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Synthesis, Characterization, and Biological Activity of Phosphorylated/Thiophosphorylated Compounds of 2-Substituted Benzimidazoles

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ABSTRACT: *A series of phosphorylated and thiophosphorylated compounds of 2-substituted benzimidazoles have been synthesized by the reaction of $POCl_3$ and $PSCl_3$ with 2-substituted benzimidazoles in different molar ratios. The compounds have been characterized by elemental analyses, infrared, and ^1H NMR and ^{31}P NMR spectral studies. These compounds were found to be insecticidal when tested against Periplenata americana.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:154–157, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20385

INTRODUCTION

Organophosphorus compounds possess significant insecticidal, acaricidal, and fungicidal properties [1–4]. Organophosphorus compounds exert their biological action on arthropods by attacking the neural transmission system and inhibiting the function of enzyme acetylcholinesterase (AchE) [5,6]. Literature survey [7–10] has revealed that organophosphorus compounds containing heterocyclic moiety increase the protonation at the site of action of pesticides and enhance their biological activity.

Taking this into consideration and in continuation of our work on benzazolyl-synthesized organophosphorus pesticides [11–13], we have synthesized phosphoroamidates and phosphorothioamidates by reacting 2-substituted benzimidazoles with $POCl_3/PSCl_3$. A schematic presentation is given in Scheme 1.

RESULTS AND DISCUSSION

The results of IR spectral studies have been summarized in Table 1. IR spectra of compound **1a** showed absorption bands at 3400–3200 cm^{-1} assigned to aminophenyl ring. In IR spectra of compounds **1a–4b**, two absorption bands in the region 3150–3300 cm^{-1} and 1420 cm^{-1} were assigned to —NH stretching and bending vibrations of imidazolyl ring, respectively [14]. This confirmed the nondeprotonation of imidazolyl proton during phosphorylation and thiophosphorylation reactions.

In IR spectra of derivatives **2a,b–4a,b**, two strong absorption bands at 2990 $^{-}$and 2800 cm^{-1} were also observed. The presence of these twin frequencies confirmed the formation of P—NH (aryl) bond by the removal of proton from 2-substituted —NH_2 group during phosphorylation reactions [15]. This was further supported by the presence of absorption band of medium intensity at 650 cm^{-1}

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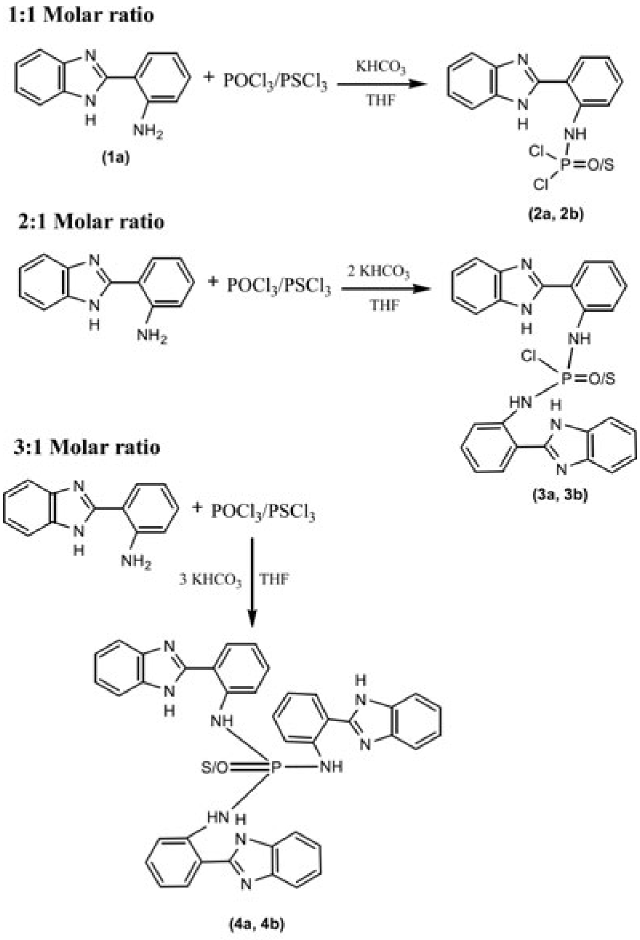

Schematic Presentation

SCHEME 1

that was assigned to P—N stretching vibrational frequency.

IR spectra of derivatives **2a**, **3a**, and **4a** showed a broad absorption band at 1220–1240 cm^{-1}, assigned to P=O stretching vibrations. Two absorption bands at 700 and 670 cm^{-1} in derivatives **2b**, **3b**, **4b** were assigned for P=S (I) and P=S (II) vibrations, respectively. The presence of P—Cl bond (**2a,b–3a,b**) was supported by the appearance of absorption bands at 510 and 580–585 cm^{-1} due to P—Cl symmetric and asymmetric stretching vibrations, respectively. Other absorption frequencies observed were assigned to stretching and bending vibrations of the benzimidazolyl ring.

In ^{1}H NMR spectra of derivatives **1a–4b**, a broad singlet was observed around 8.2–8.6 ppm due to —NH (imidazolyl) proton, showing its nondeprotonation. Aromatic protons appear as a complex multiplet in the region δ 7.2–8.2. A doublet signal was observed at 4.9–5.0 ppm due to —NH (aryl) protons. All these chemical shift values were observed in nearly same region as described by Black and Heffernan [16]. The results of study are given in Table 2. ^{31}P NMR spectra of these derivatives show signal resonance in the region δ 63.5–75.1 ppm, which indicates the purity of these compounds.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin Elmer 577 grating IR spectrophotometer.

The ^{1}H NMR spectra (chemical shifts in δ ppm) were obtained from FX90Q Jeol type spectrophotometer at 90 MHz using TMS as an internal reference. The purity of all the compounds were checked by running TLC on silica gel G plates, using pet ether–methanol mixture and visualizing spots by iodine vapors.

Synthesis of 2-Substituted Benzazole Derivatives

2-(2’-Aminophenyl)benzimidazole (**1a**) (mp 219°C) was prepared by reacting orthophenylenediamine (OPD) with anthranillic acid in freshly prepared polyphosphoric acid (PPA). Reactions were carried out according to the procedure described by Heins et al. [17] and modified by Vyas et al. [18].

Synthesis of Phosphorylated and Thiophosphorylated Derivatives

Phosphorylated derivatives were prepared in strict inert atmosphere. Dry nitrogen gas was flushed continuously during the reaction tenure.

($C_{13}H_{10}N_3$)P(O)Cl_2 and ($C_{13}H_{10}N_3$) P(S)Cl_2. 2-(2′-Aminophenyl) benzimidazole (0.001 mol) in dry THF (30 mL) was taken in a flame-dried three-necked Round Bottom (RB) flask, along with $KHCO_3$ (0.001 mol). To this mixture, the solution of $POCl_3$/$PSCl_3$ (0.001 mol) in dry THF (30 mL) was added slowly at 0°C with the help of a dropping funnel. This mixture was refluxed with continuous stirring for about 14 h. After checking the completion of reaction by TLC, the product was isolated by filtering through a closed sintered funnel to remove KCl formed as a by-product during the reaction. The filtrate was concentrated to 1/4th of its volume under reduced pressure and kept overnight in a vacuum desiccator to obtain crystals.

TABLE 1 IR Spectral Data (in cm^{-1}) of Phosphorylated and Thiophosphorylated Derivatives of 2-Substituted Benzimidazole Derivatives

Compounds	*ν_{as} NH*	*δ NH*	*ν_{as} NH_2*	*P—NH—C (aryl)*	*P=O/P=S*	*P–Cl*
1a	3150–3050	1420	3400	–	–	–
2a	2960 2870	1410	–	650	1250	510 (sym.) 585 (asym.)
2b	2980 2870	1410	–	1030 670	800 (I) 700 (II)	510 (sym.) 600 (asym)
3a	2960 2850	1410	–	1040 660	1230	515 (sym)
3b	2985 2890	1420	–	650	800(I) 690(II)	510 (sym)
4a	2990 2870	1410	–	650	1220	–
4b	2960 2850	–	–	670	800 (I) 700 (II)	–

TABLE 2 Proton NMR and ^{31}P NMR Spectra (δ, ppm) of Phosphorylated/Thiophosphorylated Derivatives of 2-Substituted Benzimidazoles

	^1H NMR			
Compounds	*—NH (imidazolyl)*	*—NH_2 (aryl)/—NH (aryl)*	*Aromatic*	*^{31}P NMR*
1a	8.4 (bs)	5.2 (s)	6.9–7.8 (m)	–
2a	8.4 (s)	5.4 (d)	7.4–8.0 (m)	72.3
3a	8.5 (s)	5.1 (d)	7.0–7.8 (m)	68.4
4a	8.6 (s)	4.9 (d)	6.9–8.0 (m)	63.5
5a	8.6 (s)	5.2 (d)	7.4–8.0 (m)	75.1
6a	8.5 (s)	5.0 (d)	6.9–7.6 (m)	70.2
7a	8.5 (s)	5.0 (d)	6.9–7.6 (m)	65.7

All values are in cm^{-1}.
bs = broad singlet; s = singlet; m = multiplet; d = doublet.

TABLE 3 Physical and Analytical Data of Phosphorylated and Thiophosphorylated Derivatives of 2-Substituted Benzimidazoles

					Elemental Analysis (Calcd) Found					
Compounds	*Molecular Weight Calculated (Found)*	*MP (°C)*	*Yield (%)*	*Color*	*C*	*H*	*N*	*P*	*Cl*	*S*
1a	209 (219)	214	82	White crystals	(74.69) 74.24	(5.29) 5.12	(20.08) 19.98	–	–	–
2a	326 (321)	218	78	Light yellow	(47.85) 47.91	(3.06) 3.14	(12.88) 12.93	(9.50) 9.53	(21.77) 21.81	–
2b	342 (348)	230	75	Yellowish white crystals	(45.61) 45.72	(2.92) 2.96	(12.28) 12.42	(9.06) 9.08	(20.76) 20.71	(9.35) 9.30
3a	499 (501)	223	80	Light brown crystals	(62.52) 62.22	(4.00) 3.95	(16.83) 16.95	(6.21) 6.30	(7.11) 7.22	–
3b	515 (510)	217^d	76	Brown crystals	(60.58) 60.70	(3.88) 3.89	(16.3) 15.90	(6.01) 5.89	(6.89) 6.78	(6.21) 6.32
4a	671 (664)	220	75	Yellow crystals	(69.70) 69.86	(4.47) 4.55	(18.77) 18.89	(4.61) 4.68	–	–
4b	687 (679)	217^d	77	Yellow crystals	(68.12) 67.78	(4.36) 4.48	(18.3) 18.12	(4.51) 4.69	–	(4.65) 4.73

Molecular weights are in whole numbers.
d = decomposed.

TABLE 4 Insecticidal Activity of Phosphorylated and Thiophosphorylated Derivatives of 2-Substituted Benzimidazoles

	Mortality (%)								
	24 h			48 h			72 h		
	20 (μgm/cm^2)	40 (μgm/cm^2)	60 (μgm/cm^2)	20 (μgm/cm^2)	40 (μgm/cm^2)	60 (μgm/cm^2)	20 (μgm/cm^2)	40 (μgm/cm^2)	60 (μgm/cm^2)
1a	14	18	20	16	22	24	–	26	26
2a	42	46	50	46	50	–	46	56	–
2b	40	44	52	46	48	54	–	52	56
3a	52	60	64	54	62	68	60	62	70
3b	48	56	58	54	62	66	58	60	66
4a	48	54	58	52	56	60	54	56	60
4b	46	52	56	50	56	58	54	56	58

$(C_{13}H_{10}N_3)_2P(O)Cl$ and $(C_{13}H_{10}N_3)_2P(S)Cl$. 2-(2′-Aminophenyl) benzimidazole (0.002 mol) and $KHCO_3$ (0.002 mol) were taken in a three-necked RB flask, and to this mixture a solution of $POCl_3/PSCl_3$ (0.001 mol) was added slowly at 0°C. The mixture was refluxed for about 15 h. Same procedure was applied to obtain the product as described above.

$(C_{13}H_{10}N_3)_3P(O)$ and $(C_{13}H_{10}N_3)_3P(S)$. 2-(2′-Aminophenyl) benzimidazole (0.003 mol) and $KHCO_3$ (0.003 mol) in dry THF (30 mL) were taken in a three-necked RB flask, and to this mixture a solution of $POCl_3/PSCl_3$ (0.001 mol) in dry THF (30 mL) was added slowly at 0°C. This mixture was refluxed for about 15 h. Product was obtained by following the same procedure as described above.

The results of analytical and physical studies are given in Table 3.

Insecticidal Activity

The insecticidal activity of derivatives **1a–4b** was determined against *Periplenata americana*.

The test was performed at room temperature in a plastic box of 10 × 10 × 12 cm^3 by the contact and topical method [19]. The percentage mortality was recorded after 48 and 72 h. Results of test are given in Table 4.

The inference drawn from the table revealed that the activity of compounds increases with the increase in the concentration. Compounds having P=O bond resulted in higher toxicity then compounds having P=S bond, with the same substituents attached to phosphorus.

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