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Synthesis of Biologically Active Phenoxy Derivatives of Substituted Benzothiazole Organophosphates

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ABSTRACT: *The reaction of S-(phenyl benzothiazolyl-2)phosphorodichloridothioate/phosphorodichloridodithioate with 2 mol of phenol/4-chlorophenol/4-nitrophenol in the presence of stoichiometric amounts of triethylamine in dry THF/CH_2Cl_2 has afforded a series of the corresponding organophosphate phenoxy derivatives (***1a, 1b, 2a, 2b****, and* **3a, 3b***). Plausible structures have been proposed on the basis of elemental analysis, IR, ^1H NMR, ^{31}P NMR, and mass spectral studies. The antibacterial activity of these organophosphate phenoxy derivatives has been evaluated against pathogenic bacteria* Staphylococcus aureus *(+ve) and* Escherichia coli *(−ve). The antifungal activity of these organophosphate phenoxy derivatives has been evaluated against pathogenic fungi* Aspergillus niger *and* Fusarium oxysporium. *The results indicate that organophosphate phenoxy derivatives are found more active than the parent compounds.*
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INTRODUCTION

Compounds containing the thiazole nucleus have proven to be efficacious as antifungal agent, and many of them have gained wide acceptance in clinical practice [1]. Benzothiazoles are a part of the molecular structure of a large number of natural products. In recent time, benzothiazole derivatives, which have valuable antifungal, antitumor, biological, and pharmacological activities, were investigated [2–7]. Some of the substituted benzothiazoles and their chelate metal complexes are being used as white organic light-emitting devices [8].

Organophosphorus compounds containing heterocyclic moiety increase the protonation at the site of pesticides and enhance their biological activity [9]. Organophosphates exert their biological action on insects and mammals by attacking the neural transmission system and inhibiting the function of acetylcholinesterase enzyme [10]. Various phosphorylated compounds of benzothiazole and amines are also associated with antifungal activities [11,12]. The reaction of phenols with phosphonates or thiophosphonates enhanced their biocidal activity [13]. In continuation of our work on organophosphates [14,15], we report here the synthesis of biologically active phenoxy derivatives of substituted benzothiazole organophosphates.

RESULTS AND DISCUSSION

The reaction of *S*-(phenyl benzothiazolyl-2) phosphorodichloridothioate/phosphorodichloridodithioate with 2 mol of phenol/4-chlorophenol/4-nitrophenol in the presence of stoichiometric amounts of triethylamine in dry THF/CH_2Cl_2 has afforded a series of the corresponding organophosphate phenoxy derivatives (**1a, 1b, 2a, 2b, 3a**, and **3b**). A schematic presentation of these reactions is given in Fig. 1, and physical properties, synthetic and analytical data of organophosphate phenoxy derivatives are given in Table 1. All these reactions are quite facile and completed in 10–12 h after

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TABLE 1 Physical Properties, Synthetic, and Analytical Data of Organophosphate Phenoxy Derivatives (**1a, 1b, 2a, 2b, 3a**, and **3b**)

S. No.	Compound	m p (°C)	Yield (%)	Analysis% Found (Calcd.) C	H	N	P	S	M. Wt. Found (Calcd.)
1.	**1a**	198–200	42	63.01 (63.15)	3.74 (3.82)	2.88 (2.94)	6.37 (6.51)	13.32 (13.48)	473.08 (475.52)
2.	**1b**	200–204	50	59.68 (61.08)	3.59 (3.70)	2.74 (2.84)	6.09 (6.30)	12.89 (13.04)	489.36 (491.58)
3.	**2a**	195–198	44	56.11 (56.28)	2.68 (3.02)	7.69 (7.88)	5.72 (5.80)	14.86 (14.99)	532.01 (533.50)
4.	**2b**	172–178	48	54.53 (54.64)	2.84 (2.93)	7.57 (7.64)	5.54 (5.64)	17.42 (17.50)	548.42 (549.57)
5.	**3a**	184–188	45	58.49 (58.60)	3.07 (3.15)	2.58 (2.73)	5.93 (6.04)	12.23 (12.51)	510.03 (512.40)
6.	**3b**	167–171	38	56.68 (56.82)	2.97 (3.05)	2.52 (2.65)	5.76 (5.86)	17.99 (18.20)	526.88 (528.47)

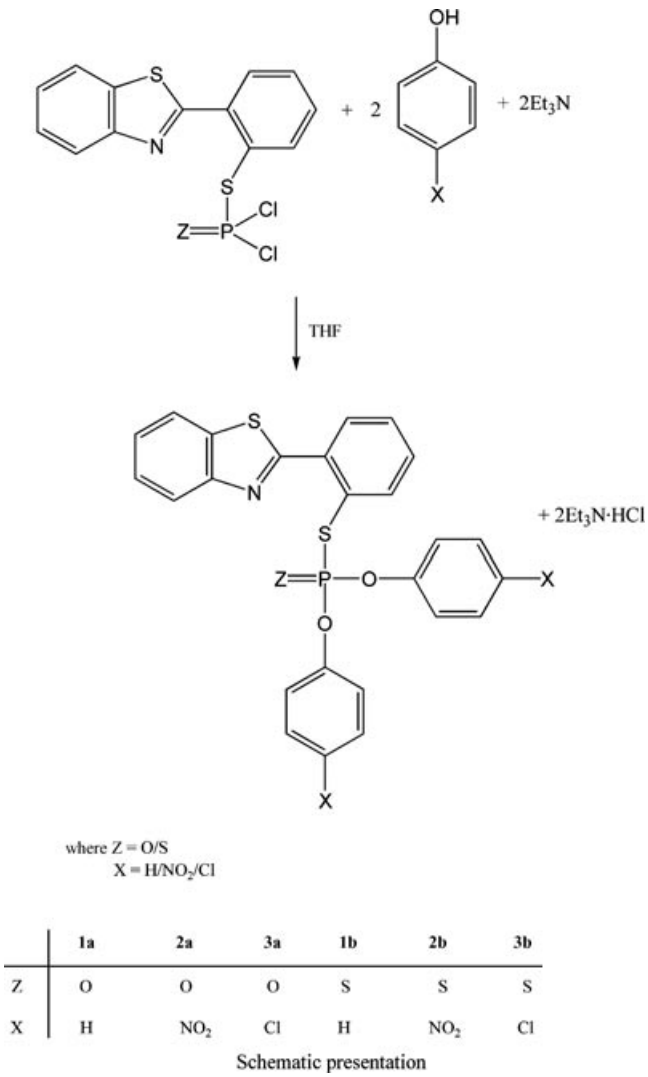

FIGURE 1 Schematic presentation of organophosphate phenoxy derivatives.

TABLE 2 Assignment of Main IR Bands (cm^{-1}) of Organophosphate Phenoxy Derivatives (**1a, 1b, 2a, 2b, 3a, 3b**)

S. No.	Compound	ν(P—O—C)	ν(P—O)	ν(P—S)	ν(NO_2)
1.	**1a**	1164–935	1205		
2.	**1b**	1130–950		790 (I) 630 (II)	
3.	**2a**	1160–935	1190		1335 1530
4.	**2b**	1155–974		788 (I) 630 (II)	1332 1225
5.	**3a**	1184–940	1182		
6.	**3b**	1135–965		775 (I) 612 (II)	

refluxing. The resulted compounds are hygroscopic and are soluble in dimethylsulfoxide.

IR Spectra

The assignments of some important bands are summarized in Table 2. The absorption band at 500–590 cm^{-1}, owing to ν*P*—Cl of *S*-(phenyl benzothiazolyl-2)phosphorodichloridothioate/phosphorodichloridodithioate, disappeared in the spectra of organophosphate phenoxy derivatives (**1a, 1b, 2a, 2b, 3a**, and **3b**). New bands appeared in the region 935–1184 cm^{-1} due to ν*P*—O—C (aryl). The ν*P*=O band is observed at 1182–1205 cm^{-1}. The ν*P*=S (I) and ν*P*=S (II) bands are observed at 775–790 cm^{-1} and 612–650 cm^{-1}, respectively [16].

^1H NMR and ^{31}P NMR Spectra

The characteristic signals in ^1H NMR and ^{31}P NMR spectra of organophosphate phenoxy derivatives (**1a, 1b, 2a, 2b, 3a, 3b**) are summarized in Table 3. All

TABLE 3 ^{1}H NMR and ^{31}P NMR spectral Data of organophosphate Phenoxy Derivatives (**1a, 1b, 2a, 2b, 3a, 3b**)

S. No.	*Compounds*	*^{1}H NMR*	*^{31}P NMR*
1.	**1a**	7.0–7.4 (m, 18H, Ar-**H**)	64.3
2.	**1b**	7.1–7.4 (m, 18H, Ar-**H**)	69.2
3.	**2a**	7.2–7.6 (m, 16H, Ar-**H**)	59.0
4.	**2b**	7.2–7.5 (m, 16H, Ar-**H**)	63.4
5.	**3a**	7.4–7.8 (m, 16H, Ar-**H**)	62.1
6.	**3b**	7.4–8.2 (m, 16H, Ar-**H**)	66.4

the organophosphate phenoxy derivatives show multiplets in the region of δ 7.0–8.2 ppm attributable to the aromatic protons of a phenyl ring along with 2-substituted phenyl and a benzothiazolyl ring. The ^{31}P NMR spectra of organophosphate phenoxy derivatives (**1a, 1b, 2a, 2b, 3a, 3b**) have been observed at somewhat downfield at δ 59.0–69.2 ppm [17].

Mass Spectra

The splitting pattern of the mass spectrum of **2a** is represented in Fig. 2. The molecular ion peak appears at m/z 562, confirming the formation of **2a**. This peak after removal of two *p*-nitrophenoxy radicals in the subsequent steps generates the ions at m/z 422.9 and 278, respectively. Further fragmentation involves removal of the radical PO, and a peak appears at m/z 240. It may further lose the sulfur radical, and a peak appears m/z 208.12. This peak after removal of a phenyl moiety produces an ion

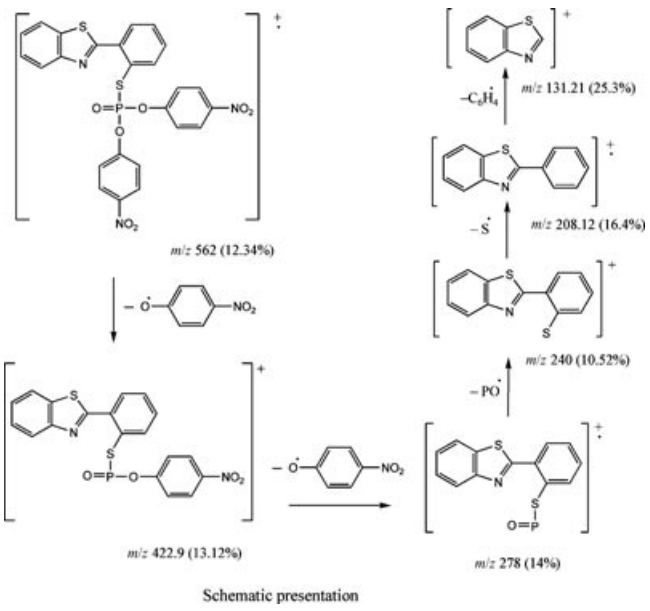

FIGURE 2 Splitting pattern of the mass spectrum of **2a**.

TABLE 4 Mass Spectral Data of **2a**

Compound	*m/z (%)*
2a	562 (12.34%), 422.9 (13.12%), 278 (14%) 240 (10.52), 208.12 (16.4%) 131.21 (25.3%)

at m/z 131.21. The intensity of all the peaks is very weak. Relative abundance of the ions is represented in Table 4.

ANTIBACTERIAL ACTIVITY

The results of the antibacterial activity of organophosphate phenoxy derivatives (**1a, 1b, 2a, 2b, 3a, 3b**) have been compared with standard streptomycin. The organisms selected for the studies are *Staphylococcus aureus* (+ve) and *Escherichia coli* (−ve). The antibacterial activity was evaluated by a paper disk plate method. The results of antibacterial screening of **1a, 1b, 2a, 2b, 3a**, and **3b** showed that 4-chlorophenol derivatives show the highest bactericidal activity among all the derivatives, but they show less activity than standard streptomycin. All the results are summarized in Table 5.

ANTIFUNGAL ACTIVITY

The results of antifungal activity of organophosphate phenoxy derivatives (**1a, 1b, 2a, 2b, 3a, 3b**) are summarized in Table 6. The organophosphate phenoxy derivatives have been screened for fungicidal properties against *Aspergillus niger* and *Fusarium oxysporium* at concentrations of 50 and 200 ppm. The radial growth method was used to check an activity against fungi by taking Dithane M-45 as a standard. The inference drawn from the table revealed that the activity of organophosphate phenoxy derivatives increases with the increase in the concentration and derivatives having P=S bonds are more toxic than derivatives having P=O bonds. The toxicity of all these organophosphate phenoxy derivatives is quite high, but it is less than the standard Dithane M-45.

EXPERIMENTAL

All commercial reagents and solvents were dried and distilled by common methods before use. Phosphorus oxychloride/phosphorus thiochloride were purchased from Fluka. Melting points were determined by the capillary method and are uncorrected. All operations were carried out in dry equipment under nitrogen atmosphere. ^{1}H NMR data were recorded on JEOL FX 90Q/JEOL AL 300 MHz FT NMR

TABLE 5 Antibacterial Screening Data of Organophosphate Phenoxy Derivatives (1a-1b, 2a-2b & 3a-3b)

		Diameter of Inhibition Zone (mm) after 24 h (Concentration in ppm)			
		Staphylococcus aureus *(+ve)*		Escherichia coli *(−ve)*	
S. No.	*Compound*	*250*	*500*	*250*	*500*
1.	**1a**	17	24	18	24
2.	**1b**	19	25	19	26
3.	**2a**	20	27	22	28
4.	**2b**	26	29	26	29
5.	**3a**	25	28	25	29
6.	**3b**	30	32	28	31
	Streptomycin (Standard)	34	45	32	52

spectrometer in $CDCl_3$ using TMS as an internal reference. The ^{31}P NMR spectra were recorded on a JEOL AL 300 MHz FT NMR spectrometer at 121.49 MHz in $CDCl_3$ using TMS and 85% H_3PO_4 as internal and external reference, respectively, at room temperature. IR spectra were recorded on a Perkin–Elmer 577 grating spectrometer in KBr disks in the region 4000–425 cm^{-1}. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer. Chlorine was estimated volumetrically by using Volhard's method. Phosphorus was estimated as ammonium phosphomolybdate. The molecular weights were determined by using the Rast Camphor method.

Synthesis of S-(Phenyl Benzothiazolyl-2)O,O-(diphenyl)thiophosphate **1a***/phosphorodithioate* **1b**

A solution of phenol (0.002 mol) in dry THF was added dropwise with continuous stirring in a solution of *S*-(phenyl benzothiazolyl-2) phosphorodichloridothioate/phosphorodichloridodithioate (0.001 mol) in THF and Et_3N (0.002 mol) in dry THF. The mixture was refluxed for 14–16 h. Then, it was cooled and $Et_3N{\cdot}HCl$ formed was filtered off with a closed sintered funnel. It was then concentrated to one fourth of its volume under reduced pressure and was kept in a vacuum desiccator to obtain crystals. Recrystallization was done in dry ethanol.

Synthesis of S-(Phenyl Benzothiazolyl-2)O,O-di(4-nitrophenyl)thiophosphate **2a***/phosphorodithioate* **2b**

A solution of 4-nitrophenol (0.002 mol) in dry THF was added dropwise with continuous stirring in a solution of *S*-(phenyl benzothiazolyl-2) phosphorodichloridothioate/phosphoro-dichloriododithioate (0.001 mol) in THF and Et_3N (0.002 mol) in dry THF. The mixture was refluxed for 14–16 h. Then the reaction was carried out in a similar manner as described above.

Synthesis of S-(Phenyl Benzothiazolyl-2)O,O-di(4-chlorophenyl)thiophosphate **3a***/phosphorodithioate* **3b**

A solution of 4-chlorophenol (0.002 mol) in dry THF was added dropwise with continuous stirring in

TABLE 6 Fungitoxic Screening Data of Organophosphate Phenoxy Derivatives (1a-1b, 2a-2b & 3a-3b)

		Percentage Mycelial Inhibition			
		Aspergillus niger *(ppm)*		Fusarium oxysporium *(ppm)*	
S.No.	*Compound*	*50*	*200*	*50*	*200*
1	**1a**	22.8	80.4	24.6	71.2
2	**1b**	42.6	85.4	47.8	80.4
3	**2a**	24.4	86.2	26.3	76.5
4	**2b**	47.3	87.6	53.2	84.4
5	**3a**	32.2	92.1	36.6	78.9
6	**3b**	50.4	92.2	60.1	91.9
	Dithane M-45	87.0	100.0	76.0	100.0

a solution of *S*-(phenyl benzothiazolyl-2) phosphorodichloridothioate/phosphorodichloridodithioate in dry THF. Then, the reaction was carried out in a similar manner as described above.

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