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Facile Synthesis of New Organophosphorus Compounds with -N–P(O)–N- Linkage: Reaction between 2-Pyrazoline and Phosphorodichloridates/Phosphonic Dichloride

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ABSTRACT

Condensation of 3-benzoyl-4-phenyl-2-pyrazoline with various aryl phosphorodichloridates or trichloromethylphosphonic dichloride in the presence of a base resulted in the formation of arylbis(3-benzoyl-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl)phosphinates and trichloromethyl-bis(3-benzoyl-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl)phosphonate. The structures of the title compounds were confirmed by elemental analyses, IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra. The EI mass spectrum of one member of the family is discussed. These compounds were found to possess good antibacterial and antifungal activity. © *1997 John Wiley & Sons, Inc.*

INTRODUCTION

Pyrazoline derivatives have attracted much attention due to their wide range of applications [1,2]. Many of their derivatives have been found to be good analgesics, antipyretics, antiinflammatories, germicides, and antifungal agents [3,4]. Several cyclic and acyclic phosphorus compounds containing a functional group having a nitrogen atom are known to exhibit antitumour activity [5–8]. Many organophosphorus compounds are also proven pesticides, antimicrobicides, and flame retardants [9,10]. This common applicability of these two derivatives influenced us to design and synthesize new organophosphorus—pyrazolinyl derivatives with an -N–P(O)–N- linkage.

RESULTS AND DISCUSSION

The chalcone **3** obtained by the reaction of benzaldehyde (**1**) with acetophenone **2** afforded 3-benzoyl-4-phenyl-2-pyrazoline (**4**) on reaction with diazomethane [11]. The reaction of **4** with **5** was carried out conveniently at relatively low temperatures (-10 to 0°C) in diethyl ether. Triethylamine was used as a base to scavenge the liberated hydrochloric acid, thereby facilitating the formation of **6**. The reactions were completed in 5–7 hours. The products were obtained as light-yellow crystalline solids after recrystallizing them from a benzene–hexane (1:1) mixture (Table 1, Scheme 1).

Their IR spectra (Table 1) showed characteristic absorption bands at 1315–1290 (P=O), 788–745 (P–N), 1555–1530 (C=N), 1625–1600 (C=O), 946–937 and 1240–1214 (P–O–$C_{aromatic}$), 840 (P–C), and 780 (C–Cl) cm^{-1} [12–16], confirming the presence of the pyrazolinyl-phosphorus linkage.

^{1}H NMR spectra (Table 2) exhibited signals in the range of δ 7.14–8.28, accounting for the aromatic protons of phenyl, benzoyl, and phenoxy moieties in **6**. The H(4) and H(5) signals exhibited an ABX pat-

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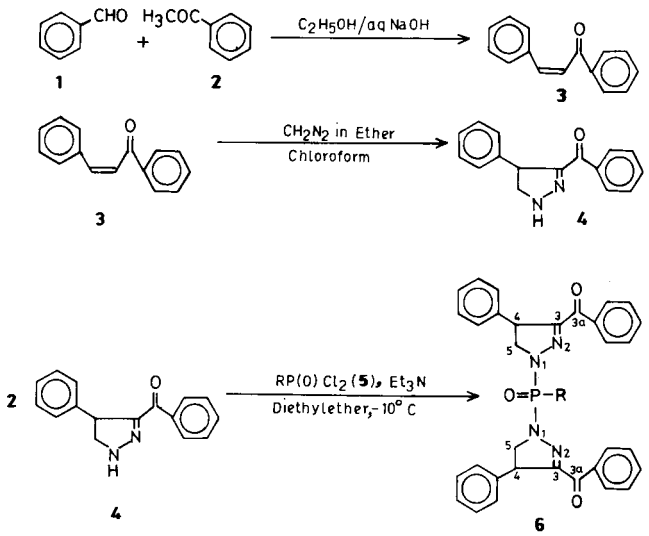
TABLE 1 Synthetic and IR Data of Aryl/Trichloromethyl bis(3-Benzoyl-4,5-dihydro-4-phenyl-1*H*-pyrazol-1-yl)phosphinates/phosphonate (**6**)

					C,H,N Analysis Found (*Calcd*) (%)			*IR Spectra* (cm^{-1})					
Compd	*Molecular Formula*	*Mp*[a] (°*C*)	*Reaction Time* (*hours*)	*Yield*[b] (%)	*C*	*H*	*N*	*P=O*	*P–N*	*C=N*	*C=O*	*P–O–C*(aromatic) *O–C*	*P–O*
6a	$C_{38}H_{31}N_4O_4P$	180–181	5	46	71.39 (71.46)	4.84 (4.79)	8.70 (8.77)	1296	765	1555	1610	937	1215
6b	$C_{39}H_{33}N_4O_4P$	157–159	6	44	71.69 (71.77)	4.94 (5.09)	8.50 (8.58)	1294	753	1554	1614	938	1223
6c	$C_{39}H_{33}N_4O_4P$	160–161	6	45	71.69 (71.77)	5.18 (5.09)	8.54 (8.58)	1310	750	1530	1600	945	1240
6d	$C_{38}H_{30}ClN_4O_4P$	136–137	5	43	67.73 (67.81)	4.55 (4.49)	8.28 (8.32)	1285	765	1540	1625	946	1214
6e	$C_{38}H_{30}ClN_4O_4P$	140–141	7	48	67.69 (67.81)	4.53 (4.49)	8.30 (8.32)	1290	745	1530	1600	935	1230
6f	$C_{33}H_{26}Cl_3N_4O_3P$	128–130	5	52	58.12 (58.29)	4.04 (3.85)	8.22 (8.24)	1315	788	1539	1603	840 (P–C)	780 (C–Cl)

[a]Recrystallized from benzene:hexane (1:1).
[b]Yields were reported after one recrystallization.



R
5a, 6a; C_6H_5O
5b, 6b; 2-$CH_3C_6H_4O$
5c, 6c; 4-$CH_3C_6H_4O$

R
5d, 6d; 2-ClC_6H_4O
5e, 6e; 4-ClC_6H_4O
5f, 6f; CCl_3

SCHEME 1

tern [1,2], appearing at δ 3.65–4.96 (5-H_A), 3.65–4.24 (5-H_B), and 4.65–4.96 (4-Hx). Their coupling with phosphorus did not allow us to analyze the signals further. ^{31}P NMR signals of these compounds appeared in the range $\delta = +1.047$ to $+4.320$ (Table 2).

In the ^{13}C NMR spectra (Table 3), C(4) and C(5) gave signals in the region δ 48.72–49.23 and 53.82–58.02, respectively. The low intense peaks at δ 186.13–191.20 and 202.01–202.74 were attributed to the tertiary carbons C(3) and C(3a), respectively. This downfield shift is attributed to their extended conjugation with the aromatic ring and the pyrazoline moiety. The signals for the aromatic carbons of phenyl, benzoyl, and aryloxy moieties appeared at δ 127.17–140.89, 128.29–141.04, and 119.16–161.03, respectively [17–19]. The methyl carbons on the phenoxy moiety in **6b** and **6c** resonated at δ 17.30 and 30.89, respectively. The observed upfield shift for the methyl group attached to C(2) (**6b**) was attributed to its γ-interaction with the exocyclic oxygen [17,18]. The trichloromethyl carbon in **6f** gave a signal at δ 110.86.

Although the mass spectrum of **6d** did not show any $M^{+\cdot}$ ion, the presence of a relatively high abundant ion at *m/z* 470 $(M\text{-}PhCO,Ph)^+$ and other daughter ions at *m/z* 393 $(M\text{-}PhCOPh,2Ph)^+$, 365 $(M\text{-}PhCO,2Ph,CO)^+$, 354 $(M\text{-}PhCO,2Ph,C_2HN)^+$, and 250 (2-pyrazoline) confirms the structure of the molecule.

Antibacterial activity of the title compounds was evaluated by following the method of Vincent and Vincent [20], and their antifungal activity was screened by the Horsfall and Rich [21] procedure.

All compounds exhibited moderate activity against gram-positive bacterial species, *Bacillus subtilis* and *Staphylococcus aureus* at 500 ppm. They showed variable activity against *Curvularia lunata* (67–98%). *Fusarium oxysporum* (71–99%) and *Helmenthosporium oryzae* (70–100%) fungal species.

TABLE 2 ^{1}H and ^{31}P NMR Spectral Data of **6a–6f**

Compd. No.	*5-H_A*	*5-H_B*	*4-H_X*	*R*	*^{31}P NMR*
6a	4.17–4.24	4.36–4.43	4.87–4.94	8.13–8.18 (m,4H,Ar–H) 7.38–7.56 (m,8H,Ar–H) 7.20–7.34 (m,13H,Ar–H)	+3.242
6b	4.14–4.21	4.36–4.45	4.85–4.90	8.20–8.26 (m,4H,Ar–H) 7.42–7.63 (m,8H,Ar–H) 7.16–7.32 (m,12H,Ar–H) 2.14 (s,3H,2′-CH_3)	+4.321
6c	4.15–4.22	4.38–4.47	4.90–4.96	8.24–8.28 (m,4H,Ar–H) 7.48–7.66 (m,8H,Ar–H) 7.16–7.32 (m,12H,Ar–H) 2.16 (s,3H,4′-CH_3)	+1.047
6d	4.16–4.23	4.39–4.47	4.91–4.96	8.24–8.27 (m,4H,Ar–H) 7.45–7.66 (m,8H,Ar–H) 7.15–7.36 (m,12H,Ar–H)	+2.017
6e	4.16–4.21	4.38–4.45	4.91–4.95	8.25–8.27 (m,4H,Ar–H) 7.48–7.65 (m,8H,Ar–H) 7.17–7.34 (m,12H,Ar–H)	+1.942
6f	3.65–3.78	3.90–4.09	4.65–4.70	8.06–8.10 (m,4H,Ar–H) 7.41–7.51 (m,8H,Ar–H) 7.14–7.37 (m,8H,Ar–H)	+4.314

TABLE 3 ^{13}C Chemical Shifts of Compounds **6a–6f**

	Compounds					
Carbon No.	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**
Pyrazolinyl						
3	186.13	186.15	186.16	187.10	186.20	191.20
3a	202.70	202.01	206.95	202.70	202.74	202.04
4	49.11	49.11	49.36	48.72	49.43	49.13
5	57.84	57.73	53.82	57.51	53.83	58.02
Benzoyl						
1	141.04	141.01	137.37	135.35	137.45	137.20
2 & **6**	129.93	129.93	129.45	129.87	129.48	129.76
3 & **5**	128.72	128.91	128.29	128.32	128.64	128.94
4	137.19	137.20	130.34	133.98	134.23	134.47
Phenyl						
1	140.88	140.89	134.24	132.17	134.23	133.80
2 & **6**	128.89	127.93	128.61	129.03	128.32	128.32
3 & **5**	127.92	127.20	127.17	127.97	127.20	127.88
4	132.15	132.16	130.34	132.25	130.38	130.14
Aryloxy						
1	150.15	150.08	161.03	152.78	161.02	110.86 (CCl_3)
2	119.16	128.08	129.16	128.83	129.46	—
3	127.03	129.93	128.14	127.20	128.25	—
4	127.19	127.06	134.91	141.04	135.02	—
5	127.03	129.93	128.14	127.20	128.25	—
6	119.16	118.08	129.16	118.83	129.46	—
Methyl carbons	—	17.30(2′)	30.89(4′)	—	—	—

The evaluation of anticancer activity for these compounds is in progress.

EXPERIMENTAL

Melting points were determined by use of open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 instrument. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian XLAA-400 instrument at 300, 101, and 162 MHz, respectively. Elemental analyses and EI mass spectra were obtained from CDRI, Lucknow, India.

1,3-Diphenyl-2-propen-1-one (**3**) *[11]*

To a mixture of benzaldehyde (**1**, 5.3 g, 0.05 mol), acetophenone (**2**, 6.0 g, 0.05 mol), and aqueous ethanol (95%, 10 mL), aqueous sodium hydroxide (10%, 20 mL) was added dropwise with stirring, and stirring was continued for 1 hour. The reaction mixture was refrigerated overnight, and the product that had formed was filtered off and washed repeatedly with cold water. The product was obtained as light-yellow plates from a hexane–benzene (1:1) mixture and amounted to 9.2 g (78%) of **3**, mp 55–56°C (Scheme 1).

3-Benzoyl-4-phenyl-2-pyrazoline (**4**) *[11]*

To a solution of **3** (1.0 g, 4.8 mol) in chloroform (5 mL), an excess of diazomethane in ether solution was added, and the reaction mixture was kept at 0°C. The progress of the reaction was monitored by use of silica gel thin layer chromatography (TLC). After 12 hours, the reaction was deemed to be completed. The ether was evaporated, and the pyrazoline product was recrystallized from a hexane–benzene (1:1) mixture to yield 0.8 g (68%) of **4**, mp 127–128°C (Scheme 1).

Phenyl bis(*3-Benzoyl-4,5-dihydro-4-phenyl-1H-pyrazol-1-yl*) *Phosphinate* (**6a**)

To a cooled and stirred solution of **4** (0.5 g, 0.002 mol) and triethylamine (0.202 g, 0.002 mol) in dry diethyl ether (40 mL), a solution of phenyl phosphorodichloridate (**5a**, 0.225 g, 0.001 mol) was added dropwise at −10°C over 15 minutes. The stirring was continued, and the progress of the reaction was followed by TLC analysis. Completion of the reaction took 5 hours. The solid triethylamine hydrochloride that had been formed was filtered off, and the solvent was evaporated. The residue was washed with water and was recrystallized from a benzene–hexane (1:1) mixture to yield 2.93 g (46%) of **6a** as a light-yellow powder, mp 180–181°C. Anal. calcd for $C_{38}H_{31}N_4O_4P$ (638.5691): C, 71.46; H, 4.79; N, 8.77. Found: C, 71.39; H, 4.84; N, 8.70. The same procedure was adopted for the synthesis of **6b–6f**.

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