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Synthesis and Biological Activity of Phosphorylated Compounds of 2-Substituted Benzazoles

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ABSTRACT: *A series of organophosphorus derivatives have been synthesized by the reaction of phosphorylchloride with 2-(2′-hydroxyphenyl)benzimidazole and 2-(2′-hydroxynaphthyl)benzimidazole in the presence of $KHCO_3$ in dry THF in different molar ratios. Newly synthesized derivatives were tested for their insecticidal activity against Periplenata americana.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:246–249, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20533

INTRODUCTION

The phosphorylation plays a significant role in the biological system. Organophosphorus compounds possess insecticidal, pesticidal, acaricidal, and fungicidal properties [1–4]. These compounds exert their biological action on arthropods by attacking the system of neural transmission and inhibiting the function of acetylcholinesterase (AChE) [5,6]. The presence of a heterocyclic moiety in organophosphorus compounds further enhances their biological activity.

In light of physiological activities associated with organophosphorus compounds incorporating the heterocyclic moiety and in continuation of our laboratory synthesis of such compounds [7–11], we have synthesized some environment friendly, biologically active compounds by reacting 2-substituted benzimidazole derivatives with $POCl_3$ in 1:1, 2:1, and 3:1 molar ratios in dry THF (Scheme 1).

RESULTS AND DISCUSSION

IR spectra of phosphorylated derivatives are summarized in Table 1. A strong absorption band in the region 1290–1280 cm^{-1} in **2a,b–4a,b** has been ascribed to P=O stretching vibrations. The absorption bands in the region 1150–1120 cm^{-1} and 980–960 cm^{-1} have been assigned to (P)—O—C and P—O—(C) stretching vibrations, respectively. The presence of these vibrational frequencies indicates the deprotonation of the —OH group of **1a** and **1b** during the synthesis. Two strong absorption bands in the region 3250–3150 cm^{-1} and 1420 cm^{-1} characteristic of —NH stretching and bending vibrations of the imidazolyl group of a benzimidazole ring were observed in the spectra of **1a,b–4a,b**. The presence of these frequencies further supported the formation of a P—O—C bond during the synthesis of phosphorylated derivatives and nondeprotonation of the —NH group. IR spectra of **2a,b–3a,b** also showed two medium intensity bands at 530–510 cm^{-1} and 600 cm^{-1} assigned to symmetric and asymmetric stretching vibrations of the P—Cl bond, whereas these bands were found absent in IR spectra of compounds **4a–b**.

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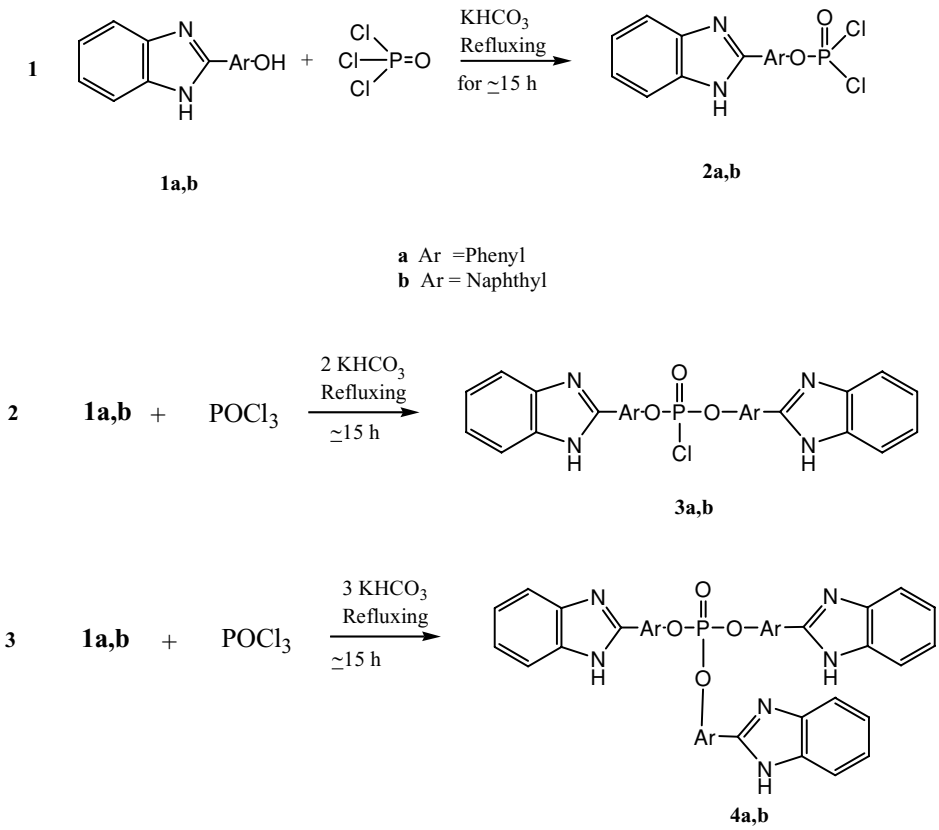

SCHEME 1

The ^{1}H NMR spectra of **1a,b–4a,b** are presented in Table 2. They showed characteristic resonance signal in the region δ 6.9–9.0 ppm as a broad singlet assigned to the imidazolyl proton. The presence of resonance signal due to the NH proton in **2a,b–4a,b** further supported the nonremoval of imidazolyl proton during the phosphorylation reaction. A multiplet has been observed in the region δ 7.5–8.0 ppm in all these derivatives and are assigned to aromatic protons of both phenyl and benzimidazolyl rings. The chemical shift values for the protons of benzimidazole moiety were observed nearly in the same region as described by Black and Heffernan [12]. A broad singlet due to —OH group at δ 10.2–10.3 ppm was observed in proton NMR spectra of derivatives **1a,b**, but this resonance signal due to hydroxyl proton of the phenyl ring was found absent in **2a,b–4a,b**, indicating the deprotonation of the —OH group during the phosphorylation reaction. This further confirmed the formation of the Ar—O—P bond during the reaction. ^{31}P spectra of **2a,b–4a,b** showed resonance signal in the region δ 60–70 ppm.

TABLE 1 IR Spectral Data of Phosphorylated Derivatives of 2-Substituted Benzimidazoles (cm^{-1})

Compounds	ν_{as} *NH*	δ *NH*	ν_{as} *OH* (δ *OH*)	*P—O—C*	*P=O*	*P—Cl*
1a	3150–3040	1420	3400 (1320)	–	–	–
1b	3150–3050	1420	3360 (1320)	–	–	–
2a	3360	1420	–	1100,980	1285	530,610
2b	3340	1420	–	1120,960	1270	510,600
3a	3350–3310	1420	–	1130,970	1290	530
3b	3350	1410	–	1120,960	1280	520,600
4a	3300	1420	–	1140,980	1280	–
4b	3300	1410	–	1130,970	1290	–

TABLE 2 NMR Spectra (δ, ppm)

Compounds	*—NH*	*—OH*	*Aromatic H*	^{31}P
1a	8.4	10.3 (bs)	6.9–7.8 (m)	–
1b	8.3	10.2 (bs)	7.1–8.0 (m)	–
2a	8.4	–	7.6–8.2 (m)	68.1
2b	8.6	–	7.4–8.0 (m)	66.4
3a	8.6	–	7.4–8.0 (m)	66.2
3b	8.5	–	7.4–8.0 (m)	67.4
4a	8.5	–	6.9–8.0 (m)	64.6
4b	8.4	–	7.4–8.0 (m)	64.3

bs = Broad singlet; s = singlet; m = multiplet.

EXPERIMENTAL

Stringent precautions were taken to exclude moisture during the experimental manipulations. Solvents were dried by standard methods. Melting points were determined in open capillaries and are uncorrected. Carbon and hydrogen analyses were performed on a Perkin–Elmer CHNO/S analyzer. IR spectra of compounds were recorded on a Perkin–Elmer 577 grading IR spectrometer. The ^1H NMR spectra (chemical shifts in δ ppm) were recorded on a FX 90Q Jeol-type spectrophotometer at 90 MHz using TMS as an internal reference. The purity of all the compounds was checked by TLC on silica gel 'G' plates using pet ether–methanol mixture and visualizing spots by iodine vapors. Mass spectral data are given in Table 3.

Synthesis of **1a,b**

Compounds **1a** and **1b** were prepared by reacting *o*-phenylene diamine with salicylic acid and *o*-hydroxy naphthoic acid, respectively in freshly prepared polyphosphoric acid. Reactions were carried out according to the procedure described by Heins et al. [13] and modified by Vyas et al. [14].

1a: $C_{13}H_{10}N_2O$, M. wt. calcd (found) 210 (223); M.P. 220°C; white crystals, C (calcd) found (74.27) 74.01, H (4.77) 4.69, N (13.32) 13.23.

1b: $C_{17}H_{12}N_2O$, M. wt. calcd (found) 260 (268); M.P. 130°C; violet crystals, C (calcd) found (78.44) 78.25, H (4.64) 4.51, N (10.76) 10.61.

Synthesis of **2a,b**

Dry nitrogen gas was flushed continuously during the reaction tenure. **1a/1b** (0.001 mol) in dry THF (30 mL) were taken in a flame-dried three-necked round-bottomed flask along with $KHCO_3$ (0.001 mol). To this mixture, the solution of $POCl_3$ (0.001 mol) in dry THF (30 mL) with the help of a dropping funnel was added slowly (at 0°C). This mixture was refluxed with continuous stirring for about 15 h. After checking the completion of the reaction by running TLC, the product was isolated by filtering through a closed sintered funnel. The filtrate was concentrated to one fourth of its volume under reduced pressure and was kept overnight in a vacuum desiccator to obtain crystals.

2a: $(C_{13}H_9N_2O)P(O)Cl_2$, M. wt. calcd (found) 327 (329); M.P. 242°C; brownish white crystals, C (calcd) found (47.70) 47.86, H (2.75) 2.72, N (8.56) 8.45, P (9.48) 9.42, Cl (21.71) 22.65.

2b: $(C_{17}H_{11}N_2O)P(O)Cl_2$, M. wt. calcd (found) 377 (406); M.P. 200°C; violet crystals, C (calcd) found (54.11) 54.10, H (2.91) 2.99, N (7.42) 7.49, P (8.22) 8.32, Cl (18.83) 18.90

Synthesis of **3a,b**

Compounds **1a/1b** (0.002 mol) in dry THF (30 mL) was taken in a three-necked round-bottomed flask along with $KHCO_3$ (0.002 mol). To this mixture, a solution of $POCl_3$ (0.001 mol) was added slowly (at 0°C). The mixture was refluxed for about 15 h with continuous stirring. Same procedure was applied to obtain the product as described above.

3a: $(C_{13}H_9N_2O)_2P(O)Cl$, M. wt. calcd (found) 501 (503); M.P. 259°C; creamish white, C (calcd) found (62.27) 61.33, H (3.59) 3.67, N (11.17) 11.09, P (6.18) 6.26, Cl (7.08) 6.92.

3b: $(C_{17}H_{11}N_2O)_2P(O)Cl$, M. wt. calcd (found) 601 (601); M.P. 233°C; pale violet, C (calcd) found (67.88) 68.97, H (3.66) 3.49, N (12.46) 12.30, P (5.15) 5.21, Cl (5.90) 5.83.

Synthesis of **4a,b**

Compounds **1a/1b** (0.003 mol) and $KHCO_3$ (0.003 mol) in dry THF (30 mL) were taken in a three-necked round-bottomed flask, and to this mixture a solution of $POCl_3$ (0.001 mol) in dry THF (30 mL) was added slowly (at 0°C). This mixture was refluxed for about 15 h with continuous stirring. The product was obtained by following the same procedure as described above.

4a: $(C_{13}H_9N_2O)_3P(O)$, M. wt. calcd (found) 674 (723); M.P. 234°C; creamish white, C (calcd) found (69.43) 69.55, H (4.00) 4.10, N (9.31) 9.45, P (4.59) 4.78.

4b: $(C_{17}H_{11}N_2O)_3P(O)$, M. wt. calcd (found) 824 (912); M.P. 225°C; violet, C (calcd) found (74.27) 74.36, H (4.00) 4.02, N (10.19) 10.24, P (3.76) 3.65.

TABLE 3 Mass Spectral Data of Phosphorylated Derivatives

	Compounds	*m/z* (%)
2a	$(C_{13}H_9N_2O)P(O)Cl_2$	327.11 (12), 292.26 (19), 294.16 (33), 256.66 (21), 259.31 (29), 241.7 (23), 209.36 (100), 195 (8), 117 (78), 90 (32)
2b	$(C_{17}H_{11}N_2O)P(O)Cl_2$	377.27 (18), 341.79 (30), 344.12 (33), 307.2 (19), 308.75 (27), 290.6 (28), 244.31 (100), 118.2 (14), 90 (21)
3a	$(C_{13}H_9N_2O)_2P(O)Cl$	501.2 (21), 466.21 (29), 468.1 (37), 450 (12), 257.32 (27), 241 (100), 210 (35), 118.3 (12), 90.41 (8)
3b	$(C_{17}H_{11}N_2O)_2P(O)Cl$	601 (12), 567.14 (35), 550.4 (9), 433 (17), 306.32 (14), 291.22 (78), 260 (13), 243.72 (100), 117.8 (22), 90.53 (18)
4a	$(C_{13}H_9N_2O)_3P(O)$	673.58 (20), 657.29 (12), 541.52 (8), 449.11 (20), 331 (7), 256.72 (22), 240.27 (100), 209 (33), 117.13 (77), 90 (21)
4b	$(C_{17}H_{11}N_2O)_3P(O)$	824.23 (14), 807.69 (9), 69.66 (30), 549.42 (42), 432 (10), 289.7 (6), 259.21 (100), 133.26 (23), 118.12 (20) 91 (17)

TABLE 4 Percent Insecticidal Mortality at 20, 40, and 60 $\mu g/cm^3$ after 48/72 h

Concentration ($\mu g/cm^3$)	20	40	60	20	40	60
Time (h)	48	48	48	72	72	72
1a	30	36	36	34	36	38
1b	30	34	34	32	38	42
2a	50	54	60	50	58	66
2b	50	58	66	56	60	66
3a	54	58	68	54	62	72
3b	58	64	72	60	64	74
4a	62	70	80	62	70	82
4b	68	72	80	68	74	80

INSECTICIDAL ACTIVITY

The insecticidal activity of derivatives **1a,b–4a,b** was tested against *Periplenata americana*. The test was performed at room temperature in a plastic box of $10 \times 10 \times 12$ cm^3 by the contact and topical method [15]. The percentage mortality was recorded after 48 and 72 h. The inference drawn from the results of study showed that the activity of compounds increased with the increase in the concentration. Tris-phosphorylated derivatives were found to be more effective against the pest than bis- and monophosphorylated derivatives. Results of tests are given in Table 4.

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