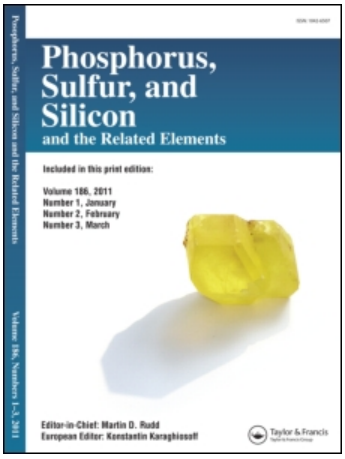

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Synthesis and Biological Activities of O, O-Dialkyl-dithiophosphoryl-S-acetoxy Triazolo Compounds

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF O, O-DIALKYL-DITHIOPHOSPHORYL-S-ACETOXY TRIAZOLO COMPOUNDS

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In this article, we introduce organic phosphorus moiety into triazole ring to prepare O-dialkyl-dithiophosphoryl-S-acetoxy triazolo compounds and characterize their structures by elementary analysis and ^{1}HNMR and IR spectral data. From the results of biological activity screening, we found that the O-dialkyl-dithiophosphoryl-S-acetoxy triazolo compounds show lower fungicidal activities and their structures need to be optimized for the better.

Keywords: Biological activities; organic phosphorus; synthesis; triazole

INTRODUCTION

Organic phosphorus compounds are biologically versatile as they are pesticides, fungicides, and herbicides,[1–4] and many compounds have been commercialized. At the same time, triazole compounds also possess pesticidal, herbicidal, and fungicidal activities and plant growth regulation activities.[5–11] The introduction of organic phosphorus in triazole compounds not only reduces the toxicity of organic phosphorus compounds on mammalian, but also expands the application scope of triazole compounds. However, triazole compounds containing organic phosphorus are seldom reported.[12,13] To study the biological activities of all kinds of triazole compounds, we incorporated organic phosphorus moiety in triazole compounds to prepare O-dialkyl-dithiophosphoryl-S-acetoxy triazolo compounds. The syntheses of these compounds are outlined in Schemes 1, 2, and 3.

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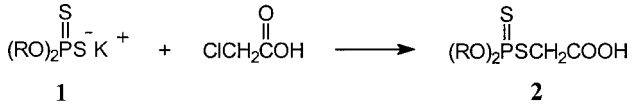
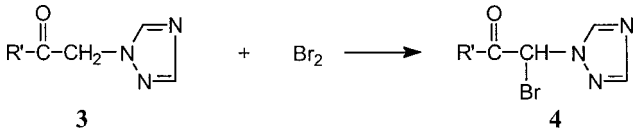


SCHEME 1



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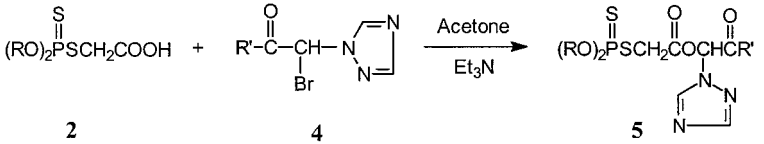

R = Me, Et, *n*-Pr, *i*-Pr
R' = $(CH_3)_3C$, 4-FC_6H_4

SCHEME 3

RESULTS AND DISCUSSION

Preparation of O-Dialkyl-dithiophosphoryl-S-acetoxy Triazolo Compounds (5)

During the course of our experiment, we found that the intermediate **3** was unstable and decomposed for some time to a unknown solid. Thus, compounds **3** must be freshly prepared before using.

The base is necessary to this reaction. Results show that no product was obtained when the base was absent. At the same time, we tested such bases as triethylamine, pyridine, and potassium carbonate. Here, the reactant became very complex and no obvious product was detected using potassium carbonate as a base. When we used pyridine as a base, the same result was observed. Only using triethylamine, were we able to obtain the desired result. On the other hand, the reaction temperature is an important factor in the reaction. A higher temperature lead to dark color and complicated unknown compounds; at room temperature or a lower temperature, desired results were observed. In the end, we found that the intermediate **3b** is more reactive than **3a**, as it reacts at lower temperature.

TABLE I The IR Data of Compounds **5**

	IR (υ/cm^{-1}, film)				
Compd.	C═O	C═N (triazole)	C—H (triazole)	P═S	P—O—C
5a	1727.7, 1751.3	1505.9, 1476.9	3102.5	654.1	1009.4, 1173.7, 771.2
5b	1726.3, 1751.8	1504.9, 1475.3	3109.0	668.3	1000.4, 1180.1, 793.0
5c	1723.5, 1754.4	1503.0, 1467.3	3108.0	658.5	993.4, 1180.5, 757.6
5d	1723.8, 1758.4	1503.4, 1478.9	3112.0	653.1	994.7, 1182.5, 749.4
5e	1704.6, 1758.1	1507.0, 1440.4	3108.5	654.2	1006.1, 1153.9, 783.7
5f	1704.7, 1756.1	1506.8, 1459.3	3103.5	656.8	977.4, 1154.2, 747.6
5g	1707.8, 1752.8	1506.9, 1461.8	3100.0	649.2	995.6, 1154.6, 771.3

Characterizations of O-Dialkyl-dithiophosphoryl-S-acetoxy Triazolo Compounds

The IR spectrum of the O-dialkyl-dithiophosphoryl-S-acetoxy triazolo compounds exhibited two sharp bands around 1700∼1750 cm^{-1} due to the two C═O functions, whereas the bands around 650 cm^{-1} and 1000 cm^{-1} were attributed to P═S and P—O—C groups respectively. The other data was outlined in Table I.

With respect to the ^{1}HNMR spectra, there is much difference because of the different substituents R and R′. When R is *i*-Pr, the two *i*-propoxy bonded to phosphorus atom are not equal to appear two doublet peaks. But the difference is so small that triplet peaks were observed. While R is Me, Et, and *n*-Pr, the two alkyoxy groups are equal and the same chemical shifts were observed. At the same time, different substituent R′ also affect the chemical shift of the methenyl group bonded to triazole ring. When R′ is *i*-butyl, it appeared as singlet peak at δ 7.3, while R′ is 4-FC_6H_4, the singlet peak was observed at δ 8.5–8.7. The detailed data was shown in Table II.

Biological Activities Results

We selected some compounds **5** to test their fungicidal and insecticidal activities and found that they possess some fungicidal but no insectididal activities. Some results of these compounds are outlined in Table III.

EXPERIMENTAL

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

TABLE II The IR Data of Compounds **5**

Compd.	^{1}HNMR δ (ppm), J_{P-H}(Hz) ($CDCl_3$/TMS)
5a	1.15 (s, 9H, 3 × CH_3), 3.73 (d, 2H, CH_2S, J_{P-H} =15.33), 3.78 (d, 6H, 2 × CH_3O, J_{P-H} =15.22), 7.36 (s, 1H, CH), 8.05 (s, 1H, Tr-H), 8.51 (s, 1H, Tr-H)
5b	1.13 (s, 9H, 3 × CH_3), 1.29 (t, 6H, 2 × $\underline{CH_3}CH_2O$), 3.73 (d, 2H, CH_2S, J_{P-H} =17.77), 4.15 (m, 4H, 2 × $CH_3\underline{CH_2}O$, J_{P-H} =15.22), 7.31 (s, 1H, CH), 8.00 (s, 1H,Tr-H), 8.36 (s, 1H, Tr-H)
5c	0.96 (t, 6H, 2 × $\underline{CH_3}CH_2CH_2O$), 1.18 (s, 9H, 3 × CH_3), 1.72 (m, 4H, 2 × $CH_3\underline{CH_2}CH_2O$), 3.79 (d, 2H, CH_2S, J_{P-H} =17.73), 3.98 (m, 4H, 2 × $CH_3\underline{CH_2}CH_2O$), 7.38 (s, 1H, CH), 8.08 (s, 1H, Tr-H), 8.55 (s, 1H, Tr-H)
5d	1.19 (s, 9H, 3 × CH_3), 1.34 (t, 12H, 2 × $(\underline{CH_3})_2CH$), 3.82 (d, 2H, CH_2S, J_{P-H} =17.39), 4.81 (m, 2H, 2 × $(CH_3)_2\underline{CH}$), 7.39 (s, 1H, CH), 8.09 (s, 1H, Tr-H), 8.52 (s, 1H, Tr-H)
5e	1.33 (t, 6H, 2 × $\underline{CH_3}CH_2O$), 3.80 (d, 2H, CH_2S, J_{P-H} =18.34), 4.13 (m, 4H, 2 × $CH_3\underline{CH_2}O$), 7.12~7.22, 7.91~7.98 (m, 4H, C_6H_4), 7.82 (s, 1H, Tr-H), 8.05 (s, 1H, Tr-H), 8.56 (s, 1H, CH)
5f	0.95 (t, 6H, 2 × $\underline{CH_3}CH_2CH_2O$), 1.71 (m, 4H, 2 × CH_3CH_2 CH_2O), 3.81 (d, 2H, CH_2S, J_{P-H} =17.87), 4.06 (m, 4H, 2 × $CH_3CH_2\underline{CH_2}O$), 7.13~7.22, 7.91~8.02 (m, 4H, C_6H_4), 7.84 (s, 1H, Tr-H), 8.07 (s, 1H, Tr-H), 8.71 (s, 1H, CH)
5g	1.31 (t, 12H, 2 × $(\underline{CH_3})_2CHO$), 3.83 (d, 2H, CH_2S, J_{P-H} =17.54), 4.81 (m, 2H, 2 × $(CH_3)_2\underline{CHO}$), 7.12~7.23, 7.93~8.01 (m, 4H, C_6H_4), 7.85 (s, 1H, Tr-H), 8.07 (s, 1H, Tr-H), 8.68 (s, 1H, CH)

on a 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. Refractive indices were obtained by use of Abbe refractometer. All temperatures and pressures are uncorrected.

TABLE III The Fungicidal Activities of Compounds **5**

	Fungicidal activities (%)							
	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*
5a	5	0	0	4.8	0	7.7	2.8	0
5b	0	0	0	9.5	10	11.5	2.8	0
5c	10	10	0	0	0	3.8	5.6	0
5d	0	10	0	0	0	11.5	2.8	6.7
5e	15	0	49.6	9.5	0	7.7	5.6	6.7

TABLE IV Some Data of Compounds of **1** and **2**

Compd.	R	m.p. (°C)	Yield (%)	Compd.	R	n_D^{25}	Yield (%)
1a	Me	190∼2	52.3	**2a**	Me	1.5070	98.0
1b	Et	213∼4	48.7	**2b**	Et	1.5078	96.0
1c	*n*-Pr	168∼70	44.1	**2c**	*n*-Pr	1.5056	86.9
1d	*i*-Pr	204∼6	40.2	**2d**	*i*-Pr	1.5046	97.1

Preparations of Intermediates

Preparation of O,O-Dialkylphosphinothioylthioacetic Acetic Acid 2[14,15]

According to the literature procedure, potassium O,O-diethylphosphorodithioate[14] was treated with chloracetic acid in acetone to give the liquid that was purified by silicon gel column chromatography using petroleum ether as eluent to give the compound **2b**, yield 96.0%, n_D^{25} 1.5078, ^{1}HNMR (δ/ppm, $CDCl_3$): 134 (t, 6H, 2 × $\underline{CH_3}CH_2O$), 3.67 (d, 2H, CH_2S J_{P-H} =17.54 Hz), 4.11–4.23 (m, 4H, 2 × $CH_3\underline{CH_2}O$), 9.98(brs, 1H, COOH).

Similarly, other compounds **2** were prepared from the corresponding potassium, and some data of compounds **1** and **2** were shown in Table IV.

Preparations of Bromo Ketone 4[16]

Triazolo ketone **3** was treated with bromine in acetic acid and sodium acetate anhydride to give the crude products **4a** and **4b** which not purified for the next step, yield 84.4% and 95.4%.

Preparations of O-Dialkyl-dithiophosphoryl-S-acetoxy Triazolo Compounds 5

To the mixture of O, O-dimethylphosphinothioylthioacetic acetic acid **2a** 1.08 g (5.0 mmol), and 30 mL of dry acetone, was added 0.56 g (5.5 mmol) Et_3N by stirring at room temperature. After addition, the mixture was cooled to 0∼5°C with ice-water bath, 1.23 g (5.0 mmol) 3, 3-dimethyl-1-bromo-1-(1H-1, 2, 4-triazolo-1-yl)-2-butanone **3a** in 5 mL of dry acetone was added to the reactant, then triethylamine hydrobromide appeared. After the addition was completed, the ice-water bath was removed and the mixture was stirred for 4 h at room temperature. The solvent was evaporated off under reduced pressure, and the residue was diluted with 30 mL of CH_2Cl_2 and washed with water and dried over $MgSO_4$. After removal of solvent, the residue was separated by silicon gel chromatography using ethyl acetate/petroleum ether as eluent to give the viscous liquid, 1.54 g, yield 80.8%. The other compounds **5b–5d** were prepared by the same procedure.

TABLE V The Data of Compounds **5**

Compd.	R	R′	m.p. (°C)	Yield (%)	Elementary analyses (% calcd.) C	H	N
5a	Me	$(CH_3)_3C$	Viscous liquid	80.8	37.80 (37.79)	5.09 (5.25)	10.89 (11.02)
5b	Et	$(CH_3)_3C$	Viscous liquid	80.2	41.10 (41.08)	5.62 (5.87)	10.17 (10.27)
5c	*n*-Pr	$(CH_3)_3C$	Viscous liquid	65.6	43.67 (43.94)	6.19 (6.41)	9.34 (9.61)
5d	*i*-Pr	$(CH_3)_3C$	46∼48	62.5	43.98 (43.94)	6.16 (6.41)	9.33 (9.61)
5e	Et	4-FC_6H_4	Viscous liquid	77.8	43.04 (42.95)	3.99 (4.25)	8.87 (9.39)
5f	*n*-Pr	4-FC_6H_4	Viscous liquid	61.3	45.08 (45.47)	4.71 (4.84)	8.68 (8.84)
5g	*i*-Pr	4-FC_6H_4	Viscous liquid	59.5	45.64 (45.47)	4.47 (4.84)	8.40 (8.84)

Similarly, to the mixture of 1.22 g (5.0 mmol) O, O-diethylphosphinothioylthioacetic acetic acid **2b**, 0.56 g (5.5 mmol) Et_3N, and 30 mL of acetone, was added 1.42 g (5.0 mmol) α-(1H-1,2,4-triazolo-1-yl)-α-bromo-*para*-fluoroacetonphenone **3b** in 5 mL of acetone at 0∼5°C. After the addition, the mixture was stirred for 2 h under this condition. Then the reactant was poured into 50 mL of ice-water, extracted with 3×20 mL of chloroform, washed with water twice, and dried over $MgSO_4$. After removal of solvent, the residue was isolated by silicon gel chromatography using ethyl acetate/petroleum ether as eluent to give viscous liquid **5e**, 1.74 g, yield 77.8%.

According to the same procedure, the title compound **5f**, **5g** were obtained and all compounds prepared were characterized by element analysis, HNMR and IR spectral data, their relevant data being listed in Tables I, II, and V.

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