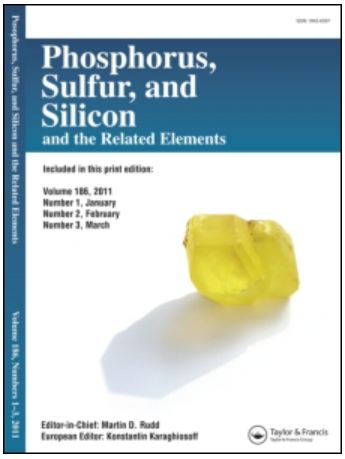

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(3-ALKYL-2-THIAZOLYLIDENAMIDO)-THIOPHOSPHATES-SYNTHESIS AND FUNGICIDAL ACTIVITY

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3-Alkyl-2-thiazolylidenaminodichlorophosphines **1** react with *p*-cresol and sulfur as well as with diethylamine and sulfur to give new classes of monothiophosphoric esters, namely (3-alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl)thiophosphates **3** and (3-alkyl-2-thiazolylidenamido)bis(diethylamido)thiophosphates **4**, respectively. The products exhibit fungicidal activity against the pathogen *Macrophomina phaseolina*.

Key words: 3-Alkyl-2-thiazolylidenaminodichlorophosphines, (3-alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl)thiophosphates, (3-alkyl-2-thiazolylidenamido)bis(diethylamido)thiophosphates, ^{1}H-, ^{31}P-NMR spectra, fungicidal activity.

INTRODUCTION

The phosphoric esters and thiophosphoric esters are known for their insecticidal and fungicidal activities, and attempts have been made to introduce different heterocyclic moieties in these compounds to augment their bioactivity.[1] Thiazole is a typical heterocyclic system which is found in the structures of numerous pesticides, fungicides, herbicides, and nematocides.[2] In view of these properties, thiazole is introduced in various molecules by direct cyclization or by the reaction of the precursors already bearing the thiazole ring.

We have recently developed a facile method for the preparation of aminodichlorophosphines from the reaction of *N*-cycloiminium salts with phosphorus trichloride in presence of triethylamine and reported the synthesis of (3-alkyl-2-thiazolidinylidenamino)dichlorophosphines and (3-alkyl-2-benzothiazolinylidenamino)dichlorophosphines,[3] (1-alkyl-2-pyridinylidenamino)dichlorophosphines,[4] and (3-alkyl-2-thiazolylidenamino)dichlorophosphines.[5]

The reaction of dichlorophosphino derivatives with alcohols[6–9] and secondary amines,[7,9] followed by oxidation with sulfur, afford dialkylthiophosphonates and thiophosphonicdiamides, respectively. The nucleophilic substitution of chlorine in dichlorocyclodiphosphazanes by cresol has also been reported.[10]

These results indicate the possibility of the use of 3-alkyl-2-thiazolylidenaminodichlorophosphines[5] as precursors for the synthesis of amidodiarylthiophosphates and trisamidothiophosphates. The successful synthesis of two new classes of organophosphorus compounds, namely (3-alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl)thiophosphates **3** and (3-alkyl-2-thiazolylidenamido)bis(diethylamido)-thiophosphates **4** and their fungicidal activity are reported here.

TABLE I

Physical and spectral data of the compounds **3,4**

Cpd.	R	R^1	mp. °C	Yield (%)	Mol. Form.	^{31}P-NMR ($CDCl_3$):δ ppm	^{1}H-NMR($CDCl_3$): δ ppm (J Hz)
3a	H	C_6H_5	127-30	36	$C_{24}H_{23}N_2O_2PS_2$	59.6	2.28 (s, 6 H; CH_3), 5.05 (s, 2 H; N-CH_2), 6.43 (dd, $^3J_{HH}$ = 5.0, $^5J_{PH}$ = 1.5, 1 H; H-5), 6.79 (dd, $^3J_{HH}$ = 5.0, $^5J_{PH}$ = 3.0, 1 H; H-4), 7.1-7.5 (m, 13 H; phenyl).
3b	H	CO_2CH_3	Syrup	66	$C_{20}H_{21}N_2O_4PS_2$	59.5	a
3c	H	$CO_2C_2H_5$	90-92	71	$C_{21}H_{23}N_2O_4PS_2$	59.5	1.17 (t, $^3J_{HH}$ = 6.7, 3 H; CH_2-$\underline{CH_3}$), 2.21 (s, 6 H; Ar-CH_3), 4.10 (q, $^3J_{HH}$ = 7.1, 2 H; $\underline{CH_2}$-CH_3), 4.51 (s, 2 H; N-CH_2), 6.32 (d, $^3J_{HH}$ = 4.9, 1 H; H-5), 6.64 (d, $^3J_{HH}$ = 5.4, 1 H; H-4), 6.7-7.1 (m, 8 H; phenyl).
3d	C_6H_5	C_6H_5	Syrup	55	$C_{30}H_{27}N_2O_2PS_2$	58.6	2.06 (s, 6 H; CH_3), 4.85 (s, 2 H; N-CH_2), 6.18 (s, 1 H; H-5), 6.5-7.4 (m, 18 H; phenyl).
4a	H	C_6H_5	65-67	75	$C_{18}H_{29}N_4PS_2$	65.7	0.96 (t, $^3J_{HH}$ = 7.1, 12 H; N-CH_2-$\underline{CH_3}$), 3.05 (dq, $^3J_{PH}$ = 12.8, $^3J_{HH}$ = 6.6, 8 H; N-$\underline{CH_2}$-CH_3), 4.96 (s, 2 H; N-$\underline{CH_2}$-C_6H_5), 6.18 (dd, $^3J_{HH}$ = 4.9, $^5J_{PH}$ = 1.5, 1 H; H-5), 6.62 (dd, $^3J_{HH}$ = 4.9, $^5J_{PH}$ = 2.2, 1 H; H-4), 7.1-7.3 (m, 5 H; phenyl).

4b	H	CO_2CH_3	Syrup	51	$C_{14}H_{27}N_4O_2PS_2$	65.7	0.99 (t, $^3J_{HH}$ = 7.1, 12 H; N-CH_2-$\underline{CH_3}$), 3.02 (dq, $^3J_{PH}$ = 12.8, $^3J_{HH}$ = 6.6, 8 H; N-$\underline{CH_2}$-CH_3), 3.67 (s, 3 H; OCH_3), 4.49 (s, 2 H; N-$\underline{CH_2}$-CO_2CH_3), 6.23 (dd, $^3J_{HH}$ = 4.9, $^5J_{PH}$ = 1.5, 1 H; H-5), 6.69 (dd, $^3J_{HH}$ = 4.9, $^5J_{PH}$ = 2.2, 1 H; H-4).
4c	H	$CO_2C_2H_5$	78-80	80	$C_{15}H_{29}N_4O_2PS_2$	65.8	0.99 (t, $^3J_{HH}$ = 7.1, 12 H; N-CH_2-$\underline{CH_3}$, 1.20 (t, $^3J_{HH}$ = 7.1, 3 H; OCH_2-$\underline{CH_3}$, 3.02 (dq, $^3J_{PH}$ = 12.8, $^3J_{HH}$ = 6.6, 8 H, N-$\underline{CH_2}$-CH_3), 4.10 (q, $^3J_{HH}$ = 7.1, 2 H; $O\underline{CH_2}$-CH_3), 4.47 (s, 2 H; N-$\underline{CH_2}$-$CO_2C_2H_5$), 6.21 (dd, $^3J_{HH}$ = 4.9, $^5J_{PH}$ = 1.5, 1 H; H-5), 6.66 (dd, $^3J_{HH}$ = 5.0, $^5J_{PH}$ = 2.3, 1 H; H-4).
4d	C_6H_5	C_6H_5	Syrup	80	$C_{24}H_{33}N_4PS_2$	64.8	0.93 (t, $^3J_{HH}$ = 7.5, 12 H; CH_3), 2.94 (dq, $^3J_{PH}$ = 14.0, $^3J_{HH}$ = 7.5, 8 H; N-$\underline{CH_2}$-CH_3), 4.95 (s, 2 H; N-$\underline{CH_2}$-C_6H_5), 6.12 (d, $^5J_{PH}$ = 1.5, 1 H; H-5), 6.9-7.5 (m, 10 H; phenyl).

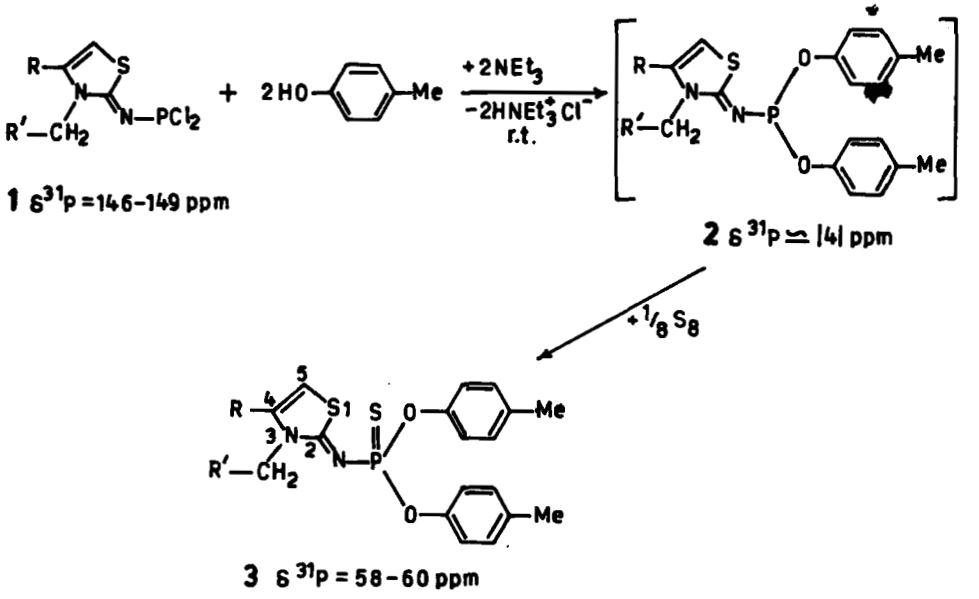
a Could not be obtained in pure form

RESULTS AND DISCUSSION

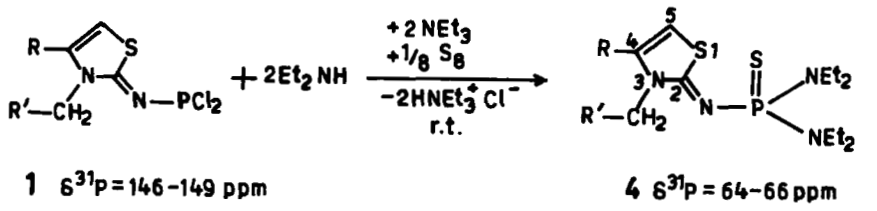
(3-Alkyl-2-thiazolylidenamino)dichlorophosphines **1**, obtainable from the reaction of 3-alkyl-2-aminothiazolium bromides with phosphorus trichloride,[5] react with *p*-cresol (2 equivalent) and sulfur (1/8 equivalent) in the presence of triethylamine (2 equivalent) to form (3-alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl)thiophosphates **3** (Scheme 1).

Although initial formation of (3-alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl) phosphite **2** can be detected by ^{31}P-NMR ($\delta^{31}P \approx 141$),[11,12] it cannot be isolated in the pure state. (3-Alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl)thiophosphates **3** are obtained as white crystalline solids (**3a, 3c**) or as syrupy mass (**3b, 3d**). The reaction of 3-alkyl-2-thiazolylidenaminodichlorophosphines **1** with diethylamine and sulfur under similar conditions affords (3-alkyl-2-thiazolylidenamido)bis(diethylamido)thiophosphates **4** (Scheme 2). The products are stable yellow crystalline solids (**4a, 4c**) except **4b** and **4d** which are obtained as syrupy masses.

The progress of the reaction is monitored by ^{31}P-NMR spectroscopy. The conversion of the dichlorophosphines into the corresponding products is revealed by the disappearance of the ^{31}P-NMR signal of the former ($\delta^{31}P$ = 146–149),[5] ac-



SCHEME 1



SCHEME 2

companied by the appearance of a new signal in the upfield region. The ^{31}P-NMR signal of **3** and **4** appears in the range δ58–60 and δ64–66, respectively, which is characteristic for such compounds having tetracoordinated phosphorus.[11] In ^{1}H-NMR spectra, it is found that protons of **3** and **4** experience a small shielding with respect to those of the corresponding precursors **1**,[5] N—CH_2 ($\Delta\delta$. = 0.11–0.34), H-4 ($\Delta\delta$ = 0.31–0.48) and H-5 ($\Delta\delta$ = 0.36–0.62). Furthermore, H-4 and H-5 in **3** and **4** show long range coupling with phosphorus (H-4, $^{5}J_{PH}$ = 2.19–3.0; H-5, $^{5}J_{PH}$ = 1.46–1.50). The three bond coupling of the methylene protons of dieth-

TABLE II

Fungicidal activity of the compounds **1,3,4**

Cpd.	Average radial growth of M. phaseolina in mm (range)	Sclerotia formation
1a	75.37 (72-78)	+ + +
1b	76.37 (73-80)	+ + +
1c	79.87 (78-82.50)	+ + +
1d	72.75 (70.50-76)	+ + +
3a	53.37 (50-56)	+ +
3b	43.00 (42-45)	+ +
3c	53.25 (50-60)	+ +
3d	41.50 (32-50)	+ +
4a	30.00 (27-35)	+
4b	31.87 (30-35)	+
4c	33.25 (32.50-35)	+
4d	23.50 (22-24.50)	+
Control	87.75 (85-90)	+ + +
	SEM± 1.80	+Few
	CD5% 5.16	+ + Several
	GM 53.99	+ + + Abundant
	CV% 6.67	

ylamino group with phosphorus ($^3J_{PH}$ = 12.8–14.0) is in accordance with the reported value.[13]

FUNGICIDAL ACTIVITY

The synthesized products **3** and **4** show fungicidal activity against the pathogen *Macrophomina phaseolina*, and the results of the study in terms of radial growth and sclerotia formation are given in Table II. Statistical analysis of data reveals 5.16 mm to be the critical difference at 5 percent for control average radial growth of 87.75 mm. Grading for sclerotia formation correlates the radial growth.

A technique employing poisoning of nutrient medium with test compound to evaluate its fungitoxic property[1] reveals substantial such property in the compounds tested. The compounds **4a–d** exhibit stronger fungitoxic property (23.50–33.25 with + sclerotia formation) than **3a–d** (41.50–53.37 with + + sclerotia formation). As compared to these data, the fungitoxic activity of the precursors **1a–d** was found to be very low (72.75–79.87 with + + + sclerotia formation). As regard the structure activity relationship, triamidothiophosphates **4** show stronger fungicidal activity than amidodiarylthiophosphates **3**. Furthermore, these limited studies reveal that the products having phenyl group at 4 position (**1d, 3d, 4d**) in the thiazole ring exhibit better activity than those having 4 position unsubstituted. However, to establish SAR still broader studies are required which are in progress.

EXPERIMENTAL

All manipulations involving phosphorus compounds were carried out under dry nitrogen using standard the Schlenk technique. Methylene chloride and diethyl ether were distilled and dried by standard procedures before use. Diethylamine and *p*-cresol were commercially available and were used after distillation. Melting points were determined on a tempo instrument and were uncorrected. NMR spectra were recorded on a Jeol FX-90-Q spectrometer. Chemical shifts were given with respect to 85% H_3PO_4 (^{31}P) as external and TMS (^1H) as internal standards.

(3-Alkyl-2-thiazolylidenamido)bis(O-4-methylphenyl)thiophosphates (**3**). *General Procedure*: To a solution of **1** (5 mmol) in methylene chloride (20 ml), triethylamine (1.0 g, 10 mmol) was added followed by *p*-cresol (1.1 g, 10 mmol) and sulfur (0.2 g, 5 mmol), and the reaction mixture was stirred for 2–3 hrs at ambient temperature (20°C). After completion of the reaction (checked by ^{31}P-NMR) the solvent was removed *in vacuo*, and the residue was extracted with diethyl ether (2 × 25 ml). The combined extracts were concentrated to 20 ml and kept in the refrigerator (0°C). The product separated out as colourless solid, which was filtered and dried *in vacuo*. In the case of **3b** and **3d**, no crystals separated, and therefore the solution was completely dried to give a syrupy mass.
3a (% Found C 61.48; H 4.61; N 5.65. Calc. for $C_{24}H_{23}N_2O_2PS_2$: C 61.78; H 4.97; N. 6.00%).

(3-Alkyl-2-thiazolylidenamido)bis(diethylamido)thiophosphates (**4**). *General Procedure*: The above procedure was followed using diethylamine (0.7 g, 10 mmol) in place of *p*-cresol. On keeping the concentrated ether extract in the refrigerator (0°C), a yellow solid was obtained. However, in the case of **4b** and **4d**, no crystals formed, and the solution was completely dried to give a syrupy mass.
4a (% Found C 54.21; H 7.29; N 14.00. Calc. for $C_{18}H_{29}N_4PS_2$: C 54.51; H 7.37; N 14.13%).

Evaluation of fungicidal activity: The poison food technique was followed for testing the compound for their fungicidal activity. The pathogen (*Macrophomina phaseolina*) was isolated from the groundnut crop (*Arachis hypogaea* L.) on 2% Potato-dextrose agar (PDA) medium. The desired concentration (250 ppm) of the test compound was obtained in warm sterile PDA medium. This poisoned medium was poured into petriplates (90 mm diameter). For each treatment, the plate was inoculated by inoculum disc of 3 mm diameter cut from the margin of a 6-day old culture of the test pathogen and incubated at 26 ± 1°C. Suitable control was maintained where no test compound was added. The radial growth was measured diagonally after 6 days. Sclerotial observations were also recorded. The experiment was replicated four times.

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