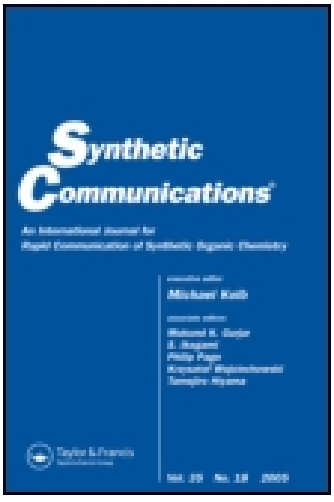

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Synthesis of Novel (3a,S)-1-Aryl/aryloxy/alkoxy-3a,4-dihydro-3H-1λ^5-[1,3,2]oxazaphospho[3,4-a] indole-1-ones, Thiones, and Selenones

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Synthesis of Novel (3a,S)-1-Aryl/aryloxy/alkoxy-3a,4-dihydro-3*H*-1λ^5-[1,3,2]oxazaphospholo [3,4-a] indole-1-ones, Thiones, and Selenones

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Abstract: Synthesis of novel (3a,S)-1-aryl/aryloxy/alkoxy-3a,4-dihydro-3*H*-1λ^5-[1,3,2]oxazaphospholo [3,4-a] indole-1-ones, thiones, and selenones was achieved in two steps with high yields from 2,3-dihydro-1*H*-indol-2(S)yl methanol (**1**) and dichlorophenyl phosphine/ethyl dichlorophosphite (**2a** and **b**) in the presence of triethylamine in dry THF followed by treatment with hydrogen peroxide, sulfur, and selenium. The compounds **4g–k** have been synthesized by the direct cyclocondensation of **1** with different substituted phenyl phosphorodichloridates (**2c–e, g**) and bis(2-chloroethyl) phosphoramidic dichloride (**2f**).

Keywords: Dichlorophenyl phosphine, 2,3-dihydro-1*H*-indol-2(S)yl methanol, 2-ethyl(S)-carboxyindole

INTRODUCTION

Extensive investigation of compounds containing P-N linkages by numerous research groups have led to many interesting and far-reaching developments.[1] Organophosphorus heterocycles bearing P-N functionality have shown antitumor, pesticidal, and medicinal activity.[2–4] Since the ingenious introduction of chiral catalysts containing the N-P═O structural framework

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by Wills,[5–7] there has been an increasing interest in the development of novel classes of chiral catalysts containing the N-P═O structural framework. A few chiral catalysts containing the N-P═O structural framework having the (5S)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo [3.3.0] octane moiety with amino groups of varying steric requirements on phosphorus have been synthesized, and their applications in the borane-mediated asymmetric reduction of prochiral ketones to alcohols with enantiomer excess have been studied.[8–10] Recently, we turned our attention to chiral phosphoramides as part of our ongoing research program, and we have synthesized the novel chiral phosphoramides, characterized by spectral data.

RESULTS AND DISCUSSION

Synthesis of novel (3a,s)-1-aryl/aryloxy/alkoxy-3a,4-dihydro-3*H*-1λ^5-[1,3,2]oxaza phospholo[3,4-a]indole-1-ones, thiones, and selenones **4a–f** was accomplished in two steps. The synthetic route involves the cyclization of equimolar quantities of 2,3-dihydro-1*H*-indole-2(S)-yl methanol (**1**) with dichlorophenylphosphine/ethyldichlorophosphite **2a** and **b** in the presence of triethylamine in dry tetrahydrofuran at 45–50 °C. They were further converted to the corresponding oxides, sulfides, and selenides by reacting them with hydrogen peroxide, sulfur, and selenium respectively. Compounds **4g–k** were prepared by the direct cyclocondensation of equimolar quantities of **1** with various aryl phosphorodichloridates **2c–e**, **2 g**, and bis(2-chloroethyl) phosphoramidic dichloride **2f** in the presence of triethylamine in dry tetrahydrofuran at 45–50 °C. Purification of these products **4a–k** was achieved by filtering the reaction mixture to separate the triethylamine hydrochloride, evaporating the filtrate in a rotaevaporator under vacuum to obtain a residue, washing it with water, and recrystallzing it from ethanol. Physical data along with IR absorptions, elemental analysis, and ^{31}P NMR of **4a–k** are given in Table 1. Tables 2–4 contain ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra showed characteristic bands[11,12] at 1276–1228 (P═O), 807–804 (P═S), 685–684 (P═Se), 786–721 (P-N_{aliph}), and 1172–1130 (P-O_{aliph}) cm^{-1}.

The ^{1}H NMR spectra of **4a–k** (Table 2) showed[13] a doublet for H-3 at δ 3.87–3.71 (J = 38.2–25.3 Hz), and H-4 gave a signal at δ 3.53–3.31 (J = 7.3–4.8 Hz). H-3a, which is attached to the chiral carbon resonated as a multiplet in the range of 5.23–4.21 ppm. The ^{13}C NMR spectra (Table 3) were recorded for a few members of the title compounds (**4b**, **c**, **j**, and **i**). The chemical shifts for C-4a, C-5, C-6, C-7, C-8, and C-8a appeared at 128.3–127.2, 126.8–124.6, 130.0–128.1, 124.7–120.3, 136.7–129.1, and 142.6–136.2 respectively. The oxygen-bearing C-3 resonated[8] at 58.3–53.6 ppm as a doublet ($^{2}J_{POC}$ = 5.2 Hz). The carbons of C-1′, C-(2′,6′), C-(3′,5′), and C-4′ of **4b** and **4c** gave chemical shifts at δ 130.4–130.2, 132.9–132.7, 127.8–127.6, and 131.8–131.7 respectively. The carbon chemical shifts of the phenoxy group in **4g** and **4i** were observed in the expected range.[13]

Table 1. Physical, IR, and ^{31}P NMR spectral data of **4a**–**k**

Compd.	Molecular formula	Mp (°C)	Yield[a]	Elemental analysis found (Calcd.) (%)			IR (cm^{-1})			^{31}P NMR[b,c]
				C	H	N	P═O/S/Se	P-N_{aliph}	P-O_{aliph}	
4a	$C_{15}H_{14}NO_2P$	113–115	62	66.36 (66.42)	5.09 (5.16)	5.13 (5.16)	1262	721	1161	15.50
4b	$C_{15}H_{14}NOPS$	135–137	68	62.62 (62.71)	4.83 (4.87)	4.81 (4.87)	804	778	1168	16.92
4c	$C_{15}H_{14}NOPSe$	152–154	63	53.80 (53.89)	4.13 (4.19)	4.10 (4.19)	685	751	1163	19.52
4d	$C_{11}H_{14}NO_3P$	103–105	58	55.19 (55.23)	5.79 (5.85)	5.82 (5.85)	1228	786	1186	2.45
4e	$C_{11}H_{14}NO_2PS$	117–119	67	51.70 (51.76)	5.46 (5.49)	5.43 (5.49)	807	762	1172	5.13
4f	$C_{11}H_{14}NO_2PSe$	130–132	61	46.11 (46.15)	4.84 (4.89)	4.85 (4.89)	684	768	1168	6.49
4g	$C_{15}H_{14}NO_3P$	119–121	67	62.63 (62.71)	4.82 (4.87)	4.84 (4.87)	1272	754	1169	3.82
4h	$C_{15}H_{13}NO_3PCl$	123–125	63	55.92 (55.98)	4.01 (4.04)	4.30 (4.35)	1276	753	1168	3.27
4i	$C_{15}H_{13}N_2O_5P$	109–111	65	54.15 (54.21)	3.86 (3.91)	8.38 (8.43)	1276	768	1138	5.02
4j	$C_{13}H_{17}N_2O_2PCl_2$	121–123	63	46.50 (46.56)	5.02 (5.07)	8.31 (8.35)	1262	774	1130	5.12
4k	$C_{15}H_{13}NO_3PBr$	128–130	60	49.11 (49.18)	3.59 (3.55)	3.79 (3.82)	1271	758	1165	3.51

[a]Recrystallized from ethanol.
[b]Recorded in $CDCl_3$.
[c]Chemical shifts in ppm from 85% phosphoric acid.

Table 2. ^{1}H NMR spectral data[a,b] of **4a–k**

Compd.	-OCH_2-	-CH-(3a)	-CH_2-(4)	Ar-H	R
4a	3.76 (d, 34.3, 2H)	5.16–4.92 (m)	3.46 (d, 6.5)	7.76–6.86 (m, 9H)	
4b	3.73 (d, 31.7, 2H)	5.23–4.95 (m)	3.47 (d, 7.3)	7.87–7.09 (m, 9H)	
4c	3.71 (d, 33.9, 2H)	5.18–4.91 (m)	3.53 (d, 6.2)	7.08–6.86 (m, 9H)	
4d	3.87 (d, 25.4, 2H)	5.16–4.94 (m)	3.32 (d, 5.1)	7.78–7.62 (m, 4H)	4.13 (q, 2H, OCH_2) 1.29 (t, 3H, CH_3)
4e	3.87 (d, 25.3, 2H)	5.19–4.96 (m)	3.35 (d, 4.8)	7.78–7.62 (m, 4H)	4.11 (q, 2H, OCH_2) 1.29 (t, 3H, CH_3)
4f	3.86 (d, 35.2, 2H)	5.23–4.91 (m)	3.31 (d, 5.3)	7.25–7.02 (m, 4H)	4.11 (q, 2H, OCH_2) 1.28 (t, 3H, CH_3)
4g	3.87 (d, 36.1, 2H)	5.17–4.96 (m)	3.32 (d, 7.0)	7.25–6.38 (m, 9H)	
4h	3.82 (d, 25.3, 2H)	5.11–4.93 (m)	3.35 (d, 6.3)	7.51–7.23 (m, 8H)	
4i	3.71 (d, 38.2, 2H)	5.19–4.83 (m)	3.32 (d, 5.1)	7.69–7.02 (m, 8H)	
4j	3.87 (d, 31.5, 2H)	4.49–4.21 (m)	3.31 (d, 7.3)	7.44–7.11 (m, 4H)	3.65–3.41 (m, 4H, CH_2Cl) 3.77-3.74 (m, 4H, -N-CH_2)
4k	3.79 (d, 27.2, 2H)	4.82–4.27 (m)	3.30 (d, 5.9)	7.53–7.27 (m, 8H)	

[a]Recorded in $CDCl_3$.
[b]Chemical shifts in ppm.

The ^{31}P NMR chemical shifts of the compounds **4d–k** appeared in the range of 6.49–2.45 ppm. Other members **4a–c** gave ^{31}P NMR chemical shifts in the expected[14] range depending on elements present at the phosphorus atom (i.e. P═O, P═S, and P═Se). Mass spectral analysis was made for four compounds (Table 4), and the data confirmed the structures of the title compounds (**4c**, **4e**, **4i**, and **4j**).

EXPERIMENTAL

The melting points were determined on a Mel-temp apparatus and are uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 unit; ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on an AM 400- MHz spectrometer, operating at 400 MHz for ^{1}H, 100 MHz for

Table 3. ^{13}C NMR chemical shifts[a,b] of some members of **4a–k**

Compd.	-CH_2 (3)	-CH (3a)	-CH_2 (4)	C-4a	C-5	C-6	C-7	C-8	C-8a	C_1'	C_2' and C_6'	C_3' and C_5'	C_4'
4b	58.2	45.8	31.2	127.7	124.6	128.3	120.3	129.6	138.5	132.9	130.4	127.8	131.8
4c	57.1	46.3	31.1	127.6	125.2	128.1	124.7	129.1	136.2	132.7	130.2	127.6	131.7
4g	58.3	46.1	32.3	127.2	125.0	128.5	121.7	129.3	138.4	148.2	130.8	127.3	131.5
4i	53.6	45.8	35.3	127.6	125.2	128.5	123.6	128.6	137.1	154.9	120.6	125.9	144.3

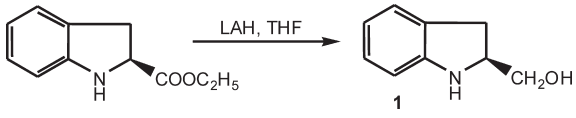
[a]Chemical shifts in ppm.
[b]Recorded in $CDCl_3$.

Table 4. Mass spectral data of **4c**, **4e**, **4i**, and **4j**

Compd.	m/z (Relative abundance)
4c	335 ($M^+ + 1$, 32), 334 ($M^{+\bullet}$, 18), 327 (9), 315 (13), 304 (7), 285 (6), 257 (17), 250 (14), 235 (28), 213 (78), 185 (22), 138 (100).
4e	256 ($M^+ + 1$, 28), 255 ($M^{+\bullet}$, 11), 241 (23), 237 (12), 212 (21), 203 (34), 197 (21), 183 (12), 177 (18), 152 (34), 138 (100).
4i	333 ($M^+ + 1$, 24), 332 ($M^{+\bullet}$, 16), 323 (3), 314 (3), 298 (5), 288 (4), 272 (8), 264 (7), 251 (12), 239 (6), 235 (12), 229 (56), 219 (9), 213 (14), 203 (8), 187 (6), 181 (9), 175 (22), 165 (9), 159 (100), 155 (12), 143 (9).
4j	339 ($M^+ + 4$, 35), 337 ($M^+ + 2$, 28), 335 ($M^{+\bullet}$, 11), 322 (5), 307 (2), 284 (16), 265 (4), 241 (3), 228 (8), 211 (5), 207 (8), 191 (4), 177 (84), 161 (57), 149 (41), 127 (36), 121 (23), 105 (15), 91 (12), 77 (13), 57 (31), 44 (100).

^{13}C, and 161.9 MHz for ^{31}P as solutions in $CDCl_3$. The chemical shifts were referenced to TMS (^1H and ^{13}C) and 85% H_3PO_4 (^{31}P) (Scheme 1).

Preparation of (2S)-2,3-Dihydro-1*H*-2-indolylmethanol (1)

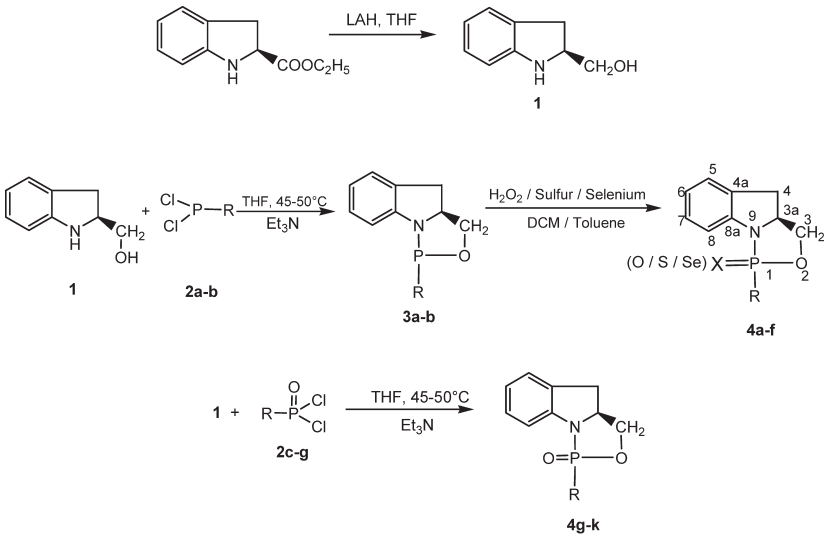


1

To a stirred and ice-cold suspension of $LiAlH_4$ (3.10 g, 0.0817 mol) in dry THF (100 mL), a solution of 2-ethyl(S)-carboxyindole (7.60 g, 0.039 mol) in dry THF (35 mL) was added dropwise. The mixture was stirred and refluxed for 3 h and then cooled, and the excess of $LiAlH_4$ was decomposed by the addition of a mixture of water (6.2 mL) and THF (50 mL). After stirring at room temperature for 1 h, the inorganic salts were filtered off and washed with hot EtOAc (3×50 mL). The combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino alcohol[14] as a crystalline product, which was filtered off, washed with Et_2O, and recrystallized from EtOAc. Yield: 4.03 g (68%), mp 127 °C.

Preparation of (3a,S)-1-Phenyl-3a,4-dihydro-3*H*-1λ^5-[1,3,2]oxazaphospholo[3,4-a]indol-1-one (4a)

To a cooled (0 °C) and stirred solution of 2,3-dihydro-1*H*-indole-2(S)yl methanol (**1**, 0.74 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 25 mL of dry tetrahydrofuran under nitrogen gas, a solution of dichlorophenylphosphine (**2a**, 0.895 g, 0.005 mol) in 10 mL of dry tetrahydrofuran was added over a period of 20 min. After completion of the addition, the temperature of the reaction



Compd.	R	X	Compd.	R
4a	C_6H_5	O	4g	OC_6H_5
4b	C_6H_5	S	4h	OC_6H_4-Cl(4′)
4c	C_6H_5	Se	4i	OC_6H_4-NO_2(4′)
4d	OC_2H_5	O	4j	$N(CH_2CH_2Cl)_2$
4e	OC_2H_5	S	4k	OC_6H_4-Br(4′)
4f	OC_2H_5	Se		

Scheme 1.

mixture was raised to 45–50 °C and stirred for 1 h to form the intermediate, 1-phenyl-3a(S),4-dihydro-3*H*-[1,3,2] oxazaphosphino[3,4-a]indole (**3a**). The progress of the reaction was judged by the thin-layer chromatography (TLC) of the reaction mixture. After completion of the reaction, it was filtered under nitrogen atmosphere. Triethylamine hydrochloride and the solvent were removed, from the filtrate in a rota-evaporator. The crude product **3a** obtained was dissolved in dichloromethane (30 mL), and hydrogen peroxide (30% H_2O_2, 0.2 mL, 0.005 mol) was added to it dropwise at 0–5 °C. The reaction mixture was brought to 45–50°C and kept with stirring for 2 h for the completion of oxidation as indicated by TLC analyses. The solvent was evaporated from the filtrate in a rota-evaporator. The resulting crude product was recrystallized from ethanol to yield 0.83 g (62%) of **4a**, mp 113–115 °C.

Preparation of (3a,S)-1-(4-Nitrophenoxy)-3a,4-dihydro-3*H*-1λ^5-[1,3,2]oxazaphospholo[3,4-a]indol-1-one (4i)

A solution of 4-nitrophenyl phosphorodichloridate (**2e**, 1.2 g, 0.005 mol) in 20 mL of dry tetrahydrofuran was added over a period of 20 min at 0 °C to

a stirred solution of 2,3-dihydro-1*H*-indol-2(S)yl methanol (**1**, 0.745 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 50 mL of dry tetrahydrofuran. After completion of the addition, the temperature of the reaction mixture was raised to 45–50 °C and kept for 3–4 h with stirring. The progress of the reaction mixture was monitored by TLC analyses. The precipitated triethylamine hydrochloride was filtered, and the filtrate, was evaporated in a rota-evaporator. The residue obtained was washed with water followed by chilled ethanol. Colorless crystals were obtained after recrystallization of the product from ethanol to yield 1.30 g (65%) of **4i**, mp 109–111 °C.

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