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Synthesis of *N*-(Thio)phosphoryl-*N*′-2-Benzoxazolyl Semicarbazides

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ABSTRACT: *We prepared the benzoxazole derivatives bearing the (thio) phosphoryl moiety by addition reactions of 2-hydrazionbenzoxazole with isothiocyanato (thio) phosphates and characterized their structures by elementary analysis and* ^{1}*H NMR and IR spectral data. From the results of biological activity screening, we found that these compounds possess some herbicidal, and plant growth regulator activities, and especially good fungicidal activity against Puccinia recondita.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:151–155, 2001

INTRODUCTION

Benzoxazole derivatives are biologically versatile as they have been found to be tranquilizers [1] and inhibitors of immune complex–induced inflammation [2] in medical applications and fungicides [3–5], herbicides [6–7], and insecticides [8] in agricultural applications. The structural variations of these compounds are that different substituents can be incorporated on the benzene ring, and diverse heterocycles and other active groups can be introduced at the 2-position in order to create good biological activity. Among the different substituents, the groups at the 2-position play a key role in their biological activities. Phosphate or thiophosphate derivatives have been extensively investigated in the area of pesticides, but not with regard to benzoxazole derivatives. Therefore, we have incorporated isothiocyanato (thio) phosphate moieties in the benzoxazole ring in order to prepare novel and potentially useful compounds **8** from 2-hydrazinobenzoxazole. By biological activity screening, we have found that these compounds show broad-spectrum antifungicidal activity, especially against *Puccinia recondita*. The synthesis of these compounds is outlined in Schemes 1, 2, and 3. The intermediate 2-hydrazinobenzoxazole **4** was synthesized from 2-aminophenol in three steps; the isothiocyanato (thio) phosphate **7** was synthesized in two steps and the total yield was 43.9–76.2%. The title compounds **8** were prepared at room temperature, or slightly higher, and were purified by silica gel column chromatography.

EXPERIMENTAL

^{1}HNMR spectra were recorded in $CDCl_3$ as solvent on an AC-P200 instrument using tetramethylsilane (TMS) as an internal standard. IR spectra were measured 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 an Abbe refractometer. All temperatures and pressures are uncorrected.

Preparation of 2-Hydrazinobenzoxazole **4** *[1,9,10]*

Into a 250 mL four-necked flask was placed 2-aminophenol (19.1 g, 0.175 mol), KOH (10.09 g, 0.18

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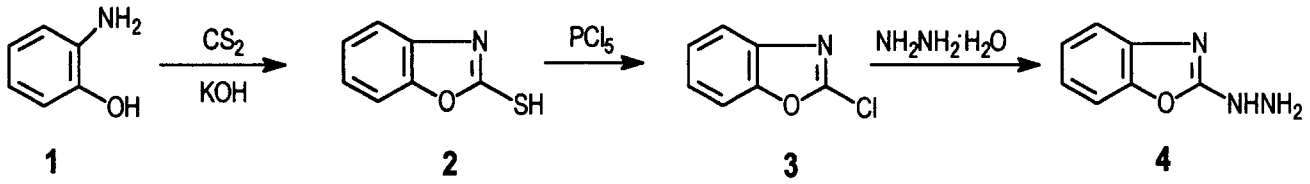
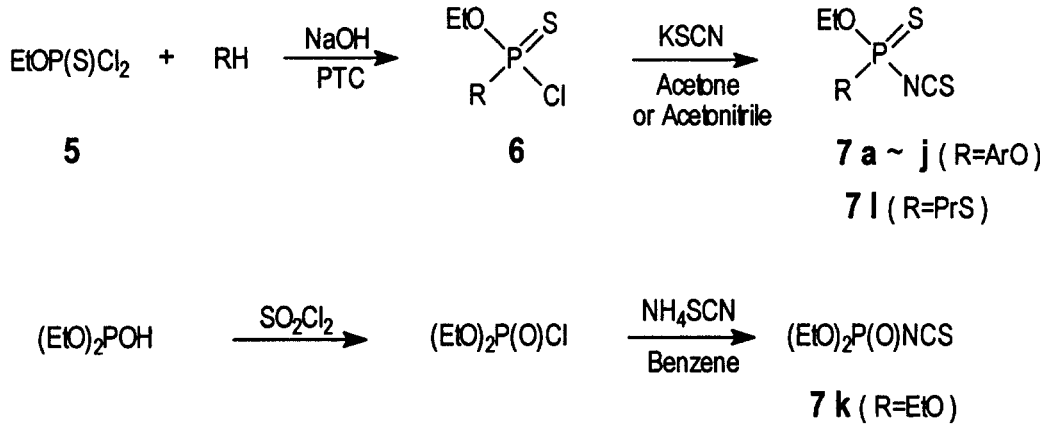
mol), CS_2 (13.68 g, 0.18 mol), 150 mL of 95% ethanol, and 30 mL of water. The mixture was heated under reflux for 3 hours. Norite (7.0 g) was then added cautiously, and after the mixture had been heated at reflux temperature for 10 minutes, the norite was filtered off. The filtrate was heated to 60–70°C, 200 mL of warm (60–70°C) water was added, and the solution was neutralized with 15 mL of acetic acid in 30 mL water. The product **2** precipitated and was filtered off and dried, (m.p. 194–196°C, yield 78.2% [lit. 193–195°C, 80%]).

To the product **2** (18.75 g, 0.124 mol) dissolved



SCHEME 1



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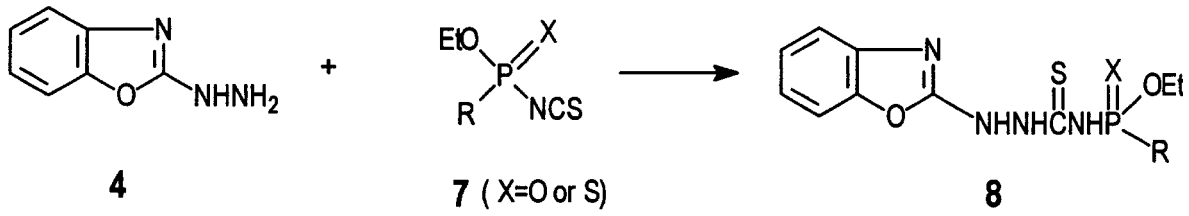

SCHEME 3

TABLE 1 The Data of Compounds **7a–7l**

Compound	*R*	*Yield (%)*	n_0^{22}	*Compound*	*R*	*Yield (%)*	n_0^{22}
7a	C_6H_5O	66.3	1.5765	**7g**	4-$CH_3C_6H_4O$	66.3	1.5609
7b	2-ClC_6H_4O	60.3	1.5784	**7h**	2,4-$ClBrC_6H_4O$	56.1	1.6010
7c	4-$NO_2C_6H_4O$	49.9	1.6050	**7i**	2,4-$Cl_2C_6H_4O$	43.9	1.5902
7d	4-BrC_6H_4O	62.9	1.5928	**7j**	2,4-$CH_3ClC_6H_4O$	58.5	1.5650
7e	4-ClC_6H_4O	67.0	1.5712	**7k**	EtO	73.9	1.4732
7f	2,4-$Me_2C_6H_4O$	58.9	1.5436	**7l**	Prs	76.2	1.5630

TABLE 2 The Data of Compounds **8**

Compound	R	X	m.p. (°C)	Yield (%)	Elementary Analysis (%, Cald.)		
					C	H	N
8a	C_6H_5O	S	144–146	70.7	47.06 (47.06)	4.37 (4.17)	13.69 (13.73)
b	2-ClC_6H_4O	S	131–133	70.2	43.60 (43.39)	3.87 (3.62)	12.61 (12.66)
c	4-$NO_2C_6H_4O$	S	109–111	70.6	42.06 (42.38)	3.53 (3.53)	15.17 (15.45)
d	4-BrC_6H_4O	S	184–186	77.6	39.27 (39.43)	3.87 (3.91)	11.21 (11.50)
e	4-ClC_6H_4O	S	183–185	59.6	43.40 (43.39)	3.49 (3.62)	12.58 (12.66)
f	2,4-$Me_2C_6H_3O$	S	thick liquid	65.5	49.74 (49.54)	4.87 (4.82)	12.83 (12.85)
g	4-$CH_3C_6H_4O$	S	113–115	75.8	48.25 (48.34)	4.99 (4.51)	13.18 (13.27)
h	2,4-$ClBrC_6H_3O$	S	149–150	66.2	36.86 (36.82)	2.88 (2.88)	10.72 (10.74)
i	2,4-$Cl_2C_6H_3O$	S	73–75	87.0	40.37 (40.25)	3.23 (3.15)	11.94 (11.74)
j	2,4-$CH_3ClC_6H_4O$	S	135–137	73.4	44.52 (44.69)	3.86 (3.95)	12.03 (12.27)
k	EtO	O	151–152	71.4	41.76 (41.86)	5.03 (4.94)	15.99 (16.28)
l	PrS	S	134–135	85.9	40.42 (40.00)	4.78 (4.87)	14.05 (14.36)

TABLE 3 The IR Spectral Data of Compounds **8**

Compound	IR (KBr, cm^{-1})				
	P=S(O)	P–N	P–O–C	P–O–Ar	C=S
8a	664.0	973.9	773.7, 1027.5, 1157.0	919.2, 1196.2	1605.7
8b	654.4	960.1	764.1, 1024.1, 1120.7	914.4, 1217.5	1611.2
8c	666.8	963.4	741.9, 1023.3, 1152.2	901.6, 1210.2	1610.9
8d	666.4	968.5	755.0, 1024.8, 1177.1	919.2, 1204.7	1606.8
8e	671.1	972.8	762.8, 1025.1, 1155.7	941.9, 1205.3	1606.7
8f	677.3	956.3	746.3, 1024.8, 1157.6	913.2, 1204.5	1612.8
8g	676.2	951.2	747.1, 1026.3, 1155.0	912.4, 1187.7	1611.1
8h	662.3	966.3	747.4, 1024.4, 1155.6	903.8, 1244.8	1611.2
8i	660.1	956.6	798.7, 1023.5, 1153.1	907.4, 1222.6	1610.8
8j	665.7	956.5	738.7, 1026.4, 1165.5	921.1, 1225.6	1611.6
8k	1177.0	973.5	774.0, 1030.4, 1109.5	/	1653.2
8l	655.3	950.4	745.3, 1025.7, 1153.6	/	1609.3

in 150 mL of benzene, PCl_5 (31.27g, 0.15 mol) was added dropwise. The mixture was heated to reflux for 2 hours, the solvent was evaporated, and the residue was distilled under reduced pressure to give 2-chlorobenzoxazole **3**, (b.p. 99–100°C/10 mmHg, a solid when cooled, m.p. 8°C, 14.9 g, yield 78.3%).

A solution of 2-chlorobenzoxazole **3** prepared as described previously (9.69 g, 0.063 mol) in 5 mL of dioxane was added dropwise and with stirring to 85% hydrazine hydrate (20.5 g, 0.35 mol), the mixture being maintained at a temperature that did not rise above 30°C. After the addition was completed, the mixture was stirred at room temperature for 30 minutes and then diluted with 30 mL of cold water. The 2-hydrazinobenzoxazole product **4** was collected, washed with water, dried, and recrystallized from ethanol to give needles, (8.25 g, yield 87.9%, m.p. 154–155°C [lit. 152–53°C]); elementary analysis:

TABLE 4 The ^{1}HNMR Spectral Data of Compounds **8**

Compound	*^{1}HNMR δ (ppm, $CDCl_3$/TMS) $J_{H\text{-}H}$, $J_{P\text{-}H}$ (Hz)*
8a	1.32 (t, 3H, CH_3, $J_{H\text{-}H}$ = 7.06), 4.26 (dq, 2H, CH_2), $J_{P\text{-}H}$ = (7.41), 6.78–7.28 (m, 10H, C_6H_5, C_6H_4 on benzoxazole ring, NH)
8b	1.35 (t, 3H, CH_3, $J_{H\text{-}H}$ = 5.69), 4.37 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 7.30), 6.85–7.30 (m, 9H, C_6H_4, C_6H_4 on benzoxazole ring, NH)
8c	1.36 (t, 3H, CH_3, $J_{H\text{-}H}$ = 4.47), 4.29 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 7.20), 6.96–6.99, 7.30–7.37, 8.10–8.26 (m, 9H, C_6H_4, C_6H_4 on benzoxazole ring, NH)
8d	1.34 (t, 3H, CH_3, $J_{H\text{-}H}$ = 4.42), 4.24 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 7.25), 6.84–7.38 (m, 9H, C_6H_4, C_6H_4 on benzoxazole ring, NH)
8e	1.29 (t, 3H, CH_3, $J_{H\text{-}H}$ = 6.86), 4.24 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 9.61), 7.15–7.29 (m, 9H, C_6H_4, C_6H_4 on benzoxazole ring, NH)
8f	1.32 (t, 3H, CH_3, $J_{H\text{-}H}$ = 6.85), 2.21 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.20 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 9.24), 6.82–7.46 (m, 8H, C_6H_3, C_6H_4 on benzoxazole ring, NH)
8g	1.30 (t, 3H, CH_3, $J_{H\text{-}H}$ = 7.11), 2.25 (s, 3H, CH_3), 4.18 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 9.21), 6.78–7.04, 7.39–7.41 (m, 9H, C_6H_4, C_6H_4 on benzoxazole ring, NH), 8.73 (brs, 2H, 2NH)
8h	1.37 (t, 3H, CH_3, $J_{H\text{-}H}$ = 4.17), 4.33 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 9.39), 7.20–7.49 (m, 8H, C_6H_3, C_6H_4 on benzoxazole ring, NH), 11.0 (brs, 2H, 2NH)
8i	1.33 (t, 3H, CH_3, $J_{H\text{-}H}$ = 7.15), 4.27 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 9.39), 6.95–7.40 (m, 8H, C_6H_3, C_6H_4 on benzoxazole ring, NH), 8.48 (brs, 2H, 2NH)
8j	1.31 (t, 3H, CH_3, $J_{H\text{-}H}$ = 6.97), 2.26 (s, 3H, CH_3), 4.19 (dq, 2H, CH_2, $J_{P\text{-}H}$ = 9.18), 6.92–7.11, 7.44–7.47 (m, 8H, C_6H_3, C_6H_4 on benzoxazole ring, NH), 8.28 (brs, 2H, 2NH)
8k	1.30 (t, 6H, $2CH_3$, $J_{H\text{-}H}$ = 7.05), 4.15 (dq, 4H, $2CH_2$, $J_{P\text{-}H}$ = 7.96), 6.77–6.84, 7.08, 7.30 (m, 5H, C_6H_4 on benzoxazole ring, NH), 8.19 (brs, 2H, 2NH)
8l	0.96 (t, 3H, CH_3), 1.35 (t, 3H, CH_3), 1.68 (m, 2H, CH_2), 2.88 (dt, 2H, CH_2S, $J_{P\text{-}H}$ = 6.67), 4.20 (dq, 2H, CH_2O, $J_{P\text{-}H}$ = 9.32), 6.88–7.67 (m, 5H, C_6H_4 on benzoxazole ring, NH)

Calcd: C, 56.38%, H, 4.69%, N, 28.19%; Found: C, 56.04%, H, 4.51%; N, 27.93%.

Preparation of O-Ethyl-O-aryl-isothiocyanatothiophosphate **7**

Preparation of **7a–7j.** [11–14] To a solution of the substituted phenol (0.02 mol) and NaOH (0.8 g, 0.02 mol) in 5 mL of H_2O was added *O*-ethylthiophosphorodichloridate (3.60 g, 0.02 mol) and then a catalytic amount of a phase transfer catalyst (PTC). The mixture was stirred at 30–40°C for 2 hours, allowed to stand overnight, and then extracted with 100 mL of benzene. The organic phase was washed with 20 mL of water, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude *O*-ethyl-*O*-arylthiophosphorochloride **6** for the next step.

To a mixture of KSCN (1.94 g, 0.02 mol) and 20 mL of acetonitrile was added the crude product **6**, and the mixture was stirred at room temperature for 4–5 hours, diluted with 20 mL of ethyl ether, and filtered. The filtrate was concentrated to give crude product **7**, which was purified by silica gel column chromatography to give a total yield of 43.9–67%. The relevant data of compounds **7** are shown in Table 1.

Preparation of **7k.** According to the literature procedure [15,16], *O,O*-diethylphosphoryl chloride was reacted with NH_4SCN in benzene to give a crude product that was purified by distillation under reduced pressure, (b.p. 70–74°C/133 Pa, yield 73.9%, n_D^{22} 1.4732 [lit. n_D^{20} 1.4749]).

Preparation of **7l.** A similar procedure was used with **6** (R = PrS) instead of **6** (R = ArO) to yield **7l** (76.2%, n_D^{22} 1.5630).

Preparation of Title Compounds **8**

To a solution of 2-hydrazinobenzoxazole **4** (0.15 g, 1.0 mmol) in 20 mL of ethanol was added *O*-ethyl-*O*-phenylisothiocyanatothiophosphate **7a** (0.26 g, 1.0 mmol) at room temperature. The reaction mixture was stirred at room temperature with thin-layer chromatography monitoring for about 2 hours. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give a white solid, 0.29 g, yield 70.7%, m.p. 144–146°C.

Similarly, other compounds of the type **8** were prepared from the corresponding isothiocyanato (thio) phosphate **7**, reaction with compound **4** taking place at room temperature or slightly higher. All compounds prepared were characterized by elemen-

tary analysis, and ^{1}HNMR and IR spectral data, their relevant data being given in Tables 2–4.

RESULTS AND DISCUSSION

Characterization of Title Compounds **8**

The title compounds **8** were characterized by elementary analysis and ^{1}H NMR and IR spectroscopy. With respect to the ^{1}HNMR spectra, the resonance of the NH adjacent to the P atom overlapped those of benzoxazole and benzene rings and are not easy to describe. The other two NH groups appeared at δ = 8–9 or 11.0 or did not appear at all. The main reason is that the two NH groups are very labile. The methylene group of the ethoxyl group bonded to phosphorus appears as a multiplet because of being coupled by the H atoms in CH_3 and the P atom; when CH_3 was decoupled, doublet peaks were observed, and the coupling constant was 8–10 Hz. With regard to the IR spectra, the band around 660 cm^{-1} was attributed to the P=S function, while that at 1177 cm^{-1} in compound **8k** was attributed to the P=O group, and the group C=S was responsible for the band at about 1600 cm^{-1}.

Biological Activity of Title Compounds **8**

We selected some compounds **8** to test their biological activities and found that these compounds displayed moderate degrees of fungicidal activity and also to some degree, herbicidal and plant growth regulation activities. Compounds **8a** and **8k** showed 90% activity against *Puccinia recondita* at 500 ppm. The relationship of structure and activity indicates that the electron-donor groups on phenyl increase the activity, while electron-withdrawing groups decrease the activity.

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