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Synthesis of 2-Substituted-2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole 2-Oxides/Sulfides

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ABSTRACT: *Syntheses of 2-aryloxy/2-chloro ethoxy-2, 3-dihydro-5-benzoyl-1H-1, 3, 2-benzodiaza-phosphole 2-oxides* **3a–h** *were accomplished by reactions of equimolar quantities of 3,4-diaminobenzophenone (***1***) with various aryl/chloroethoxy phosphorodichloridates* **2a–g** *and* **2h** *in the presence of triethylamine at 50–60°C. Compounds* **3i–k** *were prepared by reacting 3,4-diaminobenzophenone (***1***) with aryl thiophosphorodichloridates* **2i–k** *under similar conditions. They were characterized by IR, ^{1}H, ^{13}C, and ^{31}P NMR spectral data. Some of these products possessed siginificant antimicrobial activity* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:340–345, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10044

INTRODUCTION

Intensive investigations of compounds containing P—N linkages by numerous research groups have led to many interesting and far reaching developments [1]. Organophosphorus compounds containing a benzodiazaphosphole ring have acquired much importance because of their insecticidal, bactericidal, antiviral, and anticarcinogenic properties [2–4]. The search for a satisfactory drug for cancer also produced many new phosphorus heterocyclic compounds [5,6], and many of them possessed significant antitumor activity [6,7]. In continuation of our interest in the syntheses of new phosphorus heterocycles, preparation of the title compounds was accomplished.

RESULTS AND DISCUSSION

Syntheses of 2-aryloxy-/2-chloroethoxy–2,3-dihydo-5-benzoyl-1*H*-1,3,2-benzo-diazaphosphole 2-oxides **3a–h** and syntheses of 2-substituted 2,3-dihydro-5-benzoyl-1*H*-1,3,2-benzodiazaphosphole 2-sulfides **3i–k** were achieved by the cyclocondensation of equimolar quantities of 3,4-diaminobenzophenone (**1**) with aryl/chloroethoxy phosphorodichloridates **2a–h** and aryl thiophosphorodichloridates **2i–k** in dry toluene–tetrahydrofuran mixture (3:1) in the presence of triethylamine at 50–60°C (Scheme 1). Purifications of **3a–h** and **3i–k** were achieved by filtering off of the triethylamine hydrochloride, evaporation of the filtrate, washing of the residue with water and recrystallization of the solid products from aqueous 2-propanol. Their structures were established by elemental analyses, IR, ^{1}H, ^{13}C, and ^{31}P NMR spectral data (Tables 1–3).

The IR spectra of **3a–h** and **3i–k** (Table 1) showed bands at 3230–3372 (P—NH), 1617–1644 (C=O), 1221–1290 (P=O), 768–797 (P=S), 1162–1221, and 952–975 (P—O—C_{aro}), 1080 and 907 (P—O—C_{ali}) [8–11].

In their ^{1}H spectra (Table 2), a singlet for H-4 was observed at δ 6.73–7.32 for **3**. The doublets at

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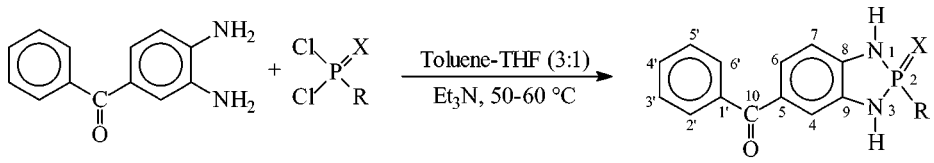

3a-h (X=O)

R

3 (a) OC_6H_4-CH_3(2")
(b) OC_6H_4-CH_3(4")
(c) OC_6H_5
(d) OC_6H_4-Cl(2")
(e) OC_6H_4-Cl(4")
(f) OC_6H_3-$(CH_3)_2$(2",5")
(g) OC_6H_3-$(CH_3)_2$(2",6")
(h) OCH_2CH_2Cl

3i-k (X=S)

R

3(i) OC_6H_4-CH3(4")
(j) OC_6H_4-Cl(4")
(k) OC_6H_5

SCHEME 1

δ 6.26–7.08 ($J = 8.1$–8.5 Hz) are for H-6. The other doublets found at δ 6.89–7.68 ($J = 8.1$–8.5 Hz) are attributed to H-7. The aryloxy moitey protons of **3a–h** and **3i–k** exhibited multiplets in the range of δ 6.98–7.84. The chloroethoxy group protons in **3h** appeared as a multiplet at δ 3.42–4.22. The signals for C-5 benzoyl protons in **3** were found as a complex multiplet at δ 6.82–7.84. The broad signals at δ 5.24–6.32 are for amidic protons which are confirmed by a D_2O exchange.

The ^{13}C NMR chemical shifts (Table 3) were recorded for some members of the title compounds (**3a–d, 3g, 3i**, and **3j**). Patterns for C-4 and C-7 were doublets at 112.67–116.12 ($J = 12.0$–12.8 Hz) and 116.22–122.20 ($J = 12.0$–12.8 Hz). The chemical shifts at 138.98–140.12 and 125.52–127.31 were assigned for C-5 and C-6, respectively. In the case of C-1′, C-(2′,6′), C-4′, and C-(3′,5′), the order of chemical shifts was 138.24–139.78, 128.92–129.49, 131.12–131.79, and 128.94–129.48. The nitrogen-bearing C-8 and C-9 exhibited signals downfield at 141.73–144.73 and 138.98–139.78. The signals for C-1′ appeared at 149.86–153.25. The C-2′ and C-6′ methyl groups in **3a** and **3g** appeared upfield at 16.53 and 16.91 ppm, respectively, because of their γ-interaction with exocyclic oxygen [12–14]. The signals for the carbonyl group (C-10) occurred at 193.74–195.04. The ^{13}C NMR chemical shifts for **3e, 3f, 3h**, and **3k** were not assignable because of the poor quality of the spectrum since the compounds are meagerly soluble in DMSO.

The ^{31}P NMR signals appeared in the range of −6.30 to 15.88 ppm from 85% H_3PO_4 [15–17].

ANTIMICROBIAL ACTIVITY

The compounds **3a–e** and **3i** were screened for antifungal activity on *Aspergillus flavus, Penicillium notatum, Helminthosporium anomalum,* and *Fusarium oxysporum,* according to the literature technique [18], by using Griseofulvin as a standard at two different concentrations 10 and 20 μg. Most of the compounds exhibited significant toxicity (Table 4) against all fungi. Antibacterial activity was also assessed using the reported procedure [19], on *Bacillus subtilis* and *Klebsiella pneumoniae* (Table 4). Compounds **3d, 3e**, and **3i** displayed strong action against the above bacteria.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Luknow, India. The purity of the compounds was checked by thin-layer chromatography (TLC; Silica gel 1H, BDH, hexane/ethyl acetate 2:3). All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1483 unit. The ^1H and ^{13}C NMR spectra were taken on Varian Gemini 300 and 400 MHz NMR spectrometers operating at 300 and 400 MHz, respectively. The ^{31}P NMR spectra were taken on a

TABLE 1 Physical and IR Data of Compounds **3**[a]

				Analysis Found (Required) (%)			IR (cm^{-1})					
											P—O—C (aro)	
Compound	*M.P. (°C)*	*Yield (%)*	*Mol. Formula*	*C*	*H*	*N*	*C=O*	*P=O*	*P=S*	*P—NH*	*P—O*	*O—C*
3a	168–170 (d)	58	$C_{20}H_{17}N_2PO_3$	65.78 (65.93)	4.62 (4.70)	7.64 (7.68)	1621	1290	–	3354	958	1183
3b	140–142 (d)	54	$C_{20}H_{17}N_2PO_3$	65.82 (65.93)	4.59 (4.70)	7.65 (7.68)	1617	1279	–	3358	960	1192
3c	152–154 (d)	52	$C_{19}H_{15}N_2PO_3$	65.05 (65.14)	4.26 (4.31)	8.07 (7.99)	1618	1258	–	3346	954	1196
3d	68–70 (d)	45	$C_{19}H_{14}N_2PO_3Cl$	59.26 (59.31)	3.78 (3.66)	7.36 (7.28)	1628	1261	–	3372	955	1190
3e	76–78 (d)	48	$C_{19}H_{14}N_2PO_3Cl$	59.23 (59.31)	3.72 (3.66)	7.22 (7.28)	1619	1254	–	3366	952	1192
3f	280–282 (d)	60	$C_{21}H_{19}N_2PO_3$	66.62 (66.66)	5.12 (5.06)	7.46 (7.40)	1642	1232	–	3280	965	1202
3g	293–295 (d)	57	$C_{21}H_{19}N_2PO_3$	66.75 (66.66)	5.18 (5.06)	7.32 (7.40)	1640	1221	–	3286	936	1162
3h	146–148 (d)	52	$C_{15}H_{14}N_2PO_3Cl$	53.41 (53.50)	4.26 (4.19)	8.22 (8.31)	1644	1286	–	3230	907 ($P—O_{ali}$)	1080 ($O—C_{ali}$)
3i	188–190 (d)	45	$C_{20}H_{17}N_2PO_2S$	63.28 (63.14)	4.41 (4.50)	7.24 (7.36)	1620	–	797	3348	906	1221
3j	161–163 (d)	42	$C_{19}H_{14}N_2PO_2SCl$	56.82 (56.93)	3.58 (3.52)	6.84 (6.93)	1632	–	792	3296	959	1194
3k	48–150 (d)	39	$C_{19}H_{15}N_2PO_2S$	62.17 (62.28)	4.06 (4.12)	7.68 (7.64)	1642	–	768	3362	975	1218

Note: Et_3N/triethyl amine; THF, tetrahydrofuran.
[a]Recrystallized from aqueous 2-propanol.

TABLE 2 ^{1}H and ^{31}P NMR Spectral Data[a] of **3** (δ from TMS)

Compound	*H-(4,6,7)*[b]	*OAr—H*	*OAr—CH_3*	*O=CC_6H_5*	*NH*	*^{31}P NMR*[c]
3a	7.15 (s, 1H, 4-H), 6.63 (d, 8.2, 1H,6-H), 7.47 (d, 8.2, 1H,7-H)	7.20–7.59 (m, 4H)	2.22 (s, 3H)	7.02–7.84 (m, 5H)	5.91 (brs, 2H)	−5.61, −6.30
3b	7.26 (s, 1H, 4-H), 6.74 (d, 8.5, 1H, 6-H), 7.39 (d, 8.5, 1H, 7-H)	6.98–7.42 (m, 4H)	2.25 (s, 3H)	6.82–7.52 (m, 5H)	5.85 (brs, 2H)	−5.42, −6.04
3c	6.78 (s, 1H, 4-H), 6.26 (d, 8.1, 1H, 6-H), 7.02 (d, 8.1, 1H, 7-H)	7.40–7.65 (m, 5H)	–	7.21–7.56 (m, 5H)	–	−5.53, −5.95
3d	7.03 (s, 1H, 4-H), 6.67 (d, 8.2, 1H, 6-H), 7.18 (d, 8.2, 1H, 7-H)	7.62–7.68 (m, 4H)	–	7.53–7.58 (m, 5H)	5.27	−5.30, −5.97
3e	7.09 (s, 1H, 4-H), 6.82 (d, 8.3, 1H, 6-H), 7.12 (d, 8.3, 1H, 7-H)	7.24–7.53 (m, 4H)	–	6.97–7.44 (m, 5H)	5.45 (brs, 2H)	−5.16, −6.08
3f	7.02 (s, 1H, 4-H), 6.94 (d, 8.4, 1H, 6-H), 7.26 (d, 8.4, 1H, 7-H)	7.31–7.46 (m, 3H)	2.04 (s, 3H, 2″-CH_3) 2.16 (s, 3H, 5″-CH_3)	7.17–7.39	6.20	15.26, 15.48
3g	6.73 (s, 1H, 4-H), 6.60 (d, 8.2, 1H, 6-H), 6.89 (d, 8.2, 1H, 7-H)	7.54–7.84 (m, 3H)	2.15 (s, 6H, 2″,6″ -$(CH_3)_2$)	(7.16–7.40) (m, 5H)	6.32 (brs, 2H)	15.72, 15.88
3h	7.15 (s, 1H, 4-H), 6.53 (d, 8.3, 1H, 6-H), 6.96 (d, 8.3, 1H, 7-H)	OCH_2CH_2Cl 3.42–4.22 (m, 4H)	–	7.21–7.51 (m, 5H)	5.62 (brs, 2H)	–
3i	7.21 (s, 1H, 4-H), 6.81 (d, 8.2, 1H, 6-H), 7.37 (d, 8.2, 1H, 7-H)	7.41–7.72 (m, 4H)	2.55 (s, 3H)	7.31–7.67 (m, 5H)	5.37 (brs, 2H)	–
3j	7.32 (s, 1H, 4-H), 7.08 (d, 8.4, 1H, 6-H), 7.68 (d, 8.4, 1H, 7-H)	7.38–7.84 (m, 4H)	–	7.18–7.56 (m, 5H)	5.85 (brs, 2H)	–
3k	6.82 (s, 1H, 4-H), 6.49 (d, 8.1, 1H, 6-H), 7.34 (d, 8.1, 1H, 7-H)	7.80–7.74 (m, 5H)	–	7.34–7.49 (m, 5H)	5.24 (brs, 2H)	–

[a]Recorded in DMSO-d_6.
[b]Values in parentheses are coupling constants; *J* in Hz.
[c]^{31}P chemical shifts were expressed in δ from 85% H_3PO_4 as external standard.

Varian Gemini 400 MHz NMR spectrometer operating at 162 MHz. All spectra were recorded using DMSO-d_6 with TMS as the internal reference for ^{1}H and ^{13}C and 85% H_3PO_4 external reference for ^{31}P NMR.

3,4-Diaminobenzophenone (**1**) was procured from Aldrich Chemical Company, Milwaukee, and was used without further purification.

2-(2″6″-Dimethylphenoxy)-2,3-dihydro-5-benzoyl-1 H-*1,3,2-benzodiazaphosphole 2-oxide (***3g***)*

A solution of 2″,6″-dimethylphenyl phosphoro dichloridate (**2g**, 0.476g, 0.002 mol) in 25 ml of dry toluene was added dropwise over a period of 20 min to a stirred solution of 3,4-diaminobenzophenone (**1**, 0.424 g, 0.02 mol) and triethylamine (0.404 g, 0.04 mol) in 30 ml of dry toluene and 10 ml of tetrahydrofuran. After completion of the addition, the temperature of the reaction mixture was slowly raised to room temperature and stirred for 2 h. Later the reaction mixture was heated to 50–60°C and maintained for 4 h with stirring. The completion of the reaction was monitored by TLC analysis. The condensed product, which was insoluble in toluene, was separated by filtration. The gummy solid obtained was washed with water to remove residual traces of triethylamine hydrochloride and dried. The solid obtained was recrystallized from aqueous 2-propanol: yield 57%, m.p. 293–295°C. Anal. calcd for $C_{21}H_{19}N_2PO_3$ (378.3634): C, 66.66; H, 5.06; N, 7.40. Found: C, 66.75; H, 5.18; N, 7.32.

TABLE 3 ^{13}C NMR Data of Compounds of **3**[a] (δ from TMS)[b]

Carbon Atoms	**3a**	**3b**	**3c**	**3d**	**3g**	**3i**	**3j**
C-1′	139.56	139.42	139.23	139.78	138.24	138.98	138.46
C-2′-6′	129.49	129.44	129.35	129.13	128.94	129.22	128.92
C-4′	131.15	131.12	131.46	131.18	131.79	131.67	131.72
C-3′,5′	129.43	129.48	129.40	129.13	128.94	129.22	129.41
C-10	194.18	194.26	193.96	194.35	195.04	193.74	194.23
C-4	113.24 (12.4)	113.18 (12.5)	116.12 (12.2)	112.67 (12.0)	113.30 (12.6)	114.67 (12.8)	114.28 (12.5)
C-5	139.56	140.12	139.62	139.78	139.40	138.98	139.42
C-6	126.95	126.78	127.20	125.52	127.00	127.31	127.26
C-7	118.10 (12.4)	118.06 (12.5)	119.21 (12.2)	116.22 (12.0)	119.44 (12.6)	122.20 (12.8)	122.02 (12.5)
C-8	142.54	142.62	143.51	141.73	142.80	144.73	144.36
C-9	139.56	139.54	139.41	139.78	139.40	138.98	139.04
C-1″	150.45	150.49	150.54	149.86	153.25	151.67	152.24
C-2″	129.43	129.42	126.48	131.18	131.79	122.20	121.92
C-3″	130.70	130.68	130.79	128.40	129.35	129.18	129.24
C-4″	125.47	125.42	126.08	125.52	124.46	123.10	122.86
C-5″	126.95	126.86	127.02	123.37	129.35	129.78	129.62
C-6″	124.12	123.96	124.26	116.22	119.44	122.20	121.84
	16.53 (2″-CH_3)	20.02 (4″-CH_3)			(2″-CH_3) 16.91 (6″-CH_3)	20.24 (4″-CH_3)	

[a]Not recorded for **3e, 3f, 3h**, and **3k**.
[b]Data in parentheses are coupling constants J_{P-C} (in Hz).

TABLE 4 Antifungal and Antibacterial Activities of Compounds **3** in Terms of Zone of Inhibition (mm)

	Fungi								*Bacteria*	
	Aspergillus flavus		*Penicillium notatum*		*Helminthosporium anomolum*		*Fusarium oxysporum*		*Bacillius subtilis*	*Klebsiella pneumoniae*
Compound	*10 μg*	*20 μg*	*10 μg*	*20 μg*	*10 μg*	*20 μg*	*10 μg*	*20 μg*	*10 μg*	*10 μg*
3a	–	–	–	–	10	18	5	12	–	–
3b	–	–	–	–	11	20	4	9	–	–
3c	–	–	6	12	6	15	10	14	–	–
3d	10	22	2	4	10	20	–	–	14	16
3e	8	15	5	9	9	17	–	–	11	15
3i	14	24	12	21	12	18	4	8	10	12

Empty entries indicate no activity.

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