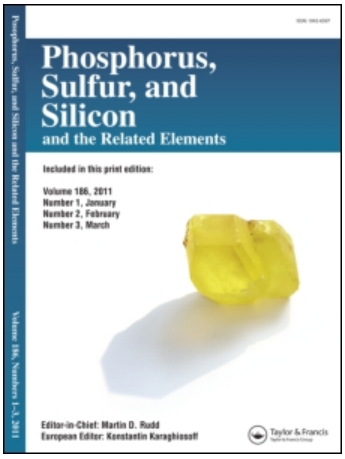

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SYNTHESES AND BIOLOGICAL ACTIVITIES OF 1,2,4-TRIAZOLO-[3,4-*B*][1,3,4]THIADIAZOLE DITHIOPHOSPHATES

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SYNTHESES AND BIOLOGICAL ACTIVITIES OF 1,2,4-TRIAZOLO-[3,4-b][1,3,4]THIADIAZOLE DITHIOPHOSPHATES

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In this article, we incorporated the organic phosphorus group on to a triazolothiadiazole ring to prepare the title compounds fused 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole heterocyclic compounds. From the results on biological activities, we found that most compounds showed weak activities, and thus the structures need to be further optimized for improved activity.

Keywords: Biological activity; organic phosphorus; synthesis; triazolothiadiazole

Since Kanaoka[1] described initially the synthesis of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole, many triazolothiadiazole derivatives have been reported to possess fungicidal, insecticidal, herbicidal, antimicrobial, bactericidal, and plant growth regulator activities.[2–10] The structure variations of these compounds include different substituents such as alkyl, aryl, and heterocycle which were introduced at the 3- or 6-position.[11–19] However, among these different compounds, no compound containing organophosphorus moiety was reported. Therefore, we have incorporated an organophosphorus moiety on to a triazolothiadiazole ring at the 6-position in order to prepare the novel and potentially useful title compounds. The synthesis route is outlined in Scheme 1.

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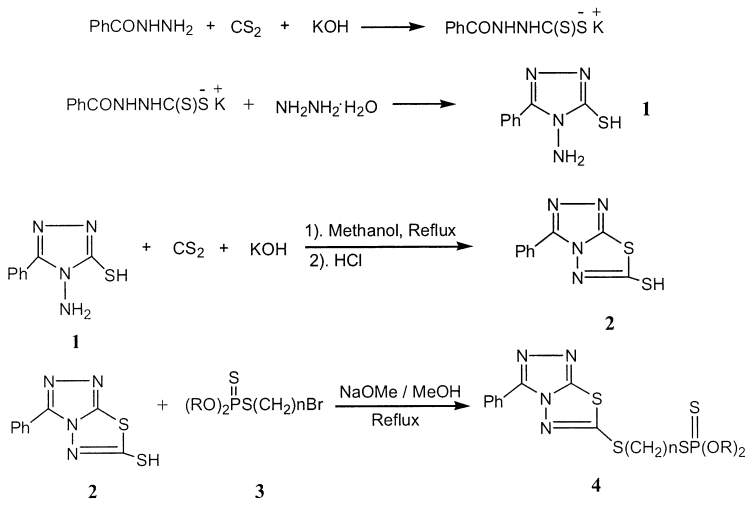
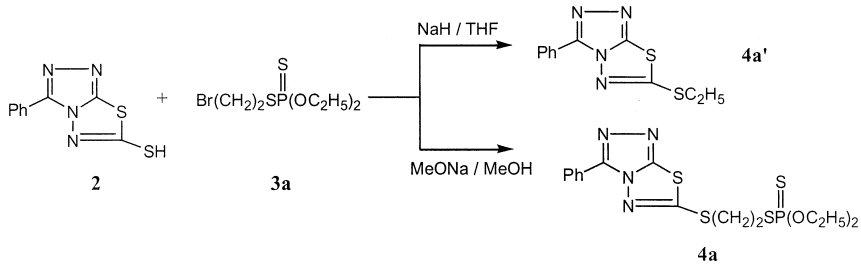


SCHEME 1

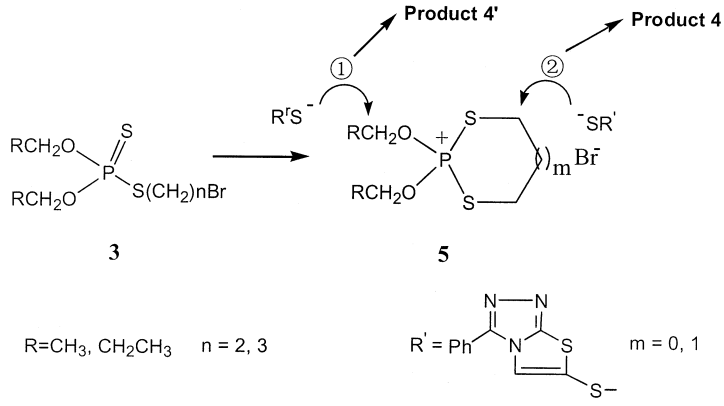
RESULTS AND DISCUSSION

Preparations of the Title Compounds 4

The key intermediate **2** was prepared from benzoyl hydrazine in 3 steps and then was treated with bromoethyl phosphorodithionate **3**. In this reaction, when intermediate **2** reacted with intermediate **3a** in aqueous sodium hydroxide at room temperature with tetrabutylammonium bromide (**TBAB**) as a phase transfer catalyst, no title compound **4a** formed. Even when the reaction temperature was raised to 70∼80°C, no desired compound **4** appeared. This is because the starting material **3** is easily hydrolyzed in aqueous sodium hydroxide at room temperature. When compound **2** reacted with compound **3a** in NaH/THF system, only a small amount of the title compound **3a** was produced but a new compound formed which was determined by elementary analysis, ^{1}HNMR, and GC-MS to be the byproduct **4a′**. ^{1}HNMR (δ, ppm, DMSO/TMS): 1.42 (t, 3H, CH_3), 3.36 (dt, 2H, CH_2), 7.57 (d, 3H, 3H on the C_6H_5), 8.18 (d, 2H, 2H on the C_6H_5). Calcd: C% 50.38, H% 3.82, N% 21.37; found: C% 50.28, H% 3.56, N% 21.68. Calcd. for $C_{11}H_{10}N_4S_2$(M): 262, found: 262 (GC-MS), m.p. 154∼5°C. After several experiments, we found that the desired compound **4** was obtained in good yields only in a NaOMe/MeOH system at refluxing temperature. The other compounds were obtained in the same way. These results appear in Scheme 2. All the title compounds were determined by elementary analyses, ^{1}HNMR,



SCHEME 2



SCHEME 3

and IR spectrum data. The detail data are outlined in Tables I, II, and III.

A possible reaction mechanism is outlined in Scheme 3. In the caustic solution, the sulfur atom of P═S bond attacks the carbon atom adjacent to bromo atom of the starting material **3** to produce the intermediate **5**. The cyclic 1,3-disulfurphosphane **5** is easily attacked by nucleophiles by means of ① and ② because of rich positive charge in phosphorus atom. The nucleophile R'S attacks the different carbon atoms to produce different products **4** and **4′**.

Characterizations of Title Compounds

In the ^{1}HNMR spectrum, the two alkoxy groups binding phosphorus of the compounds **4** are equivalent when R is Et and *n*-Pr. However the two alkoxy groups on phosphorus atom are not equivalent when R is *i*-Pr, and show two doublets. With regard to the IR spectra, the bands around 650 cm^{-1} and 1000 cm^{-1} were attributed to P═S and P─O─C

TABLE I The Physical Data of Compounds **4**

Compd.	n	R	m.p. (°C)	Yield (%)	Elementary Analysis (%, Cald.) C	H	N
4a	2	Et	65∼7	69.5	40.20 (40.36)	4.07 (4.26)	12.53 (12.56)
4b	3	Et	32∼4	62.3	41.79 (41.74)	4.39 (4.57)	11.85 (12.17)
4c	2	*n*-Pr	63∼4	61.9	43.23 (43.04)	4.55 (4.85)	11.90 (11.82)
4d	3	*n*-Pr	54∼5	57.4	44.00 (44.26)	5.00 (5.12)	11.37 (11.48)
4e	2	*i*-Pr	93∼4	56.9	42.70 (43.04)	4.83 (4.85)	11.87 (11.82)
4f	3	*i*-Pr	54∼6	50.6	44.23 (44.26)	5.12 (5.12)	11.46 (11.48)

groups, respectively. The detail spectrum data are outlined in Tables II and III.

Biological Activities Results

From the screening results for biological activities, the title compounds show low fungicidal activities, and therefore the structures need to be optimized. The results are shown in Table V.

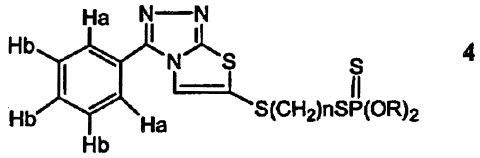
EXPERIMENTAL

^{1}HNMR spectra were recorded in $CDCl_3$ on an AC-P200 instrument using TMS as an internal standard. IR spectra were measured on a

TABLE II The IR Data of Compounds **4**

Compd.	IR (KBr or film, cm^{-1}) P═S	P─S	P─O─C	C═C, C═N (heterocycle)
4a	658.1	547.1	1007.1, 1176.9, 769.3	1478.6, 1453.6, 1430.5
4b	654.6	519.3	1006.6, 1153.8, 761.4	1463.4, 1451.9, 1432.7
4c	660.7	505.6	987.3, 1144.9, 762.8	1466.9, 1455.4, 1432.5
4d	653.5	513.7	980.6, 1173.1, 759.5	1466.6, 1455.1, 1430.8
4e	644.1	509.0	981.7, 1173.8, 760.9	1468.5, 1459.2, 1435.1
4f	651.8	557.2	985.4, 1173.0, 773.8	1460.1, 1452.4,1433.2

TABLE III The ^{1}HNMR Spectral Data of Compounds **4**



4

Compd.	^{1}HNMR δ (ppm, $CDCl_3$/TMS)
4a	1.29 (t, 6H, 2 × C<u>H</u>$_3$CH$_2$O), 3.36 (dt, 2H, SCH$_2$C<u>H</u>$_2$SP), 3.67 (t, 2H, SC<u>H</u>$_2$CH$_2$SP), 4.14 (m, 4H, 2 × CH$_3$C<u>H</u>$_2$O), 7.51 (d, 3H, 3 × Hb), 8.33 (t, 2H, 2 × Ha)
b	1.35 (t, 6H, 2 × C<u>H</u>$_3$CH$_2$O), 2.26 (m, 2H, SCH$_2$C<u>H</u>$_2$CH$_2$SP), 3.05 (dt, 2H, SCH$_2$CH$_2$C<u>H</u>$_2$SP), 3.52 (t, 2H, SC<u>H</u>$_2$CH$_2$CH$_2$SP), 4.16 (m, 4H, 2 × CH$_3$C<u>H</u>$_2$O), 7.56 (d, 3H, 3 × Hb), 8.35 (m, 2H, 2 × Ha)
c	0.95 (t, 6H, 2 × C<u>H</u>$_3$CH$_2$CH$_2$O), 1.72 (m, 4H, 2 × CH$_3$C<u>H</u>$_2$CH$_2$O), 3.34 (m, 2H, SCH$_2$C<u>H</u>$_2$SP), 3.69 (t, 2H, SC<u>H</u>$_2$CH$_2$SP), 4.07 (m, 4H, 2 × CH$_3$CH$_2$C<u>H</u>$_2$O), 7.53 (d, 3H, 3 × Hb), 8.31 (m, 2H, 2 × Ha)
d	0.96 (t, 6H, 2 × C<u>H</u>$_3$CH$_2$CH$_2$O), 1.75 (m, 4H, 2 × CH$_3$C<u>H</u>$_2$CH$_2$O), 2.27 (m, 2H, SCH$_2$C<u>H</u>$_2$CH$_2$SP), 3.16 (dt, 2H, SCH$_2$CH$_2$C<u>H</u>$_2$SP), 3.51 (t, 2H, SC<u>H</u>$_2$CH$_2$CH$_2$SP), 4.09 (m, 4H, 2 × CH$_3$CH$_2$C<u>H</u>$_2$O), 7.58 (d, 3H, 3 × Hb), 8.41 (m, 2H, 2 × Ha)
e	1.31 (dd,12H, 2 × (C<u>H</u>$_3$)$_2$CHO), 3.36 (dt, 2H,SCH$_2$C<u>H</u>$_2$SP), 3.67 (t, 2H, SC<u>H</u>$_2$CH$_2$SP), 4.81 (m, 2H, 2 × (CH$_3$)$_2$C<u>H</u>O), 7.51 (d, 3H, 3 × Hb), 8.28 (q, 2H, 2 × Ha)
f	1.33 (dd, 12H, 2 × (C<u>H</u>$_3$)$_2$CHO), 2.29 (m, 2H, SCH$_2$C<u>H</u>$_2$CH$_2$SP), 3.05 (dt, 2H, SCH$_2$CH$_2$C<u>H</u>$_2$SP), 3.51 (t, 2H, SC<u>H</u>$_2$CH$_2$CH$_2$SP), 4.77 (m, 2H, 2 × (CH$_3$)$_2$C<u>H</u>O), 7.53 (d, 3H, 3 × Hb), 8.34 (m, 2H, 2 × Ha)

Nicolet 5DX IR spectrometer. Elemental analyses were conducted on an MF-3 automatic analyzer. Melting points were determined on an MP-500 melting point apparatus. All temperatures and pressures are uncorrected.

TABLE V The Fungicidal Activities of Compounds **4**

	Fungicidal activities (inhibition%)							
	In vivo (500 ppm)			In vitro (50 ppm)				
Compd.	*S. sclerotiorum*	*P. recibduta*	*B. cinerea*	*A. solani*	*P. asparagi*	*P. piricola*	*G. zeae*	*C. arachidicola*
4a	5	30	0	4	40	15	22	0
b	10	50	43	14	30	7	16	6
c	0	10	0	9	0	3	11	0
d	8	0	0	0	10	3	5	0
e	0	20	0	0	0	3	8	0
f	12	0	48	4	20	3	8	13

Preparation of 3-Phenyl-6-mercapto-1,2,4-Triazolo[3,4-b]-1,3,4-thiadiazole 2[20,21]

To the solution of 5.6 g (0.10 mmol) of KOH in 150 mL of methanol was added 19.2 g (0.10 mmol) of 3-phenyl-4-ammino-5-mercapto-1,2,4-triazolo **1**, and then 20 mL of CS_2 was added. After the mixture was heated to reflux for 24 h, the solvent was removed under reduced pressure, the residue was poured into 200 mL of water and the latter was acidified with concd. HCl to yield a white solid. The solid was filtered and recrystallized (pyridine) to obtain 14.33 g of a white crystal **2**, yield 61.2%, m.p. 208∼210°C (lit[21] m.p. 210°C).

Preparations of the Title Compounds 4

To the solution of 0.006 g (1.0 mmol) of NaOMe in 15 mL of dry methanol was portionly added 0.23 g (1.0 mmol) of 3-phenyl-6-mercapto-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (**2**) with stirring, and then 0.35 g (1.2 mmol) of O, O-diethyl-S-(2-bromoethyl)dithiophosphotate (**3a**)[22] was added. After the addition, the mixture was heated to reflux with stirring for 4∼5 h. When the reaction was completed, the mixture was cooled to room temperature, diluted with 20 mL of water, and extracted with 30 mL × 3 of dichloromethane. The combined organic extracts were washed with 30 mL × 3 of water and dried over $MgSO_4$. After removal of the dichloromethane, the residue was purified by silicon gel chromatography using ethyl acetate/petroleum ether (5:1) as eluent to give white crystals of **4a**, 0.31 g (69.5%). The other compounds **4** were prepared by the same procedure, and their data are listed in Tables I, II, and III, respectively.

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