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Synthesis and spectral characterization of some new 2-(substituted)-5-methyl/chloro-2,3-dihydro-1,3,2 λ^5 -benzoxazaphosphol - 2 -thiones / -2- ones

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ABSTRACT

Synthesis of 2-(substituted)-5-methyl / 5-chloro-2,3-dihydro-1,3,2 λ^5 -benzoxaza-phosphol-2-thiones / 2-ones was accomplished in a two-step process. The structures of these compounds were confirmed by analytical and spectral data (IR, ¹H, ¹³C, ³¹P NMR and Mass).

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KEYWORDS

4-methyl-2-aminophenol;
4-chloro-2-aminophenol;
Thiophosphoryl chloride;
Phosphoryl chloride;
Phenols;
Aromatic amines.

INTRODUCTION

Organophosphorus compounds being ubiquitous in nature, found multifaceted applications^[1,2]. Organophosphorus esters are commercial pesticides^[2] and insecticides^[3-6]. Cyclophosphamide is a well known anticancer agent^[7]. This background provided great impetus for a systematic research in the synthesis of new organophosphorus heterocycles containing O, N, and S with potential bio-activity.

Organic compounds containing two same or different facile groups such as -NH₂, -OH, -SH were largely used as substrates in the synthesis of organophosphorus heterocycles. Reagents like phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, their alkyl / aryl derivatives and alkyl / aryl phosphites were used for cyclocondensation, in the preparation of intermediates and final products.

Koizumi et al.^[8] reported the formation of 2-phenoxy 3,4-dihydro-1H-1,3,2-benzoxazaphosphole-2-oxides by reacting 2-amino phenol with phenyl phosphoro dichloridates.

Syam Prasad et al.^[9] reported the synthesis of 5-substituted-2-(methoxy phenyl)-3H-benzo[1,3,2]-oxaza phosphole-2-sulfides by the condensation of 4-chloro/methyl amino phenol with Lawesson's reagent. Zimmer and Sill^[10] prepared the pyridine analog of Benzodiazophosphole-2-oxide and this compound also proved to be an effective anti-cancer agent. Venkateswarlu et al.^[11] reported the synthesis of 2-(substituted)-1,3,2 λ^5 -oxazaphosphinan-2-ones/-2-thiones from 3-aminopropanol.

Organophosphorus cyclic compounds with oxygen, sulfur or nitrogen in the ring system are expected to be more active due to the presence of hetero atoms. In view of this applicability, synthesis of new 2-substi-

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tuted-5-methyl / 5-chloro-2,3-dihydro-1,3,2 λ^5 -benzoxazaphosphol-2-thiones / -2-ones was accomplished with good to moderate yields.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and were uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer FT-IR 1000 spectrophotometer. The ^1H , ^{13}C and ^{31}P NMR spectra were taken on Bruker ACF NMR spectrophotometer operating at 400 MHz, 100 MHz and 161.89 MHz respectively, in CDCl_3 and were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectral data were collected on LCMS-2010A, Shimadzu Spectrometer.

Synthesis of 5-methyl-2-(2-toluidino)-2,3-dihydro-1,3,2, λ^5 -benzoxazaphosphol-2-thione (6)

Phosphoryl chloride (0.31 g, 0.002 mole) in 20 mL of benzene was added drop wise over a period of 20 minutes to a stirred solution of 4-methyl-2-aminophenol (0.245 g, 0.002 mole) and TEA (0.404 g, 0.004 mole) in 30 mL of dry benzene at 0°C . After the addition, the temperature of the reaction was raised to 45 – 55 $^\circ\text{C}$ and the reaction mixture was stirred for 4 hours. Completion of the reaction was monitored by TLC analysis (hexane and ethyl acetate 3:1). After cooling the reaction mixture, 2-methyl aniline (0.201 g, 0.002 mole), TEA (0.201 g, 0.002 mole) were added at 20°C *in situ* and raised the temperature to 45 – 55 $^\circ\text{C}$. Stirring of the reaction mixture was continued for 4 hours. Completion of the reaction was monitored by TLC (hexane and ethyl acetate 3:1). The precipitated triethylamine hydrochloride was removed by filtration and the solvent was removed from the filtrate in a rota-evaporator. The residue was purified by column chromatography on silica gel (60-120 mesh) as adsorbent using hexane and ethyl acetate (2:1) as an eluent to afford the analytically pure 5-methyl-2-(2-toluidino)-2,3-dihydro-1,3,2 λ^5 -benzoxazaphosphol-2-one (6). All other compounds are prepared by following the same procedure.

RESULTS AND DISCUSSION

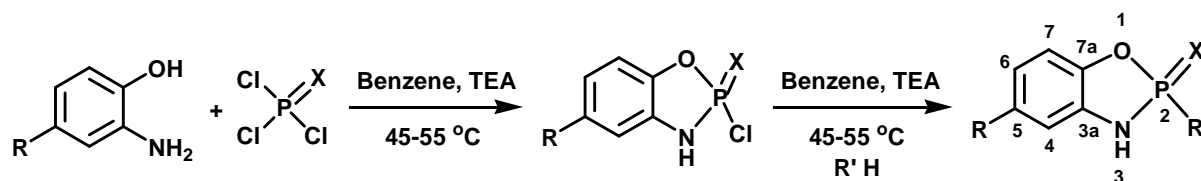
A simple two-step procedure, for the synthesis

of 2-substituted bezoxazaphosphol-2-thiones/-2-ones with moderate yields has been employed. Synthesis of the title compounds (3-12) was accomplished in a two-step process. The synthetic route involves the condensation of 4-methyl-2-aminophenol / 4-chloro-2-aminophenol (1) with thiophosphoryl chloride / phosphoryl chloride in dry benzene in the presence of triethylamine (TEA) at 45 - 55 $^\circ\text{C}$ with the continuous stirring of the reaction mixture for 4-6 hours to afford the corresponding intermediate 2-chloro-5-methyl-2,3-dihydro-1,3,2 λ^5 -benzoxazaphosphol-2-thione / 2-chloro-5-chloro-2,3-dihydro-1,3,2 λ^5 -benzoxazaphosphol-2-one (2). The progress of the reaction was followed by TLC (hexane - ethyl acetate, 3:1).

In the second step, the intermediate compound (2) was reacted *in situ* with various phenols and aromatic amines, in dry benzene in the presence of TEA to obtain the title compounds (3-12) in moderate yields. The triethylamine hydrochloride formed in the reaction being insoluble in benzene was separated by filtration. The second step of the reaction was completed at 45-55 $^\circ\text{C}$ by continuous stirring of the reaction mixture for 3-5 hours. The progress of the reaction was followed by TLC (hexane – ethyl acetate, 3:1). The crude products obtained after removing the solvent, from the filtrate by rota-evaporator, were purified by column chromatography on silica gel (hexane-ethyl acetate, 7:3). All the title compounds were readily soluble in polar solvents and melted in the range of 135 – 162 $^\circ\text{C}$ (3-8) and 214 – 226 $^\circ\text{C}$ (9-12). Their yields were in the range of 50-81%.

The synthetic and analytical data of compounds (3-12) are given in the TABLE 1. The IR data and ^{31}P NMR data are presented in TABLE 2. The compounds (3-12) exhibited stretching frequencies in the regions 709-772 (P=S), 1227-1233 (P=O), 3361-3470 (N-H) and 940-1022, 1160-1219 cm^{-1} (P-O-C_(aromatic))^[12].

The proton NMR spectral data of the compounds are furnished in the TABLE 3. The aromatic protons showed a complex multiplet in the region δ 6.3 – 7.5 ppm. C-5-CH₃ proton signal appeared as singlet in the range of δ 2.11 – 2.32. Ar-NH_(endocyclic) proton resonated in the region of δ 5.45-5.69 ppm as a doublet with J a value \approx 20 Hz due to its coupling with the



Comp.	R'	R	X	Comp.	R'	R	X
3		Me	S	8		Me	S
4		Me	S	9		Cl	O
5		Me	S	10		Cl	O
6		Me	S	11		Cl	O
7		Me	S	12		Cl	O

Scheme 1

TABLE 1 : Physical and analytical data of the compounds (3-12)

Comp.	m.p. °C	Yield (%)	Molecular Formula	Elemental Analysis Found (Calcd.) %		
				C	H	N
3	135-137	67	C ₁₆ H ₁₃ N ₂ PSO ₂	58.65 (58.53)	3.89 (3.96)	8.46 (8.53)
4	138-140	69	C ₁₄ H ₁₄ NPSO ₂	57.82 (57.73)	4.76 (4.81)	4.87 (4.81)
5	146-148	81	C ₁₇ H ₁₄ NPSO ₂	62.41 (62.38)	4.22 (4.28)	4.19 (4.28)
6	152-154	72	C ₁₄ H ₁₅ N ₂ PSO	57.85 (57.93)	5.21 (5.17)	9.72 (9.65)
7	156-158	64	C ₁₃ H ₁₂ N ₃ PSO ₃	48.63 (48.59)	3.69 (3.73)	13.12 (13.08)
8	160=162	58	C ₁₇ H ₁₅ N ₂ PSO	62.57 (62.57)	4.57 (4.60)	8.62 (8.58)
9	214-216	50	C ₁₂ H ₉ NPClO ₃	51.06 (51.15)	3.24 (3.19)	4.88 (4.97)
10	218-220	54	C ₁₃ H ₁₁ NPClO ₃	52.79 (52.79)	3.72 (3.72)	4.67 (4.73)
11	218-220	55	C ₁₃ H ₁₁ NPClO ₃	52.79 (52.79)	3.72 (3.74)	4.67 (4.76)
12	224-226	50	C ₁₂ H ₈ NPClO ₃	45.54 (45.57)	2.55 (2.53)	4.35 (4.43)

TABLE 2 : IR and ³¹P NMR data for the compounds (3-12)

Comp.	I R Frequencies in cm ⁻¹					³¹ P NMR ^a ppm δ
	P=S	P=O	-NH	P-O-C _(aromatic)		
				P-O	O-C	
3	709	-	3411	940	1160	67.37
4	751	-	3470	962	1202	59.62
5	769	-	3394	980	1194	66.56
6	772	-	3372	1022	1219	62.15
7	750	-	3361	994	1178	64.42
8	762	-	3422	998	1192	61.79
9	-	1227	3418	955	1206	-41.5
10	-	1233	3413	955	1214	-41.5
11	-	1229	3415	951	1206	-41.5
12	-	1229	3414	956	1210	-41.5

a = 85% H₃PO₄ external standard

These amidic protons presence were confirmed by a D₂O exchange experiments.

The ¹³C NMR spectral data of these compounds (3-12) are presented in TABLE 4. ¹³C NMR spectral data was assigned based on additivity rules, intensity of signals, carbon coupling with phosphorus

neighbouring phosphorus^[13]. Ar-NH_(exocyclic) proton of 6, 7, 8 resonated as doublet in the region of δ 6.29 – 8.07 ppm with a J value in the range of 8.0 – 9.2 Hz.

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TABLE 3: ¹H NMR spectral data^{ab} of compounds (3-12)

Comp.	Ar-H	C-5-CH ₃	Ar-NH (endocyclic)	Ar-NH (exocyclic)
3	6.44-7.49 (m, 9H)	2.11 (s, 3H)	5.56 (d, J=20.0 Hz)	-
4	6.38-7.23 (m, 7H)	2.17 (s, 3H)	5.64 (d, J=20.0 Hz)	-
5	6.47-7.31 (m, 10H)	2.24 (s, 3H)	5.69 (d, J=20.0 Hz)	-
6	6.34-7.32 (m, 7H)	2.26 (s, 3H)	5.67 (d, J=20.0 Hz)	6.29 (d, J=8.0 Hz)
7	6.43-7.23 (m, 7H)	2.17 (s, 3H)	5.45 (d, J=20.0 Hz)	8.07 (d, J=9.2 Hz)
8	6.39-7.27 (m, 10H)	2.32 (s, 3H)	5.54 (d, J=20.0 Hz)	8.0 (d, J=8.0 Hz)
9	6.5-7.1 (m)	-	5.6 (d, J=20.0 Hz)	-
10	6.5-7.1 (m)	-	5.6 (d, J=20.0 Hz)	-
11	6.5-7.0 (m)	-	5.6 (d, J=20.0 Hz)	-
12	6.5-7.5 (m)	-	5.6 (d, J=19.6 Hz)	-

a = TMS as internal standard b = ppm δ

and model compounds. The oxygen attached carbon (7a) is resonated as a doublet in the region δ 141.20-143.86 (d, ²J_{P-O-C} = 10 Hz) and C-3a gave a doublet in the range δ 130.1 - 131.27 (d, ³J_{P-N-C} ≈ 10 Hz). The down field signal of C-7a is due to *ortho* effect of oxygen atom. Nitrogen attached carbon (3a) is also deshielded and resonated in the range δ 130.1 -131.3 as a doublet (d, ²J_{P-O-C} / ²J_{P-N-C} = 2-4 Hz), C-1' is resonated as a doublet due to coupling with phosphorus in the region of δ 115.0 -121.05 (d, ²J_{P-O-C} = 5 Hz). The remaining carbons are resonated in the expected region. ³¹P NMR spectral data for all the title compounds are given in TABLE 2. ³¹P NMR chemical shifts of these compounds appeared in the region 59.62 – 67.37 ppm for compounds (3-8) and for compounds (9-12) with a value – 41.5 ppm^[14]. The LCMS data of compounds (6-12) are presented in the TABLE 5.

TABLE 4: ¹³C NMR spectral data^a of compounds (3-12)

Comp.	Chemical Shifts in δ ppm
3	115.5 (C-4), 121.7 (C-5), 127.7 (C-6), 115.5 (C-7), 142.4 (C-7a), 130.4 (C-3a), 20.6 (C-5-CH ₃), 152.3 (C-1'), 110.1 (C-2'), 127.7 (C-3'), 120.4 (C-4'), 147.8 (C-5'), 118 (C-6'), 128.5 (C-7'), 117.8 (C-8'), 142.4 (C-9')
4	116.0 (C-4), 120.3 (C-5), 127.8 (C-6), 116.0 (C-7), 141.8 (C-7a), 130.2 (C-3a), 20.4 (C-5-CH ₃), 146.2 (C-1'), 116.3 (C-2'), 129.6 (C-3'), 120.6 (C-4'), 134.4 (C-5'), 122.7 (C-6')
5	116.4 (C-4), 119.2 (C-5), 129.3 (C-6), 115.2 (C-7), 141.8 (C-7a), 130.6 (C-3a), 20.8 (C-5-CH ₃), 110.6 (C-1'), 152.3 (C-2'), 116.6 (C-3'), 129.8 (C-4'), 127.4 (C-5'), 122.6 (C-6'), 125.8 (C-7'), 126.0 (C-8'), 133.7 (C-9'), 129.7 (C-10')
6	115.0 (C-4), 119.8 (C-5), 130.7 (C-6), 115.0 (C-7), 141.9 (C-7a), 130.7 (C-3a), 20.6 (C-5-CH ₃), 141.9 (C-1'), 115.0 (C-2'), 119.8 (C-3'), 117.7 (C-4'), 130.7 (C-5'), 119.8 (C-6'), 18.6 (C-2'CH ₃)
7	115.7 (C-4), 120.7 (C-5), 130.2 (C-6), 116.2 (C-7), 142.5 (C-7a), 130.9 (C-3a), 20.0 (C-5-CH ₃), 150.3 (C-1'), 129.6 (C-2'CH ₃), 126.8 (C-3'CH ₃), 118.3 (C-4')
8	116.6 (C-4), 120.2 (C-5), 129.03 (C-6), 116.3 (C-7), 141.2 (C-7a), 130.1 (C-3a), 20.3 (C-5-CH ₃), 141.0 (C-1'), 110.2 (C-2'), 126.9 (C-3'), 118.1 (C-4'), 127.8 (C-5'), 126.8 (C-6'), 124.3 (C-7'), 120.7 (C-8'), 123.8 (C-9'), 132.9 (C-10')
9	120.68 (C-4), 124.06 (C-5), 129.28 (C-6), 110.54 (C-7), 143.81 (C-7a), 131.27 (C-3a), 143.84 (C-1'), 124.69 (C-2'), 131.06 (C-3'), 125.27 (C-4'), 129.26 (C-5'), 121.10 (C-6')
10	120.54 (C-4), 121.66 (C-5), 131.01 (C-6), 110.43 (C-7), 143.81 (C-7a), 131.22 (C-3a), 143.81 (C-1'), 125.14 (C-2'), 139.33 (C-3'), 125.37 (C-4'), 128.84 (C-5'), 117.89 (C-6') CH ₃ /CH ₂ -(21.1)
12	121.05 (C-4), 125.04 (C-5), 131.06 (C-6), 110.51 (C-7), 143.86 (C-7a), 131.06 (C-3a), 148.94 (C-1'), 125.57 (C-2'), 131.27 (C-3'), 122.80 (C-4'), 129.25 (C-5'), 120.69 (C-6')

a = TMS as internal standard

TABLE 5: Mass spectral data of compounds 3, 6-12

Compound	m/z (%)
3	331 (M+3, 6), 330 (M+2, 35), 329 (M+1, 100), 282(7)
6	292 (M+2, 15), 291 (M+1, 100).
7	322 (M+1, 3), 321 (M ⁺ , 100), 320 (M-1, 2).
8	326 (M ⁺ , 100), 325 (M-1, 3), 311(5), 282 (2)
9	318 (15), 317 (10), 316 (15), 315 (20), 314 (50), 313 (20), 312 (100)
10	316 (15), 315 (10), 314 (63), 313 (14), 312 (100) (M ⁺ +CH ₃)
11	316 (22), 314 (72), 313(15), 312(100)
12	316 (10), (M ⁺ +1), 315 (8) (M ⁺), 314 (52), 313 (14), 312 (100)

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