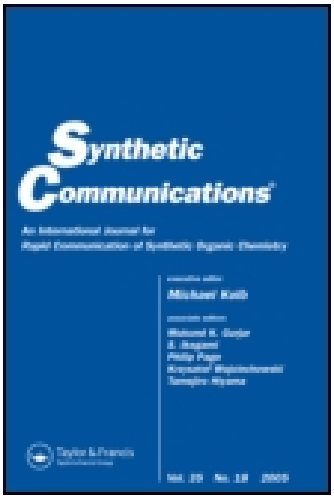

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Synthesis of New Benzoxazaphosphinine/ Benzoxazaphosphole/ Diazaphosphaphenalene-2-sulfides using Lawesson's Reagent

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Abstract: Synthesis of new benzoxazaphosphinine/benzoxazaphosphole/diazaphosphaphenalene 2-sulfides were accomplished by the reaction of Lawesson's reagent (LR) with 4-bromo-2-[(phenylamino) methyl]phenol (**1a**), 4-bromo-2-[(4-chloro/bromo/methoxy/methylphenyl-amino)methyl]phenol (**1b–e**), 4-bromo-2-[(benzylamino)methyl]phenol (**1f**), 2-amino-4-chlorophenol (**2a**)/2-amino-4-methylphenol (**2b**), 1,8-diaminonaphthalene (**3**) respectively in anhydrous toluene. Products **4a–f**, **5a–b** and **6** were characterized by IR, ^{1}H, ^{13}C, ^{31}P NMR and Mass spectra.

Keywords: benzoxazaphosphinine/benzoxazaphosphole/diazaphosphaphenalene 2-sulfides, Lawesson's reagent

INTRODUCTION

Interest has increased in the past 20 years in the chemistry of phosphorus heterocyclics because of their unique physicochemical properties[1] and potential biological activities.[2–5] Many classes of phosphorus hreterocyclic systems bearing P-O and P-N moieties such as cyclophosphamide and its derivatives are antitumor agents.[6] Cyclic phosphorus-containing hexapyranose analog modified at the anomeric carbon are regulators in the carbohydrate-linked life process.[7] 1,4-Dihydropyridine-5-cyclic phosphonate derivatives have

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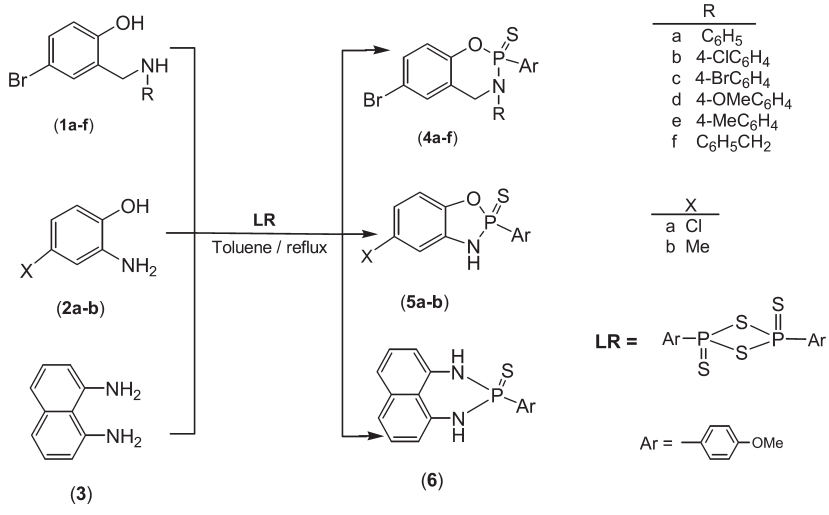
antihypertensive activity.[8] The reaction between Lawesson's reagent (LR) and aliphatic[9] and aromatic[9] diols run in boiling toluene led to exclusively cyclic anisylphosphonothioates. This readiness of diol derivatives to undergo intramolecular cyclization[10] led to the synthesis of five- and seven-membered phosphorous heterocycles. LR, widely known as a powerful thionation reagent in organic synthesis, offers another route to complexes containing P/S-based anionic ligands.[11,12] The burgeoning field of heterocyclic phosphorus compounds with LR has been fully reviewed.[10–13] As a continuation of our work[14] on synthesis and bioactive phosphorus heterocycles, a few new five- and six-membered phosphorus heterocycles have been synthesized by reacting **1a–f**, **2a–b**, and **3** with 2,4-*bis*(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (LR).

RESULTS AND DISCUSSION

On reaction with **1a–f** prepared by condensation of various aromatic amines, 4-bromophenol, and aqueous formaldehyde,[17,20] LR, **2a–b**, and **3** in anhydrous toluene in 1:1 molar ratio at reflux temperature under nitrogen atmosphere for 6–8 h afforded the heterocycles **4a–f**, **5a–b**, and **6** in moderate yields (Scheme 1). Their chemical structures are confirmed by elemental analysis; IR (Table 1); ^{1}H, ^{13}C, and ^{31}P NMR (Table 2); and mass spectra. Characteristic absorption bands for P═S, P-O, and O-$C_{(aromatic)}$ stretching vibrations were observed for them in the regions 732–763, 923–998 and 1205–1225 cm^{-1} respectively.[15,16] Compounds



Scheme 1.

Table 1. Physical and IR spectral data of **4**, **5**, and **6**

				Elemental analysis (%) found (calcd.)			IR (cm^{-1})			
Compd.	Mp (°C)	Yield (%)	Mol. formula (mol. wt)	C	H	N	P═S	P-O	$O\text{-}C_{(aromatic)}$	N-H
4a	122–124	39.6	$C_{20}H_{17}BrNO_2PS$ (446.30)	53.89 (53.82)	3.82 (3.84)	3.17 (3.14)	752	978	1212	—
4b	170–173	40.4	$C_{20}H_{16}BrClNO_2PS$ (480.74)	49.96 (49.97)	3.29 (3.35)	2.88 (2.91)	756	990	1205	—
4c	182–184	38.6	$C_{20}H_{16}Br_2NO_2PS$ (525.19)	45.82 (45.74)	3.01 (3.07)	2.61 (2.67)	753	969	1225	—
4d	142–144	38.3	$C_{21}H_{19}BrNO_3PS$ (476.32)	52.90 (52.95)	3.96 (4.20)	2.91 (2.94)	750	998	1225	—
4e	147–150	41.3	$C_{21}H_{19}BrNO_2PS$ (460.32)	54.72 (54.79)	4.06 (4.16)	3.02 (3.04)	752	989	1225	—
4f	174–176	42.0	$C_{21}H_{19}BrNO_2PS$ (460.32)	54.73 (54.79)	4.11 (4.16)	3.07 (3.04)	749	979	1216	—
5a	194–196	32.0	$C_{13}H_{11}ClNO_2PS$ (311.72)	50.12 (50.09)	3.48 (3.56)	4.43 (4.49)	738	924	1217	3215
5b	187–189	32.6	$C_{14}H_{14}NO_2PS$ (291.31)	57.69 (57.72)	4.81 (4.84)	4.83 (4.81)	742	923	1221	3219
6	210–213	40.2	$C_{17}H_{15}N_2OPS$ (326.35)	62.51 (62.56)	4.57 (4.63)	8.41 (8.58)	763	—	—	3285

Table 2. (^{1}H, ^{13}C, and ^{31}P) NMR spectral data (δ, $CHCl_3$) of **4**, **5**, and **6**

Compd.	^{1}H NMR	^{13}C NMR	^{31}P NMR
4a	6.27–8.01 (m, 12H, H_{Ar}), 3.99–4.14 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3)	—	88.59
4b	6.88–7.80 (m, 11H, H_{Ar}), 4.47–4.85 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3)	51.61, 55.40, 113.99, 114.15, 121.05, 127.37, 129.24, 129.55, 132.22, 144.90, 149.27, 162.98	77.86
4c	6.88–8.0 (m, 11H, H_{Ar}), 4.44–4.90 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3)	51.39, 55.37, 113.92, 114.08, 116.43, 120.95, 122.46, 126.49, 129.48, 131.00, 132.39, 142.38, 148.38, 163.31	77.80
4d	6.73–7.84 (m, 11H, H_{Ar}), 4.36–4.84 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3)	52.13, 55.32, 113.73, 113.94, 114.29, 119.08, 120.94, 128.27, 128.76, 129.47, 131.87, 136.54, 149.35, 163.01	78.59
4e	6.77–7.82 (m, 11H, H_{Ar}), 4.42–4.86 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3)	20.85, 51.73, 55.35, 113.77, 113.93, 116.19, 118.60, 126.21, 126.81, 129.69, 130.08, 131.92, 140.55, 149.66, 163.22	78.21
4f	6.77–8.26 (m, 12H, H_{Ar}), 4.53–5.15 (m, 2H, CH_2), 3.87 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3)	46.76, 55.52, 114.08, 117.58, 118.63, 120.23, 121.12, 127.43, 128.13, 128.63, 130.11, 132.69, 134.18, 136.22, 138.01, 150.18, 161.58, 163.95	81.08
5a	6.91–8.23 (m, 7H, H_{Ar}), 5.35 (d, $J = 10.7$ Hz, 1H, NH), 3.85 (s, 3H, OCH_3)	—	67.04
5b	6.71–8.23 (m, 7H, H_{Ar}), 5.28 (s, 1H, NH), 3.87 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3)	20.77, 55.53, 114.10, 123.23, 126.46, 127.61, 133.76, 134.43	70.96
6	6.57–7.71 (m, 10H, H_{Ar}), 5.47 (d, $J = 10.9$ Hz, 1H, NH), 3.69 (s, 3H, CH_3)	55.32, 110.10, 113.85, 114.00, 120.83, 127.12, 132.35, 136.67	43.88

4a–**f**, **5a**–**b**, and **6** exhibited a complex multiplet at 6.27–8.26 ppm for aromatic protons. Methylene protons in **4a**–**f** resonated as multiplets at δ 3.99–5.15 indicating their nonequivalence and coupling with phosphorus.[17] It is interesting to observe a doublet for the NH in **5a** and **6**, while **5b** gave as a singlet for it at δ 5.28–5.47. The observed ^{13}C NMR chemical shifts for them

are in the expected range.[17,18] ^{31}P NMR signals[19] of **4a–f**, **5a–b**, and **6** appeared at 67.04–81.08 and 43.88 ppm, respectively. The mass spectra for **4e** and **6** as representatives were recorded. **4e** (FABMS): m/z (%) = 461 [47, $(M^+ + 2)$], 459 [43, $(M^{+\bullet})$], 428 (36), 380 (17), 353 (24), 290 (40), 274 (49), 242 (25), 136 (65) and **6** (LCMS): m/z (%) = 327 [100, $(M^+ + 1)$], 279 (21), 260 (10), 238 (8), 217 (3.5), 148.9 (8).

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed at the Central Drug Research Institute, Lucknow, India. The IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit. All ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on an AMX 400-MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 161.9 MHz for ^{31}P. Compounds were dissolved in $CDCl_3$, and the chemical shifts were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P).

4-Bromo-2-[(4-chlorophenylamino)methyl]phenol (1b)

To a stirred and cooled (10–20°C) solution of aqueous formaldehyde (37%; 7.5 mL, 0.1 mol) in 1,4-dioxane (30 mL), 4-chloroaniline (11.10 g, 0.1 mol) was added at 15–20°C. To the stirred reaction mixture, a solution of 4-bromophenol (17.3 g, 0.1 mol) in 1,4-dioxane (20 mL) was added dropwise through a dropping funnel, and the resulting solution was kept at gentle reflux for 1 h. Upon removal of 1,4-dioxane and water by a rotary evaporator, a sticky mass remained, which was recrystallized with 95% ethanol to yield[20] **1b** (26.5 g, 75%), mp 80–82°C.

Similarly **1a**, and **1c–f** were prepared using corresponding aromatic amines. LR was prepared according to published procedure.[21]

General Procedure for Synthesis of 4a–f, 5a and b, and 6

A three-necked flask equipped with a dropping funnel, stirrer, dry $CaCl_2$ tube and nitrogen gas inlet was charged with 10 mL of anhydrous toluene and 1 mmol of **1a–f**, **2a–b**, and **3**. Lawesson's reagent (1 mmol) was added to the flask at room temperature, and the reaction mixture was refluxed with stirring under dry nitrogen for 6–8 h until no starting materials could be detected on thin-layer chromatography (TLC). Evaporation of solvent followed by column chromatography on silica gel using petroleum ether–ethyl acetate (8:2) as eluent afforded corresponding heterocycles **4a–f**, **5a–b**, and **6**. Their yields were determined after separation on a silica-gel column, and structures were confirmed by elemental analysis and spectral data.

CONCLUSION

A simple methodology was developed for the synthesis of several six-membered benzoxazaphosphinine 2-sulfides, benzoxazaphosphole 2-sulfides, and diazaphosphaphenalene 2-sulfide, which are of value as potential antibacterials.

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