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Received October 6, 2004

The efficient preparation of *cis*-3-(*N*-arylamino)-2-phenylnaphtho[1,3-*d*]-1,2-oxaphosphole 2-oxides **4** and **5** is described by a three-component reaction involving phenyldichlorophosphine (**2**) 1-hydroxy-2-naphthaldehyde/1-hydroxy-2-acetonaphthone (**1**) and different substituted amines (**3**) in anhydrous benzene. The stereo structure, of the products (**4** and **5**), as well as the reaction mechanism of the cyclization is discussed. The title compounds (**4** and **5**) were fully characterized by NMR and mass spectral data. Their anti microbial activity was evaluated

*J. Heterocyclic Chem.*, **42**, 775 (2005).

### Introduction.

The chemistry of organophosphorus heterocycles has received much attention due to their unique structural features and diverse application in biology and industry. A large number of them were synthesized in the past two decades [1-6]. Although several methodologies for the synthesis of various phosphorus heterocycles have been developed, only a very few approaches were reported for the synthesis of 2,3-dihydro-1,2-benzoxaphosphole 2-oxides. Ageeva [7], Miles [8] and their coworkers [9] reported two different routes for the synthesis of the 2,3-dihydro-1,2-benzoxaphosphole 2-oxide ring system. However, synthesis of the 3-amino oxazaphosphole system is not known. Herein, a new and efficient one-pot synthesis of 3-(*N*-arylamino)-2-phenylnaphtho[1,3-*d*]-1,2-oxaphosphole 2-oxides under mild conditions is reported.

### Results and Discussion.

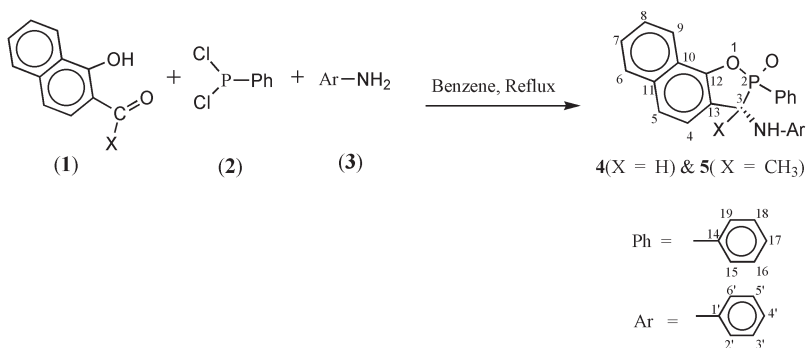
Synthesis of *cis*-3-(*N*-arylamino)-2-phenylnaphtho[1,3-*d*]-1,2-oxaphosphole 2-oxides (**4**) and (**5**) in 72-82% yield

was accomplished by Mannich-type reaction of phenyldichlorophosphine (**2**) with 1-hydroxy-2-naphthaldehyde/1-hydroxy-2-acetonaphthone (**1**) and different substituted aromatic amines (**3**) in dry benzene under reflux with stirring for 6-7 h (Scheme 1).

The possible reaction mechanism is of  $S_N2$  - type with retention of configuration. The chemical structures of all the new compounds (**4**, **5**) were confirmed by elemental analysis,  $^{31}\text{P}$ ,  $^{13}\text{C}$  and  $^1\text{H}$  NMR [10,11] (Table 1, 2, 3 and 4) and IR [12-14] (Table 1) spectral analysis. The EI/MS spectra of **4** and **5** show the existence of strong molecular ion peaks, indicating that the heterocyclic skeletons are of some stability under the EI/MS conditions.

Theoretically formation of two stereoisomers of **4** and **5** is possible in this reaction because of the presence of two different substituents at  $\text{C}_3$  and P in the rigid oxaphosphole ring. However, the  $^{31}\text{P}$  NMR spectra of **4** and **5** exhibited only one signal instead of two [14]. In the  $^1\text{H}$  NMR spectra of **4** also the  $\text{C}_3\text{-H}$  proton signal appeared as a doublet only ( $\delta = 5.69\text{-}6.12$ ,  $^2J_{\text{P,CH}}$  of  $\sim 8.0$  Hz) due to its coupling with

Scheme 1



Compd.	Ar	Compd.	Ar
<b>4a &amp; 5a</b>	C <sub>6</sub> H <sub>4</sub> Cl(4')	<b>4d &amp; 5d</b>	C <sub>6</sub> H <sub>4</sub> (OCH <sub>3</sub> )(4')
<b>4b &amp; 5b</b>	C <sub>6</sub> H <sub>4</sub> Br(4')	<b>4e &amp; 5e</b>	C <sub>6</sub> H <sub>3</sub> Cl(3')F(4')
<b>4c &amp; 5c</b>	C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> (4')	<b>4f &amp; 5f</b>	C <sub>5</sub> H <sub>4</sub> N

Table 1  
Physical, IR and  $^{31}\text{P}$  NMR Spectral Data of **4** and **5**

Compd.	mp(°C)	Yield (%)	Mol.formula (Mol.wt)	Elemental analysis Found(Calcd)%			IR			$^{31}\text{P}$ NMR
				C	H	N	P=O	P-C <sub>(aliphatic)</sub>	N-H	
<b>4a</b>	146-148	72	C <sub>23</sub> H <sub>17</sub> O <sub>2</sub> PNCl (405.6)	68.65 (68.77)	4.22 (4.23)	3.45 (3.46)	1256	736	3410	13.20
<b>4b</b>	182-184	78	C <sub>23</sub> H <sub>17</sub> O <sub>2</sub> PNBr (450.0)	61.33 (61.53)	3.80 (4.79)	3.11 (3.10)	1203	746	3448	14.31
<b>4c</b>	190-192	74	C <sub>24</sub> H <sub>20</sub> O <sub>2</sub> PN (385.2)	74.78 (74.91)	5.23 (5.22)	3.64 (3.63)	1229	732	3440	14.01
<b>4d</b>	128-130	82	C <sub>24</sub> H <sub>20</sub> O <sub>3</sub> PN (401.4)	71.81 (71.73)	5.02 (5.04)	3.49 (3.50)	1220	740	3408	13.02
<b>4e</b>	210-212	76	C <sub>23</sub> H <sub>16</sub> O <sub>2</sub> PNCIF (423.6)	65.16 (65.22)	3.81 (3.80)	3.31 (3.32)	1214	735	3404	13.34
<b>4f</b>	151-153	73	C <sub>22</sub> H <sub>17</sub> O <sub>2</sub> PN <sub>2</sub> (372.1)	70.95 (70.81)	4.60 (4.60)	7.52 (7.53)	1196	726	3440	14.65
<b>5a</b>	168-170	72	C <sub>24</sub> H <sub>20</sub> O <sub>2</sub> PNCl (420.6)	68.48 (68.62)	4.79 (4.80)	3.33 (3.34)	1210	739	3412	14.67
<b>5b</b>	205-207	76	C <sub>24</sub> H <sub>20</sub> O <sub>2</sub> PNBr (465.1)	61.93 (62.00)	4.33 (4.32)	3.01 (3.00)	1210	746	3372	14.31
<b>5c</b>	250-252	79	C <sub>25</sub> H <sub>23</sub> O <sub>2</sub> PN (400.2)	74.97 (74.89)	5.79 (5.80)	3.50 (3.51)	1230	740	3390	13.60
<b>5d</b>	231-233	81	C <sub>25</sub> H <sub>22</sub> O <sub>3</sub> PN (415.4)	72.28 (72.12)	5.34 (5.35)	3.37 (3.38)	1205	736	3422	14.02
<b>5e</b>	208-210	77	C <sub>24</sub> H <sub>19</sub> O <sub>2</sub> PNCIF (438.6)	65.67 (65.56)	4.37 (4.38)	3.19 (3.20)	1202	735	3422	14.64
<b>5f</b>	108-110	79	C <sub>23</sub> H <sub>20</sub> O <sub>2</sub> PN <sub>2</sub> (387.2)	71.29 (71.37)	5.21 (5.20)	7.24 (7.22)	1242	732	3398	14.18

Table 2  
 $^{13}\text{C}$  NMR Spectral Data of Some Members of **4** and **5** [a]

Compd.	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-3	C(3)-C
<b>4a</b>	119.16	127.34	127.34	129.91	125.16	129.21	139.32	130.26	147.45 (d, J=6.8)	147.45 (d, J=7.8)	72.52 (d, J=116.8)	-
<b>4c</b>	118.74	128.75	128.89	129.92	124.85	129.92	135.81	130.81	148.00 (d, J=7.7)	148.00 (d, J=7.75)	51.91	-
<b>4d</b>	118.76	124.89	128.76	130.27	125.295	130.273	137.521	130.01	147.73 (d, J=8.1)	147.73	51.28	-
<b>4e</b>	118.91	128.78	128.82	131.63	122.12	131.63	130.60	130.15	146.34 (d, J=8.6)	146.34 (d, J=8.6)	51.6	-
<b>5a</b>	119.24	128.66	128.66	129.78	125.005	130.065	139.30	130.06	148.02 (J=8.4)	148.02 (J=8.4)	60.29	24.30
<b>5b</b>	118.14	128.58	129.84	129.84	126.80	130.67	130.24	130.01	149.20	149.20	69.89	25.30
<b>5c</b>	118.72	128.17	128.88	130.12	125.77	130.87	137.96	130.53	148.18 (d, J=11.5)	148.18 (d, J=11.5)	61.02	24.03
<b>5d</b>	118.46	127.62	128.88	130.10	125.59	130.04	139.18	130.43	146.75	146.75	70.12	25.41
<b>5f</b>	118.11	125.29	126.22	132.09	126.92	127.68	132.66	130.11	150.44	150.44	75.22 (d, J=117.1)	22.96

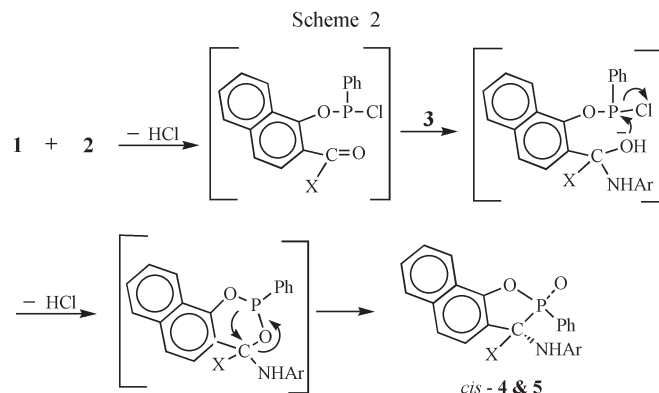
[a]J (Hz) in parenthesis.

phosphorus instead of expected doublet of doublet for two isomers [15]. The  $^2J_{\text{PCH}}$  coupling constants of *cis*-isomers in similar systems are reported in the range of 2.0 - 8.0 Hz while for the *trans*-isomer the value is 15.0 - 20.0 Hz. Appearance of only one  $^{31}\text{P}$  NMR chemical shift and C<sub>3</sub>-H NMR signal as doublet instead of doublet of doublet with coupling constant corresponding to those of *cis*-isomers in similar systems suggested that the compounds **4** and **5** formed are the *cis*-forms. The steric hindrance of the bulky

phenyl groups at C<sub>3</sub> and P appears to control the stereochemistry of this reaction.

#### Antimicrobial Activity.

All the members of **4** and **5** were screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* (10<sup>6</sup> cell/ml) by the disc diffusion method [16] in nutrient agar medium. Three concentrations of **4** and **5** (100, 250 and 500 µg/disc) dissolved in dimethylfor-



mamide (DMF) were added to each filter disc and DMF was used as control. Plates were incubated at 37 °C and examined for zone of inhibition around each disc after 24 h. The results were compared with standard antibiotic penicillin (250 µg / disc). Their antifungal activity [17] was also evaluated against *Aspergillus niger* and *Helminthosporium oryzae* at concentrations of 100, 250 and 500 µg/disc. Griseofulvin was used as reference compound. The fungal cultures were grown on potato dextrose broth at 25 °C for 72 h and finally spore suspension was adjusted to 10<sup>5</sup> spores/ml. It is interesting to observe that the 3-(4'-aminopyridine) substituted compound (**4f**) exhib-

Table 3

<sup>13</sup>C NMR Spectral Data of Some Members of 4 and 5 [a]

Compd.	<b>4a</b>	<b>4c</b>	<b>4d</b>	<b>4e</b>	<b>5a</b>	<b>5b</b>	<b>5c</b>	<b>5d</b>	<b>5f</b>
C-14	148.12 (d, J=101.5)	148.70 (d, J=81.4)	150.21 (d, J=101.9)	147.95 (d, J=103.1)	148.20 (d, J=102.5)	148.81 (d, J=101.6)	148.70 (d, J=91.5)	147.95 (d, J=105.5)	133.54 (d, J=89.1)
C-15	129.63	122.52	117.82	123.72	119.81	125.73	122.52	123.72	122.23
C-16	129.87	130.95	130.30	139.58	129.89	130.82	130.95	139.58	124.83
C-17	125.03	130.46	127.35	136.30	134.59	127.40	130.46	136.30	125.29
C-18	129.78	130.27	130.30	122.10	119.93	136.90	130.27	122.10	124.83
C-19	129.66	118.77	117.82	118.30	118.50	120.15	118.77	118.30	120.56
C-1'	139.32	139.39	139.32	135.81	136.076	146.79	139.39	135.81	132.58
C-2'	124.80	125.00	125.55	121.68	121.60	113.86	125.00	121.68	127.79
C-3'	128.78	128.84	128.82	126.72	127.43	130.44	128.84	126.72	150.44
C-4'	129.82	129.85	129.87	129.74	129.84	123.74	129.85	129.74	150.44
C-5'	128.78	128.84	128.82	126.72	127.43	130.44	128.84	126.72	128.87
C-6'	124.80	125.20	125.55	121.68	121.60	113.86	125.20	121.68	-
Ar-C/O-C	-	16.90	30.2	-	-	-	16.90	31.04	-

[a] J (Hz) in parentheses.

Table 4

<sup>1</sup>H NMR Spectral Data [a] of 4 and 5

Compd.	Aromatic-H	N-H	P-C-H/P-C-CH <sub>3</sub>	Ar-CH <sub>3</sub> / Ar-OCH <sub>3</sub>
<b>4a</b>	6.54-6.79 (m,15H)	8.12(s)	6.12 (d, J=7.9)	-
<b>4b</b>	6.52-7.78 (m,15H)	8.72(s)	5.69 (d, J = 8.1)	-
<b>4c</b>	6.85-7.30 (m,15H)	8.54(bris)	5.90 (d, J = 8.2)	2.27(s)
<b>4d</b>	6.52-8.24 (m,15H)	8.60(s)	5.67 (d, J = 8.7)	3.56(s)
<b>4e</b>	6.68-7.73 (m,14H)	8.30(s)	6.04 (d, J = 8.0)	-
<b>4f</b>	6.67-7.12 (m,15H)	8.13(s)	5.91 (d, J = 8.2)	-
<b>5a</b>	6.59-7.67 (m,18H)	8.24(s)	2.1 (d, J=8.2)	-
<b>5b</b>	7.02-7.73 (m,18H)	8.12(bris)	2.09 (d, J=7.9)	-
<b>5c</b>	7.08-7.79 (m,18H)	8.51(s)	2.12 (d, J=7.7)	2.26(s)
<b>5d</b>	7.05-8.18 (m,17H)	8.29(s)	2.08 (d, J=8.3)	3.40(s)
<b>5e</b>	6.78-7.69 (m,17H)	8.01(s)	2.09 (d, J=8.1)	-
<b>5f</b>	7.02-8.18 (m,18H)	8.18 (d, J = 7.12)	1.73 (d, J=8.5)	-

[a] J(Hz) given in parenthesis.

ited more antibacterial activity while the 3-(4'-bromophenyl) (**5b**) and 3-(4'-methyl) substituted compounds (**4c**) showed equal antimicrobial activity than that of the standard (Table 5).

Research Scholar, Department of Botany, Sri Venkateswara University, Tirupati for her help in antimicrobial studies, the Director of CDRI, Lucknow and SIF, IISC, Bangalore for the elemental and the spectral data and UGC, New Delhi for providing Financial Assistance.

Table 5  
Antimicrobial Activity of **4** and **5** in Terms of Zone of Inhibition (mm)

Compd.	Fungi						Bacteria					
	<i>Aspergillus niger</i>			<i>Helminthosporium oryzae</i>			<i>Escherichia coli</i>			<i>Staphylococcus aureus</i>		
	500	250	100	500	250	100	500	250	100	500	250	100
<b>4a</b>	21	12	5	19	10	7	24	11	5	26	11	6
<b>4b</b>	19	13	6	19	9	6	23	10	4	25	11	6
<b>4c</b>	19	10	5	18	6	4	24	12	5	21	9	-
<b>4d</b>	20	12	4	19	8	5	22	10	3	22	11	6
<b>4e</b>	18	14	4	20	10	8	22	11	5	26	10	5
<b>4f</b>	24	13	4	17	9	6	21	13	4	21	10	5
<b>5a</b>	21	12	5	20	12	6	23	10	3	20	10	6
<b>5b</b>	22	12	5	19	11	6	20	12	-	24	11	4
<b>5c</b>	19	13	3	16	8	5	21	11	5	24	12	5
<b>5d</b>	20	12	4	17	8	5	25	10	4	22	11	6
<b>5e</b>	24	14	6	19	11	6	24	9	4	20	12	5
<b>5f</b>	23	13	5	18	10	5	22	9	3	21	11	4
Control*	16			17			12			14		

\*Indicates no activity; \* Griseofulvin for fungi and Penicillin for bacteria.

## EXPERIMENTAL

Melting points were taken on Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. IR spectra were recorded as KBr pellets and Nujol mulls on a Perkin Elemer 283 unit. The  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$  NMR spectral were taken on AMX 400 MHz spectrometer operating at 400 MHz for  $^1\text{H}$ , 100 MHz for  $^{13}\text{C}$  and 161.9 MHz for  $^{31}\text{P}$ . Compounds were dissolved in  $\text{DMSO}-d_6$ . The chemical shifts in  $\delta$  were referenced to TMS ( $^1\text{H}$  and  $^{13}\text{C}$ ) and 85 %  $\text{H}_3\text{PO}_4$  ( $^{31}\text{P}$ ). Mass spectra were recorded on a Hewlett-Packard 5988 instrument.

1-Hydroxy-2-naphthaldehyde and 1-hydroxy-2-acetonaphthone (**1**) are procured from Aldrich Chemical Company, Inc, USA. Dichlorophenylphosphine (**2**) is procured from Lancaster Synthesis Ltd., Lancashire, England and were used without further purification.

### General Procedure for Preparation of **4** and **5**.

To a stirred solution of aromatic amine **3** (5 mmol) and phenyldichlorophosphine (**2**, 0.89 g, 5 mmol) in anhydrous benzene (15 ml), a solution of 1-hydroxy-2-naphthaldehyde/1-hydroxy-2-acetonaphthone **1** (5 mmol) in anhydrous benzene (15 ml) was added drop wise at room temperature. Stirring was continued at room temperature for another 0.5 h after which the mixture was heated under reflux for 6-7 h and cooled. A white precipitate formed that was collected by filtration and recrystallized from a 1:1 mixture of  $\text{CHCl}_3$ /petroleum ether (bp 60-90 °C) to give pure *cis*- **4** and **5**.

### Acknowledgements.

The authors express thanks to Ms. M D. Kamar Jahan,

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