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Synthesis of 3-(4-Methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine and Its Chalcogenides

MANJU RANI, DAVENDER KUMAR SHUKLA and ARIF ALI KHAN*

University School of Basic and Applied Sciences, Guru Gobind Singh Indraprastha University, Dwarka, Sector 16C, New Delhi-110 078, India

*Corresponding author: E-mail: khanaarif@hotmail.com

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A simple method for the synthesis of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (**2**) is described. P-Chalcogenides of (**2**) can be prepared by reacting with S, Se powder in toluene at 110 ºC. Whereas the tungsten pentacarbonyl complex (**6**) can be prepared by reacting (**2**) with $W(CO)_5CH_3CN$ in THF at 20-25 ºC.

Key Words: Phosphorous-heterocycles, Oxazaphosphinine, Phosphorous-chalcogenides.

INTRODUCTION

Organic compounds being ubiquitous in nature have found multifaceted applications. The chemistry of phosphorus-heterocycles and their derivatives have received considerable attention because of their biological activities[1,2]. Cyclophosphamide containing an oxazaphosphinine is proven alkylating antitumor agent against a wide spectrum of human cancer including slow-growing solid tumours[3]. The organophosphorus heterocycles containing O and N in a six-membered ring possess high antitumor and antimicrobial activity[4]. The clinical significance and unique confirmation and stereochemical aspects of oxazaphosphinines have attracted much interest in drug design and synthesis[5]. The common approach for the synthesis of oxazaphosphinine by cyclization with phosphoryl chloride and thiophosphoryl chloride is described in the literature[6-8].

Herein, we reported a new method to synthesize oxazaphosphinine and its chalcogenides from the readily available starting precursors.

EXPERIMENTAL

Starting materials and solvents were obtained from Merck and Spectrochem and were used with further purification. Low temperature coloumn chromatography performed with dried silica gel. IR spectra were measured on a Shimadzu IR-460 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a bruker DRX-250 Avance spectrometer at 250.0 and 62.5 MHz, respectively. Progress of reaction was monitored by TLC as well as ^{31}P NMR and no side products were observed. Mass spectra were recorded on a Shimadzu GC-MS mass spectrometer operating at an ionization potential of 20 eV.

Procedure for the preparation of compounds

Synthesis of 2-[(4-methyl-phenylamino)methyl]phenol (1): Prepared according to the literature[9].

Synthesis of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (2): A solution of phenyldichlorophosphine (2 mmol) in dry toluene (20 mL) was added drop wise to a cooled (0-5 ºC) solution of 2-[(4-methyl-phenylamino)methyl]phenol (2 mmol) and triethylamine (4 mmol) in dry toluene (40 mL). After addition, the reaction mixture was stirred for an additional 2-3 h at 20-25 ºC. The salt thus formed was removed by filteration under nitrogen and the solvent was removed under reduced pressure to obtain semi solid material. The product thus obtained was purified by low temperature column chromatography (SiO_2, 5 ºC, hexane:THF; 98:2). Evaporation of the solvents of the second fraction and recrystallization from diethyl ether at 5 ºC yielded 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo-[e][1,3,2]oxazaphosphinine as offwhite crystalline solid, yield 38 %, m.p. 116-117 ºC.

Synthesis of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine-2-oxide (3): To a pre-cooled dichloromethane solution of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (2 mmol) at -80 ºC, DMSO (3 mmol) was added drop wise and stirring was continued for 0.5 h at -80 ºC and 2 h at 20-25 ºC. The solvent was removed under reduced pressure and the product was separated by low-temperature column chromatography (SiO_2, 5 ºC, Hexane: THF; 98:2). Evaporation of the solvents of the second fraction and recrystallization from diethyl ether at 5 ºC yielded 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-benzo[e][1,3,2]-oxazaphosphinine-2-oxide as Creamish crystalline solid. Creamish crystalline solid, yield 80 %, m.p. 100-101 ºC.

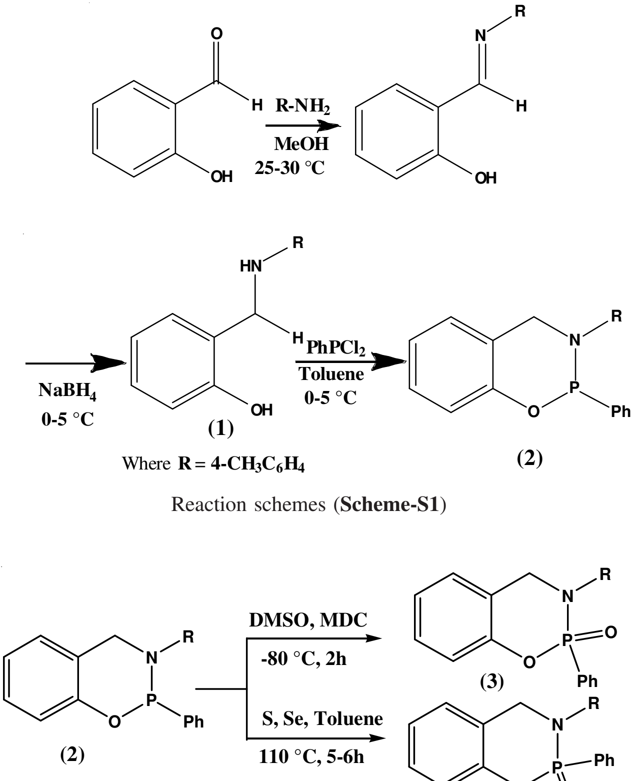
Synthesis of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine-2-sulphide (4): A solution of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (1 mmol) and elemental sulfur (10 mmol) in 20 mL toluene was heated at 108-110 ºC for 5-6 h. The resulting 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, 5 ºC, hexane: THF; 98:2). Evaporation of the solvents of the second fraction and recrystallization from diethyl ether at 5 ºC yielded 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine-2-sulphide as yellow crystalline solid. Yellow crystalline solid, Yield 28 %, m.p. 92-93 ºC.

Synthesis of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine-2-selenide (5): A solution of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (1 mmol) and elemental selenium powder (10 mmol) in 20 mL toluene was heated at 108-110 ºC for 6-7 h. The resulting reddish brown solution was filtered hot under nitrogen and concentrated under reduced pressure. The crude product thus obtained was separated by recrystallization from diethyl ether at 5 ºC yielded 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2] oxazaphosphinine-2-selinide as orange crystalline solid. Yield 32 %, m.p. 122-123 ºC.

Synthesis of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine-$W(CO)_5$ complex (6): A solution of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (1 mmol) and $W(CO)_5CH_3CN$ (1.1 mmol) in 20 mL THF was stirred at 25-30 ºC for 6-8 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, 5 ºC, hexane: diethyl ether; 98:2). Evaporation of the solvents of the second fraction and recrystallization from diethyl ether at 5 ºC yielded 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e]-[1,3,2]oxazaphosphinine-$W(CO)_5$ complex as off white crystalline solid. Yield 60 %, m.p. 100-101 ºC.

RESULTS AND DISCUSSION

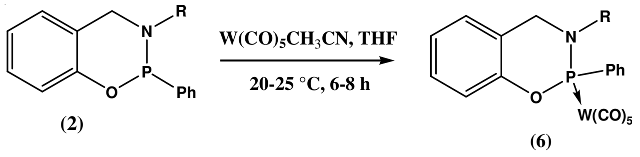
The intermediate 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine (**2**) was obtained from cyclocondensation of 2-[(4-methyl-phenylamino)methyl]-phenol with dichlorophenylphosphine in equimolar quantities in presence of triethylamine in dry toluene at room temperature (35 ºC) overnight yielded title compound. The P-oxide derivative (**3**) was selectively prepared by reacting 3-(4-methyl-phenyl)-2-phenyl-3,4dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine (**2**) with DMSO in dry MDC at -80 ºC. The P-chalcogenides (**4**) and (**5**) were prepared by reacting 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]-oxazaphosphinine with elemental sulphur and selenium powder in dry toluene at 110 ºC. Tungten pentacarbonyl complex (**6**) was prepared by reacting (**2**) with $W(CO)_5CH_3CN$ in THF at 20-25 ºC and purified by recrystallization with diethyl ether[10,11]. They were characterized by IR, ^1H, ^{13}C, ^{31}P NMR and GC-MS spectroscopic data. The infrared spectra of 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-benzo[e][1,3,2]-oxazaphosphinine-2-selenide (**5**) shows a strong and sharp absorption band at 586.3 cm^{-1} which has been assigned to -P=Se stretching absorption vibrations. The proton magnetic resonance spectrum of compound (**5**) shows two doublet at δ 4.454-4.906 for two methylene protons ($ArCH_2N$) which confirms the protons present are non equivalent. All the aromatic protons appear as multiplet 6.998-7.918 for 13H. The phosphorus magnetic resonance spectrum of compound (**5**) shows a doublet at δ 82.932 with a coupling constant of 871.3 Hz, due to phosphorous selenium coupling. In the carbon magnetic resonance spectrum of compound (**5**) shows fifteen carbon, which are well in accordance to the proposed structure. A dominant peak at δ 52.08 confirms the methylene carbon atom. Carbon bonded to endocyclic oxygen gave signals at 140.67. Rest of thirteen peaks at δ 119.30, 123.88, 124.48, 126.49, 126.78, 128.13, 128.33, 129.09, 129.57, 131.63, 131.80, 132.58, 135.95 fairly confirms the aromatic carbons. Mass spectral data of compound (**5**) shows molecular ion peaks corresponding to the molecular mass 399.02 with further fragments at 91.00 (18.00), 135.95 (41.20), 318.00 (100.00), 319.00 (23.61), 398.90 (1.87).



Where **R = 4-CH$_3$C$_6$H$_4$**

Reaction schemes (**Scheme-S1**)

Reaction scheme (**Scheme-S2**)



Reaction scheme (**Scheme-S3**)

TABLE-1
ELEMENTAL ANALYSIS OF COMPOUNDS **2-6**

Comp. No.	m.f.	Elemental analysis (%) found (calcd.)		
		C	H	N
2	$C_{20}H_{18}NOP$	75.16(75.22)	5.62 (5.68)	4.31(4.39)
3	$C_{20}H_{18}NO_2P$	71.56(71.63)	5.39 (5.41)	4.09(4.18)
4	$C_{20}H_{18}NOPS$	68.26(68.36)	5.01 (5.16)	3.89(3.99)
5	$C_{20}H_{18}NOPSe$	60.13(60.31)	4.49 (4.56)	3.50(3.52)
6	$C_{25}H_{18}NO_6PW$	46.56(46.68)	2.75 (2.82)	2.12(2.18)

TABLE-2
^{1}H NMR SPECTRAL DATA OF COMPOUNDS **2-6**

Compound No	^{1}H NMR Data
2	δ 2.260 (s, 3H, $ArCH_3$), 4.456-4.906 (dd, 2H, $ArCH_2N$), 7.032-7.944 (m, 13H, aromatic).
3	δ 2.265 (s, 3H, $ArCH_3$), 4.658-4.708 (dd, 2H, $ArCH_2N$), 7.043-7.712 (m, 13H, aromatic).
4	δ 2.271(s, 3H, $ArCH_3$), 4.509-4.820 (dd, 2H, $ArCH_2N$), 7.046-7.893 (m, 13H, aromatic).
5	δ 2.259 (s, 3H, $ArCH_3$), 4.454-4.906 (dd, 2H, $ArCH_2N$), 6.998-7.918 (m, 13H, aromatic).
6	δ 2.342 (s, 3H, $ArCH_3$), 4.104-4.667 (dd, 2H, $ArCH_2N$), 6.736-7.694 (m, 13H, aromatic).

TABLE-3
^{31}P NMR SPECTRAL DATA OF COMPOUNDS **2-6**

Compound No.	^{31}P NMR	Coupling constant
2	112.813	–
3	13.773	–
4	77.065	–
5	82.932	Doublet, J = 871.3 Hz
6	125.254	Triplet, J = 325.620 Hz

TABLE-4
^{13}C NMR SPECTRAL DATA OF COMPOUNDS **2-6**

Compound No.	^{13}C NMR Data
2	δ 20.93, 52.12, 119.24, 123.90, 124.61, 126.48, 126.80, 128.15, 128.35, 129.11, 129.59, 131.66, 132.60, 135.96, 140.76, 150.07.
3	δ 20.76, 51.63, 118.82, 123.91, 124.07, 125.14, 126.59, 128.32, 128.52, 129.24, 129.84, 130.53, 131.65, 131.78, 132.34, 139.94, 150.37.
4	δ 20.91, 52.15, 119.22, 123.85, 126.26, 126.68, 128.25, 129.13, 129.62, 131.34, 131.49, 132.29, 135.72, 140.76, 150.68.
5	δ 20.91, 52.08, 119.30, 123.88, 124.48, 126.49, 126.78, 128.13, 128.33, 129.09, 129.57, 131.63, 131.80, 132.58, 135.95, 140.67.
6	δ 21.05, 51.83, 119.60, 122.25, 122.42, 122.86, 127.41, 128.42, 128.59, 128.95, 129.04, 129.11, 130.39, 130.44, 137.48, 144.77, 144.88, 151.87, 195.30, 195.41.

TABLE-5
GC-MASS SPECTRAL DATA OF COMPOUNDS **2-5**

Compound No.	GC-Mass data
2	m/z 319.10, mass fragments 91.10 (28.25), 136.05 (100.00), 242.05 (44.65), 318.00 (22.65), 319.10 (53.59).
3	m/z 335.10, mass fragments: 91.05 (21.09), 229.05 (25.61), 244.00 (42.92), 258.05 (20.76), 270.10 (20.76), 334.10(47.53), 335.10 (100.00).
4	m/z: 351.00, mass fragments: 91.00 (22.63), 135.95 (30.32), 318.00 (100.00), 319.00 (22.13), 351.00 (15.12).
5	m/z: 399.02, mass fragments: 91.00 (18.00), 135.95 (41.20), 318.00 (100.00), 319.00 (23.61), 398.90 (1.87).

TABLE-6
INFRARED SPECTRAL DATA OF COMPOUNDS **2-6**

Compound No.	Absorption peaks (cm^{-1})
2	947.0, 1128.3 (P-O-$C_{aromatic}$)
3	1245.9 (P=O)
4	688.5 (P=S)
5	586.3 (P=Se)
6	941.2, 1155.3, 1994.3 and 2075.3 (CO)

Conclusion

An efficient method is described to synthesize 3-(4-methyl-phenyl)-2-phenyl-3,4-dihydro-2*H*-benzo[e][1,3,2]oxazaphosphinine and its chalcogenides. Simple and readily available starting materials, fairly short reaction time and good to excellent yields of the products are advantages of this method.

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