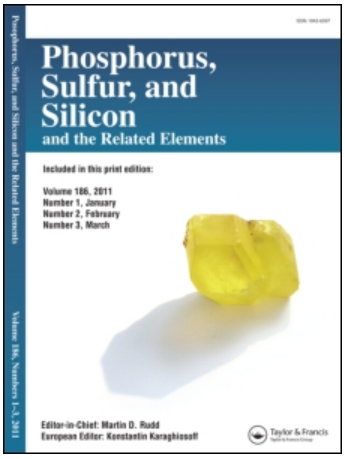

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Antifungal Activity and Some Novel Organo-Phosphorus Compounds: Preparation and Spectral Characterization

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Antifungal Activity and Some Novel Organo-Phosphorus Compounds: Preparation and Spectral Characterization

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The inhibitory effects of a recently introduced series of N-phosphorylated/thiophosphorylated compounds on Aspergillus niger and Fusarium oxysporium were examined. The derivatives were obtained in good yield by reacting 2-(2′-aminophenyl)benzoxazole with phosphorous oxychloride and thiophosphoryl chloride in different molar ratios (1:1, 2:1, and 3:1). Structure elucidation of all synthesized compounds was based on the data of elemental analysis, IR, ^{1}H NMR, and ^{31}P NMR spectra.

Keywords Antifungal; N-phosphorylated; structure elucidation

INTRODUCTION

The reported biological activity of benzoxazoles[1–3] and organophosphorus compounds,[4,5] in conjunction with our previous lab work[6] stimulated our interest to synthesize several N-phosphorylated/thiophosphorylated derivatives of 2-substituted benzoxazole. The products were purified, characterized by elemental, NMR (^{1}H, ^{31}P), and IR spectral analysis, as well as tested for antifungal activity.

RESULTS AND DISCUSSION

The NH-(phenylbenzoxazolyl-2) phosphorodichloridoamidate/phosphoro-dichloridoamidothioate, NH,NH-bis (phenylbenzoxazolyl-2) phosphorodiamido-chloridate/phosphorochloridodiamidothioate and NH, NH,NH-tri(phenylbenzoxazolyl-2) phosphorotriamidate/phosphorotriamidothioate were synthesized by the dropwise addition of

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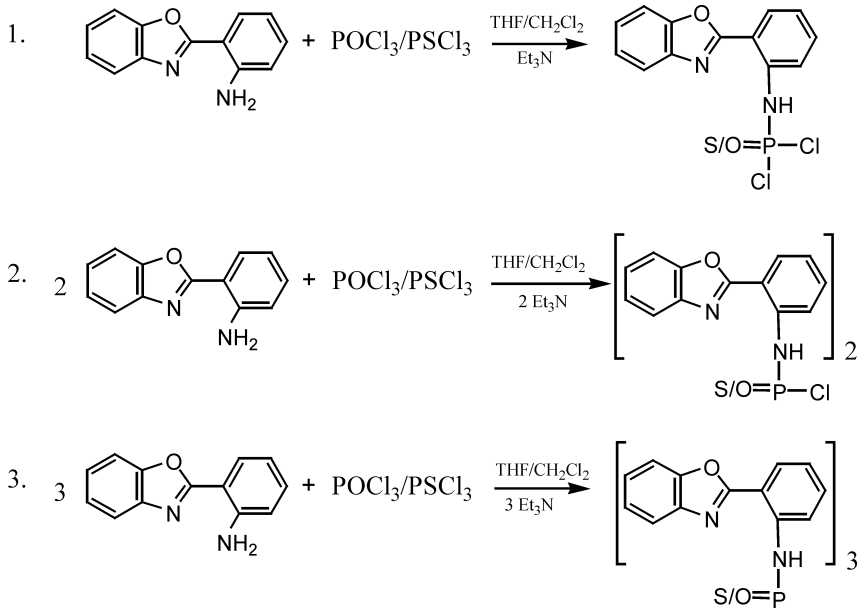
$POCl_3/PSCl_3$ (0.001 mol) in a fast stirring ice-cold solution of 2-(2'-aminophenyl)benzoxazole (0.001 mol, 0.002 mol, 0.003 mol respectively) in the presence of a stoichiometric amount of triethylamine in THF/methylene chloride (Scheme 1). Physical and elemental analysis data of all the compounds are listed in Table I.



SCHEME 1

IR Spectra

N-phosphorylated/thiophosphorylated benzoxazole derivatives were analyzed by the appearance of ν(P=0)[8] at 1260–1270 cm^{-1}, ν(P–N–C)[9] at 670–685 cm^{-1}, and 1080–1120 cm^{-1}, ν(P–Cl)[10] at 515–610 cm^{-1}, ν(P–NH) at 2910–3135 cm^{-1} and ν(P=S) at 825–840 cm^{-1} and 700–720 cm^{-1} and due to the disappearance of Ar-NH_2 stretching vibration at 3310–3400 in 2-(2′-aminophenyl)benzoxazole (Table II).

^{1}H NMR

Aromatic protons showed their signals at δ 7.1–8.2 ppm. Ar-NH_2 proton signal disappeared which was found at δ 3.8 ppm and appeared at δ 5.8–6.0 ppm for P-NH[11] of different derivatives (Table III).

TABLE I Physical Properties and Analytical Data of N-Phosphorylated and Thiophosphorylated Benzoxazole Derivatives

Reactants		Molar ratio		Melting			Analytical % Cal. (Found)						Molecular
A	B	of A:B	Compound	point (°C)	R_f value	Yield (%)	C	H	N	P	S	Cl	weight
$C_{13}H_{10}N_2O$	$POCl_3$	1:1	$C_{13}H_9N_2OP(O)Cl_2$ (yellowish green)	204	0.68	54	47.73 (47.53)	2.77 (2.60)	8.56 (8.47)	9.47 (9.38)	—	21.68 (21.60)	327.08 (325.00)
$C_{13}H_{10}N_2O$	$PSCl_3$	1:1	$C_{13}H_9N_2OP(S)Cl_2$ (light yellow)	208	0.74	58	45.50 (45.27)	2.64 (2.70)	8.164 (8.22)	9.07 (9.15)	9.34 (9.20)	20.66 (20.61)	343.14 (341.12)
$C_{13}H_{10}N_2O$	$POCl_3$	2:1	$(C_{13}H_9N_2O)_2P(O)Cl$ (Brownish green)	213	0.67	52	62.35 (62.31)	3.62 (3.71)	11.18 (11.08)	6.18	— (6.15)	7.08 (7.00)	500.88 (501.82)
$C0_{13}H_{10}N_2O$	$PSCl_3$	2:1	$(C_{13}H_9N_2O)_2P(S)Cl$ (Brown)	219	0.73	57	60.41 (60.38)	3.51 (3.48)	10.84 (10.79)	6.00 (5.95)	6.20 (6.28)	6.86 (6.99)	516.95 (518.90)
$C_{13}H_{10}N_2O$	$POCl_3$	3:1	$(C_{13}H_9N_2O)_3P(O)$ (Brown)	222	0.70	53	69.43 (69.38)	4.03 (4.00)	12.46 (12.32)	4.59 (4.42)	—	—	674.66 (671.56)
$C_{13}H_{10}N_2O$	$PSCl_3$	3:1	$(C_{13}H_9N_2O)_3P(S)$ (Brown)	230	0.76	56	67.82 (67.72)	3.94 (3.89)	12.17 (12.20)	4.48 (4.54)	4.64 (4.70)	—	690.72 (692.64)

TABLE II Assignment of Main IR Bands (cm^{-1}) of Phosphorylated and Thiophosphorylated Derivatives of 2-(2′-Aminophenyl)benzoxazole

Compound	ν(P═S)	ν(P–O)	ν(P–N–C)	ν(P–Cl)	ν(P–NH)
$C_{13}H_9N_2OP(O)Cl_2$	—	1265	1080	600 (asym)	3100
			670	618 (sym)	2910
$C_{13}H_9N_2OP(S)Cl_2$	825 (I)	—	1085	608 (asym)	3125
	700 (II)		675	520 (sym)	2927
$(C_{13}H_9N_2O)_2P(O)Cl$	—	1268	1100	605 (asym)	3108
			675	515 (sym)	2916
$(C_{13}H_9N_2O)_2P(S)Cl$	830 (I)	—	1080	610 (asym)	3127
	715 (II)		680	518 (sym)	2922
$(C_{13}H_9N_2O)_3P(O)$	—	1268	1120	—	3114
			678		2920
$(C_{13}H_9N_2O)_3P(S)$	840 (I)	—	1100	—	3135
	712 (II)		685		2927

^{31}P NMR

In ^{31}P NMR[11] spectra, only one ^{31}P resonance signal has been observed at δ 68.6–76.1 ppm (Table III).

Fungicidal Activity

All the compounds were screened for antifungal activity. Antifungal activities were screened against *Aspergillus niger* and *Fusarium oxysporium*. While screening Dithane M-45 was used as a standard. Radial Growth Method was used to a series of solution with different concentrations (50, 100, and 200 ppm) and it was found that synthesized N-phosphorylated/thiophosphorylated compounds are more toxic than the preliminary ligand 2-(2′-aminophenyl)benzoxazole. Results are summarized in Table IV.

TABLE III ^{1}H NMR and ^{31}P NMR Spectral Data of Phosphorylated and Thiophosphorylated Benzoxazole Derivatives

Compound	^{1}H NMR	^{31}P NMR
$C_{13}H_9N_2OP(O)Cl_2$	7.5–8.2 (m, 8H, Ar–**H**) 5.7 (d, 1H, P–N**H**)	75.3
$C_{13}H_9N_2OP(S)Cl_2$	7.75–8.2 (m, 8H, Ar–**H**) 5.6 (d, 1H, P–N**H**)	76.1
$(C_{13}H_9N_2O)_2P(O)Cl$	7.2–8.2 (m, 16H, Ar–**H**) 5.8 (d, 1H, P–N**H**)	71.1
$(C_{13}H_9N_2O)_2P(S)Cl$	7.3–8.1 (m, 16H, Ar–**H**) 5.6 (d, 1H, P–N**H**)	72.4
$(C_{13}H_9N_2O)_3P(O)$	7.5–8.2 (m, 24H, Ar–**H**) 6.0 (d, 1H, P–N**H**)	68.6
$(C_{13}H_9N_2O)_3P(S)$	7.1–8.0 (m, 24H, Ar–**H**) 5.7 (d, 1H, P–N**H**)	71.3

TABLE IV Fungitoxic Screening Data of Organophosphorus Derivatives Containing 2-(2′-Aminophenyl)benzoxazole

	Average % inhibition after 72 hs (Conc. in ppm)					
	Aspergillus niger			Fusarium oxysporium		
Compounds	50	100	200	50	100	200
$C_{13}H_9N_2OP(O)Cl_2$	37.8	47.1	70.3	38.0	49.2	72.5
$C_{13}H_9N_2OP(S)Cl_2$	39.2	55.1	73.9	37.2	57.1	78.2
$(C_{13}H_9N_2O)_2P(O)Cl$	43.4	59.1	78.8	45.2	59.5	81.6
$(C_{13}H_9N_2O)_2P(S)Cl$	50.4	64.5	82.1	50.8	65.7	85.3
$(C_{13}H_9N_2O)_3P(O)$	62.4	70.1	85.6	66.7	74.5	88.2
$(C_{13}H_9N_2O)_3P(S)$	70.6	82.3	92.5	72.5	86.1	93.6

EXPERIMENTAL

All the chemicals and solvents were dried and distilled by common method before use. $POCl_3/PSCl_3$ was purchased from Fluka. All operations involving phosphorus compounds were carried out in dry equipment under a nitrogen atmosphere. Melting points of all the compounds were determined by capillary method.

IR spectra were recorded on a Shimadzu 8400 S FTIR spectrophotometer in KBr discs in the region of 4000−4200 cm^{-1}. NMR spectra were recorded on JEOL FX 90Q spectrophotometer using $CDCl_3$ as a solvent. Nitrogen was estimated by Kjeldahl's method. Phosphorus was estimated as ammonium phosphomolybdate. Chlorine was estimated volumetrically by Volhard's method.

The Synthesis of the Ligand

The ligand 2-(2′-aminophenyl) benzoxazole was formed by the reported method.[12]

Synthesis of NH-(phenylbenzoxazolyl-2)phosphorodichloridoamidate/Phosphoro-Dichloridoamidothioate

To the ice-cold solution of 2-(2′-aminophenyl)benzoxazole (0.001 mol) in dry THF (30 ml) and Et_3N (0.001 mol) in dry THF (20 ml) a solution of $POCl_3/PSCl_3$ (0.001 mol) in dry THF (30 ml) was added dropwise by dropping funnel. After mixing the reactants, stirring was continued for 4 h at 0°C. Further, the reaction mixture was removed from the

ice-bath, and then it was refluxed further under nitrogen atmosphere for 14−16 h with continuous stirring. Then it was cooled and filtered through a closed sintered funnel to separate triethylamine hydrochloride ($Et_3N.HCl$) formed during the reaction. The filtrate was then concentrated to one fourth of its volume under reduced pressure and kept for crystallization in a vacuum dessicator for 2 days. The product was recrystallized in ethanol and dried in vacuo.

Synthesis of NH,NH-bis(phenylbenzoxazolyl-2)phosphorodiamidochlorodate/Phosphorochloridodiamidothioate

In a fast stirring solution of 2-(2′-aminophenyl)benzoxazole (0.002 mol) in dry THF (30 ml) and Et_3N (0.002 mol) in dry THF (30 ml), a solution of $POCl_3$/$PSCl_3$ (0.001 mol) in dry THF (30 ml) was added dropwise by dropping funnel. Then the reaction was carried out in a manner similar to described above. The product was recrystallized in ethanol and dried in vacuo.

Synthesis of NH,NH,NH-tris(phenylbenzoxazolyl-2) phosphorotriamidate/Phosphorotriamidothioate

The solution of $POCl_3$/$PSCl_3$ (0.001 mol) in dry THF (30 ml) was added dropwise in a fast stirring ice-cold solution of 2-(2′-aminophenyl)benzoxazole (0.003 mol) in dry THF (20 ml). Then the reaction was carried out in a manner similar to described above. The product was recrystallized in ethanol and dried in vacuo.

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