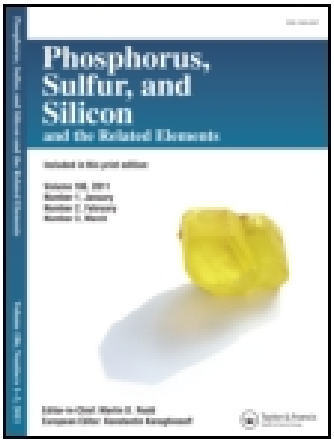

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An Efficient Route for the Synthesis of 3-(4-Bromophenyl)-2-Phenyl-3,4-Dihydro-2H-Benzo[E][,32,]Oxazaphosphinine, its P-Chalcogenides and Metal Complexes

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AN EFFICIENT ROUTE FOR THE SYNTHESIS OF 3-(4-BROMOPHENYL)-2-PHENYL-3,4-DIHYDRO-2*H*-BENZO[*E*][1,3,2]OXAZAPHOSPHININE, ITS *P*-CHALCOGENIDES AND METAL COMPLEXES

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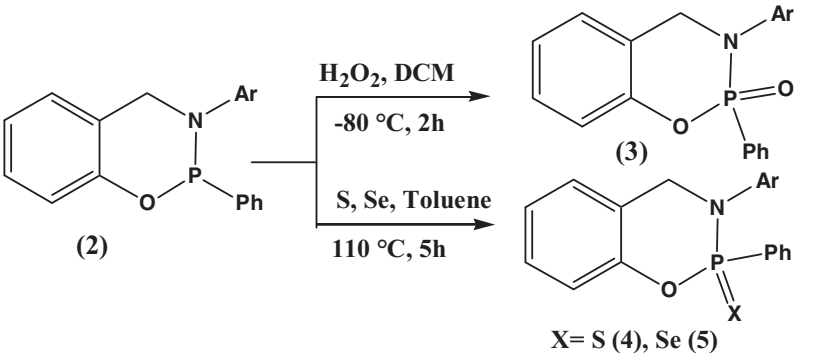
GRAPHICAL ABSTRACT



Abstract *2-[(4-bromophenylamino)-methyl]-phenol (**1**) gave substantially pure 3-(4-bromophenyl)-2-phenyl-3,4-dihydro-2H-benzo[e][1,3,2]- oxazaphosphinine (**2**) on cyclization with phenyldichlorophosphine in toluene at 0 °C. Reaction of **2** with H_2O_2 in dichloromethane gave selectively **3**. P-chalcogenides (**4** and **5**) were prepared by reacting **2** with elemental S and Se powder in toluene, whereas the tungsten pentacarbonyl complex **6** was prepared by reacting **2** with [$W(CO)_5(CH_3CN)$] in tetrahydrofuran at 25 °C.*

Supplementary materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfer, and Silicon and the Related Elements *for the following free supplemental files:* Additional figures.

Keywords 2*H*-benzo[*e*][1,3,2]oxazaphosphinine; phenyldichlorophosphine; *p*-chalcogenides; cyclization; heterocycles

INTRODUCTION

Many important medicines, dyes, and insecticides are found in the series of heterocyclic compounds, called oxazines,[1] thiazines,[2] and oxazaphosphinine.[3] They are mainly

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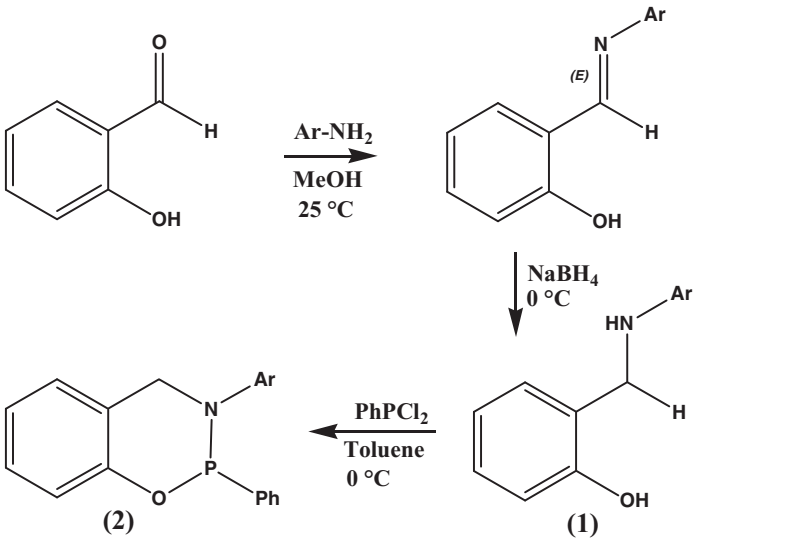
found in the polycyclic divisions in which other rings, such as the benzene ring, are fused to the oxazines, thiazine, or oxazaphosphinine rings. Cyclophosphamide containing an oxazaphosphinine is a proven alkylating antitumor agent against a broad spectrum of human cancers including slow-growing solid tumors.[4] Organophosphorus heterocycles containing oxygen and nitrogen in a six-membered ring also have high antitumor activity,[5] significant bioactivity, and outstanding medicinal properties. Therefore, the clinical significance and the unique conformational and stereochemical aspects of oxazaphosphinines have attracted much interest in drug design and synthesis.[6]

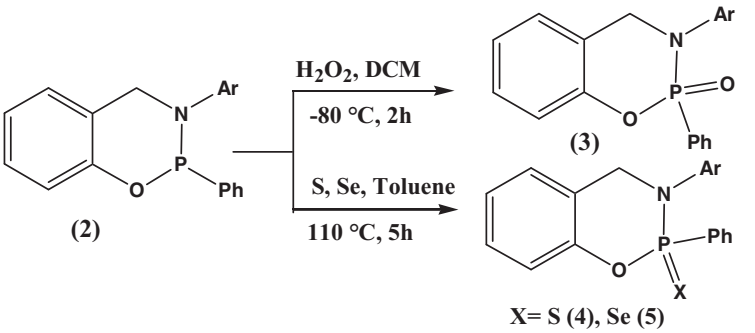
Among previous reported processes, Reddy et al.[7] has reported the synthesis of oxazaphosphinine oxides by condensation of 2-[[4-(2-hydroxy-benzylamino)-phenylamino]methyl]phenol with phosphorousoxychloride. Reddy et al.[8] presented the synthesis and chemoselective ring openining of benzoxazaphosphonones with N-sodium salt of amino heterocyclics. Keglevich et al.[9] has demonstrated the synthesis of substituted dibenzo[*c,e*][1,2]oxaphosphorine under microwave conditions in presence of $ZnCl_2$. Recently, Wagner et al.[10] has reported the spectral assignment of Phenanthrene derivatives based on 6*H*-dibezo[*c,e*][1,2]oxaphosphinine 6-oxides by NMR and quantum calculations. They have discussed the complex P–C and P–H coupling pattern and compared with the derivatives possessing different chemical environments around the phosphorus atom.

RESULT AND DISCUSSION

The synthesis of benzoxazaphosphinine involves, cyclization of 2-[(4-Bromophenylamino)-methyl]-phenol[11] (**1**) with Phenyldichlorophosphine in presence of triethylamine in dry toluene at 0 °C to afford 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2]-oxazaphosphinine **(2)** (Scheme 1). The P-oxide[12] derivative **3** was selectively prepared by reacting **2** with hydrogen peroxide (H_2O_2) in dry dichloromethane



Scheme 1



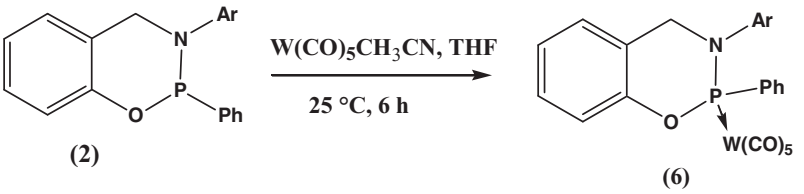
Scheme 2

at −80 °C (Scheme 2). The P-chalcogens[13] **4** and **5** were prepared by reacting 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2]oxazaphosphinine with elemental sulfur and selenium powder in dry toluene at 110 °C, respectively (Scheme 2). Tungsten pentacarbonyl complex **6** was prepared by reacting **2** with $[W(CO)_5CH_3CN]$ in tetrahydrofuran at 25 °C and purified by recrystallization with diethyl ether (Scheme 3).

All the compounds exhibited characteristic IR absorption bands for P═O, P═S, and P═Se functional groups in the normal region 1251.7, 673.1, and 584.4 cm^{-1} showing that they are not involved in hydrogen bonding. Characteristic absorption bands for P–O–(C_{ar}) and (P)–O–C($_{ar}$) stretching vibrations were observed in the region 999–935 and 1190–1150 cm^{-1} respectively.[14] Tungsten pentacarbonyl complex shows characteristic absorption bands for –CO stretching vibrations in the region 1928.7, 1996.2, and 2077.2 cm^{-1}.

In the ^1H NMR spectra, the aromatic protons resonated as multiples in the region 6.87–7.85. Methylene protons resonate as multiplets at δ 4.09–4.83 indicating their nonequivalence and coupling with phosphorus in the six-membered chair-like conformation of the benzoxazaphosphinine system. The ^{13}C NMR chemical shifts were interpreted based on comparison with carbon chemical shifts, additivity rules and intensity of the signals and coupling with phosphorus. Carbon bonded to endocyclic oxygen gave signals at 151.7–149.1. The methylene chemical shift appears in region 59.3–45.5. The carbonyl carbons of $W(CO)_5$ were appears in the region 195.1–198.9. The remaining carbon shifts were observed in the expected regions.

^{31}P NMR chemical shifts for benzoxazaphosphinine, P═O, P═S, and P═Se were observed at 112.8, 13.4, 76.7, and 82.4 respectively. Coupling constants [$^1J_{31P\text{-}77Se}$ and $^1J_{183W\text{-}31P}$] of 826.7 and 326.7 Hz respectively are within the usual ranges found.[13] GC–MS of all the compounds exhibited molecular (M^+) and characteristic daughter ion peaks at



Scheme 3

their respective expected m/z values. A dominant isotopic effect was observed for all the compounds because of having bromine atom. A pattern of +1 and +2 molecular mass was observed in mass fragments.

EXPERIMENTAL

All commercially available reagents were used after suitable purification and re-crystallization. Melting points are uncorrected. Fourier Transform Infra Red (FTIR) spectra were obtained using KBr pellets on Shimadzu FTIR-8700. Carbon, hydrogen, and nitrogen (CHN) were analyzed on a EURO EA 3000 Elemental analyzer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AV300 MHz spectrophotometer at 300, 75, and 121.5 MHz respectively in $CDCl_3$ solution with TMS as internal and 85% Phosphoric acid as external standard. The chemical shifts are reported in ppm. Chemical shifts are designated using the following abbreviations: s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were recorded on Agilent/ Shimadzu GCMS QP2010plus instrument, equipped with flame ionization detector (FID) system and fused-silica capillary columns (30 m, 0.25 mm i.d., film thickness 0.25 μm, Restek, France), Rtx-5 (95% dimethyl/5% diphenyl polysiloxane). All solvents were distilled and purified by standard procedures. TLC was performed on plates coated with silica gel 60 with F_{254} indicator; column chromatography was carried out on silica gel 60 (60–120 mesh).

Synthesis of 2-[(4-Bromophenylamino)-methyl]-phenol (1)[11]

2-[(4-Bromo-phenylamino)-methyl]-phenol was prepared by reacting salicyldehyde (12.2 g, 0.10 mole) with p-bromoaniline (17.2 g, 0.10 mole) in methanol at room temperature. The mixture was stirred at 25 °C for 60 min and poured into ice water. The separated product was collected by filtration and recrystallized with methanol. The re-crystallized Schiff base was dissolved in methanol; sodium borohydride (9.5 g, 0.25 mol) was added lot wise at 0 °C over a period of 30 min. The contents were further stirred for 3 h at 25 °C. The solvent was removed under vacuum, added water to precipitate the product. Filter the crystallized product and wash with water to get crude product. The crude product thus obtained was recrystallized with methanol to get **1** as white crystalline solid. Yield 22.5 g (81.0%), mp 125–126 °C.

Synthesis of 3-(4-Bromophenyl)-2-phenyl-3, 4-dihydro-2*H*-benzo[*e*][1,3,2]- oxazaphosphinine (2)

Under a nitrogen atmosphere, solution of phenyldichlorophosphine (0.36 g, 2 mmol) in dry toluene (20 mL) was added drop wise to a cooled (0 °C) solution of 2-[(4-Bromophenylamino)-methyl]-phenol (0.56 g, 2 mmol) and triethylamine (0.58 mL, 4 mmol) in dry toluene (40 mL). After addition, the reaction mixture was stirred for an additional 2 h at 20 °C. The salt thus formed was removed by separation under nitrogen and the solvent was removed under reduced pressure to obtain semi solid product. The product thus obtained was purified by low temperature column chromatography (SiO_2, 0 °C, Hexane: THF; 98:2). Evaporation of the solvents of the second fraction and re-crystallization from diethyl ether at 5 °C yielded **2** as white crystalline solid. Yield 0.27 g (36%); mp 118–119 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 112.8; FTIR (cm^{-1}) 979.8, 1153.4 (P–O–$C_{aromatic}$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26–4.49 (m, 2H, $ArCH_2N$), 6.68–7.67 (m, 13H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.7, 114.7, 121.2, 121.4, 122.2, 125.6, 127.6, 128.3, 128.8, 129.0, 129.4, 130.0, 130.8, 132.1, 132.3; GC–MS m/z: 383.00, Mass fragments, 199.95

(43.5), 201.95 (40.6), 303.10 (39.0), 382.05 (93.7), 383.05 (32.8), 384.05 (100.0), 385.00 (33.4); Elemental analysis Calculated for $C_{19}H_{15}BrNOP$: C, 59.40; H, 3.94; N, 3.65. Found: C, 59.38; H, 3.87; N, 3.57.

Synthesis of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-benzo[*e*][1,3,2]-oxazaphosphinine-2-oxide (3)

Under a nitrogen atmosphere, To a precooled dichloromethane solution of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2]oxazaphosphinine (0.79 g, 2 mmol) at −80 °C, H_2O_2 solution (0.34 mL, 3 mmol) was added drop wise and stirring was continued for 30 min at −80 °C and 1 h at 25 °C. The solvent was removed under reduced pressure and the product was separated by low-temperature column chromatography (SiO_2, 0 °C, Hexane: THF; 98:2). Evaporation of the solvents of the second fraction and re-crystallization from diethyl ether at 5 °C yielded **3** as off white crystalline material. Yield 0.60 g (74%); mp 124–125 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 13.4; FTIR (cm^{-1}) 1251.7 (P=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50–4.69 (m, 2H, $ArCH_2N$), 7.05–7.62 (m, 13H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.1, 118.9, 124.3, 124.8, 125.6, 126.7, 128.5, 128.7, 129.5, 130.6, 131.5, 131.7, 132.2, 132.7, 149.5; GC-MS m/z: 399.00, Mass fragments, 77.05 (28.5), 167.10 (49.7), 243.00 (20.8), 244.00 (100.0), 398.95 (79.2), 399.95 (51.8), 400.95 (75.6), 401.95 (16.0); Elemental analysis Calculated for $C_{19}H_{15}BrNO_2P$: C, 57.02; H, 3.78; N, 3.50. Found: C, 57.00; H, 3.73; N, 3.41.

Synthesis of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-benzo[*e*][1,3,2]-oxazaphosphinine-2-sulfide (4)

Under a nitrogen atmosphere, solution of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2]oxazaphosphinine (0.39 g, 1 mmol) and elemental sulfur (0.32 g, 10 mmol) in toluene 20 mL was heated at 110 °C for 5 h. The resulting dark brown solution was filtered hot under nitrogen and concentrated under reduced pressure. The crude product thus obtained was separated by low-temperature column chromatography (SiO_2, 0 °C, Hexane: THF; 98:2). Evaporation of the solvents of the second fraction and re-crystallization from diethyl ether at 5 °C yielded **4** as yellow crystalline solid. Yield 0.20 g (48%); mp 116–117 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 73.7; FTIR (cm^{-1}) 673.1 (P=S); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52–4.81 (m, 2H, $ArCH_2N$), 7.04–7.88 (m, 13H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 119.2, 119.3, 124.1, 126.7, 127.5, 127.6, 128.4, 128.6, 129.4, 131.4, 131.5, 132.1, 132.6, 149.3; GC–MS m/z: 414.9, Mass fragments, 199.85 (18.3), 303.05 (42.7), 381.90 (100.0), 382.95 (22.8), 383.95 (93.1), 384.95 (20.8), 414.90 (18.9), 416.90 (19.0); Elemental analysis Calculated for $C_{19}H_{15}BrNOPS$: C, 54.82; H, 3.63; N, 3.36. Found: C, 54.36; H, 3.73; N, 3.38.

Synthesis of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-benzo[*e*][1,3,2]-oxazaphosphinine-2-selenide (5)

Under a nitrogen atmosphere, solution of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2]oxazaphosphinine (0.39 g, 1 mmol) and elemental selenium powder (0.79 g, 10 mmol) in toluene (20 mL) was heated at 110 °C for 5 h. The resulting dark brown solution was filtered while hot under nitrogen and concentrated under reduced pressure. The crude product thus obtained was purified by re-crystallization from diethyl

ether at 5 °C yielded **5** as orange crystalline solid. Yield 0.19 g (42%); mp 132—133 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 82.4 (s, $^1J_{P\text{-}Se} = 876.7$ Hz); FTIR (cm^{-1}) 584.4 (P=Se); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.39–4.83 (m, 2H, $ArCH_2N$), 6.88–7.85 (m, 13H, aromatic); ^{1}H –Depth: δ 51.7 (s, 2H, $ArCH_2N$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.8, 119.2, 119.3, 124.1, 124.3, 126.8, 127.8, 128.3, 128.5, 129.3, 131.6, 131.8, 132.0, 132.9, 149.9; GC-MS m/z: 463.0, Mass fragments, 199.95 (30.4), 202.00 (27.9), 303.15 (39.1), 382.10 (100.0), 383.15 (23.6), 384.10 (94.1), 385.15 (23.9), 463.05 (5.2); Elemental analysis Calculated for $C_{19}H_{15}BrNOPSe$: C, 49.27; H, 3.26; N, 3.02. Found: C, 49.16; H, 3.23; N, 3.01.

Synthesis of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-benzo[*e*][1,3,2]-oxazaphosphinine-W(CO)$_5$ complex (6)

Under a nitrogen atmosphere, solution of 3-(4-Bromophenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2]oxazaphosphinine (0.38 g, 1 mmol) and $W(CO)_5CH_3CN$ (0.40 g, 1.1 mmol) in 20 mL tetrahydrofuran was stirred at 25 °C for 6 h. The resulting dark brown solution was filtered under nitrogen and concentrated under reduced pressure. The crude product thus obtained was separated by low-temperature column chromatography (SiO_2, 0 °C, Hexane: diethyl ether; 98:2). Evaporation of the solvents of the second fraction and re-crystallization from diethyl ether at 5 °C yielded **6** as off white crystalline solid. Yield 0.54 g (76%); mp 112–113°C. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ 125.5 (s, $^1J_{P\text{-}W} = 326.7$ Hz); FTIR (cm^{-1}) 1928.7, 1996.2, and 2077.2 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.09–4.67, (m, 2H, $ArCH_2N$), 6.75–7.67 (m, 13H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.7, 119.6, 121.3, 121.8, 121.9, 123.1, 127.4, 128.3, 128.9, 130.6, 130.8, 132.9, 140.7, 141.4, 146.4, 151.6, 195.2, 195.3, 198.5, 198.9; GC-MS m/z: 383.00, Mass fragments, 77.05 (22.1), 107.00 (21.0), 122.05 (21.5), 155.00 (21.2), 157.00 (20.5), 199.90 (100.0), 201.90 (98.7), 306.00 (43.1), 308.00 (43.9), 382.05 (37.2), 383.05 (78.3), 384.05 (49.9), 385.05 (75.5); Elemental analysis Calculated for $C_{24}H_{15}BrNO_6PW$: C, 40.71; H, 2.14; N, 1.98. Found: C, 40.37; H, 2.10; N, 1.89.

CONCLUSION

Triethylamine promoted low-temperature cyclization of 2-[(4-Bromophenylamino)-methyl]-phenol with Phenyldichlorophosphine gave substantially pure 3-Aryl-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3,2] oxazaphosphinine, 2-oxide, *P*-chalcogenides, and tungsten complex on further reaction with DMSO, elemental S and Se powders and with $W(CO)_5$. These novel heterocycles contain exocyclic C–O–P=X and endocyclic O–P–N bond systems are not reported so far and are likely to posses remarkable stability and biological activity, which ultimately have better prospects in the medicinal world.

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