PH 7. The solvent was removed in vacuo, and the residue was purified through vacuum liquid chromatographic technique using petroleum ether-ethyl acetate (100:1) as the eluent to give the compounds **5** (Tables I and II).

ACKNOWLEDGEMENT

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