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Synthesis and antimicrobial activity of novel tricyclic organophosphoranes

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ABSTRACT

*A new class of organophosphorus heterocycles, tricyclic phosphoranes (**4a-j**) synthesis was accomplished via two step process. It involves the preparation of monochloride intermediate (**2**) and its subsequent reaction with various phenols in dry tetrahydrofuran in the presence of TEA under reflux condition. These compounds were characterized by IR, ^{1}H, ^{13}C and ^{31}P NMR and were found to exhibit moderate to good antimicrobial activity.*

Key words: Tricyclic phosphoranes, Triethylamine, Antimicrobial activity.

INTRODUCTION

An increasing interest has been paid for several years to the chemistry of phosphorus heterocycles due to their unique physical properties, specific chemical reactivity.[1] Current literature status of organophosphorus heterocycles is poignant with the possibility of several applications not only in the life-processes but also in the several industrial sectors.[2,3] Organophosphorus heterocycles are being used as drugs in medicine,[4] pesticides in agriculture,[5] chemical warfare agents in defense, flame retardant oil and polymer additives in the industry is well established, still vast scope exists for further discovery and development in this area. In view of the various applications of organophosphorus hetero cycles compounds, series of 4-substituted phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ_5-phosphabenzo[b]naphtha [2,3-*l*] fluoren-5-yl ether(**4a-j**) have been successfully accomplished and their bio activity studies have been evaluated.

MATERIALS AND METHODS

Phenyl (11*H*, 16*H*-5,6-dioxa-11a,15b-diaza-5aλ5- phospha-3-methylbenzo [*b*]naphtho-[2,3-*l*]-fluoren-5-yl) ether

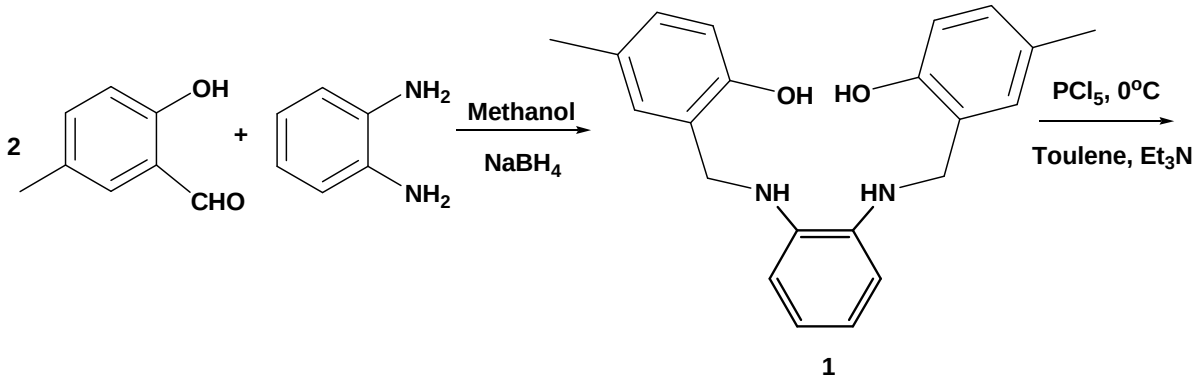
Synthesis of tricyclic phosphoranes was conveniently accomplished in a two step process. In the first step, a solution of phosphorus pentachloride (1.04 g, 0.005 mole) in dry tetrahydrofuran was added to a mixture of 2,2'-(1,2-(3-methyl phenyl bis (azanediyl)bis(methane) diphenol (1.92 g, 0.005 mole), which was prepard by using standard procedure, and triethylamine (TEA) in THF (25 mL) at 0°C over a period of 30 minutes. After the addition, temperature of the reaction mixture was slowly raised to room temperature and continued for 1h and then refluxed at 60°C for 3h. The solid triethylamine hydrochloride was filtered and the solvent was concentrated under vacuum. To the concentrated solution in THF at 0°C a solution of phenol (0.47 g, 0.005 mole) in THF was added in the presence of TEA and after completion of addition temperature was slowly raised and then refluxed at 60°C for 2h. Progress of the reaction was monitored by TLC analysis. After the completion of reaction solvent was evaporated in a under vacuum. The obtained crude product was purified by column chromatography on 60-120 silica gel mesh using ethyl acetate: hexane (1:4) as eluent to obtain 1.35 g (65%), mp 172-174 °C of pure compound **4a**.

Phenyl (11*H*, 16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3-methylbenzo[*b*]naphtho-[2,3-*l*]-fluoren-5-yl) ether (4a): Yield 65 %, mp 172-174 °C, IR (KBr) cm^{-1}: 1136 (O-C), 926 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.45-7.52 (15H, m, Ar-H), 4.89-5.02 (4H, m, 2CH_2), 2.42-2.59 (6H, m, 2CH_3); ^{13}C-NMR data: 28.7 (CH_3 (C-6&12)), 51.6 (C-4 and C-14), 128.9 (C-4a and C-13a), 130.8 (C-5 and C-13), 131.3 (C-6 and C-12), 127.6 (C-7 and C-11), 117.9 (C-8 and C-10), 150.8 (C-8a and C-9a), 137.4 (C-16 and C-21), 114.5 (C-17 and C-20), 118.5 (C-18 and C-19), 153.4 (C-1'), 118.6 (C-2' and C-6'), 132.8 (C-3' and C-5'), 124.1(C-4'); ^{31}P NMR data: δ 28.35 ; FAB-MS m/z: 468 (M+H); Anal. Calcd. for $C_{28}H_{25}N_2O_3P$: C,71.78; H, 5.38; N, 5.96. Found C, 71.70; H, 5.32; N, 5.90.

4-fluoro phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phospha-3-methyl benzo[*b*] naphtho-[2,3-*l*] fluoren-5-yl) ether(4b): Yield 60 %, mp 187-189 °C IR (KBr) cm^{-1}: 1131 (O-C), 918 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.55-7.62 (14H, m, Ar-H), 4.39- 4.66 (4H, m, -CH_2), 2.41-2.57 (6H, m, 2CH_3); ^{13}C-NMR data: 28.9 (CH_3 (C-6&12)), 54.6 (C-4 and C-14), 127.6 (C-4a and C-13a), 129.8 (C-5 and C-13), 131.0 (C-6 and C-12), 127.1 (C-7 and C-11), 115.9 (C-8 and C-10), 151.8 (C-8a and C-9a), 137.0 (C-16 and C-21), 114.0 (C-17 and C-20), 120.5 (C-18 and C-19), 148.4 (C-1'), 117.6 (C-2' and C-6'), 114.8 (C-3' and C-5'), 156.1(C-4'); ^{31}P NMR data: δ 24.29; FAB-MS m/z: 486 (M+H); Anal. Calcd. for $C_{28}H_{24}FN_2O_3P$: C, 69.13; H, 4.97; N, 5.76. Found C, 69.02; H, 4.89; N, 5.69.

4-methyl phenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3-methylbenzo [*b*] naphtho-[2,3-*l*] fluoren-5-yl) ether (4c): Yield 59 %, mp 206-208 °C IR (KBr) cm^{-1}: 1135 (O-C), 932 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.37-7.51 (14H, m, Ar-H), 4.45- 4.70 (4H, m, -CH_2-), 2.33-2.67 (9H, m, Ar-CH_3); ^{13}C-NMR data: 33.5 (CH_3 (C-6&12)), 50.9 (C-4 and C-14), 128.1 (C-4a and C-13a), 129.8 (C-5 and C-13), 123.0 (C-6 and C-12), 129.7 (C-7 and C-11), 120.3 (C-8 and C-10), 151.6 (C-8a and C-9a), 129.7 (C-16 and C-21), 113.2 (C-17 and C-20), 118.4 (C-18 and C-19), 153.7 (s, 1C,C- 1'), 116.2 (C-2' and C-6'), 132.5 (C-3' and C-5'), 133.1 (C-4'), 27.8

(C-CH_3(4'); ^{31}P NMR data: δ 36.15; FAB-MS m/z: 482 (M+H); Anal. Calcd for $C_{29}H_{27}N_2O_3P$: C, 72.19; H, 5.64; N, 5.81. Found C, 72.11; H, 5.58; N, 5.74.



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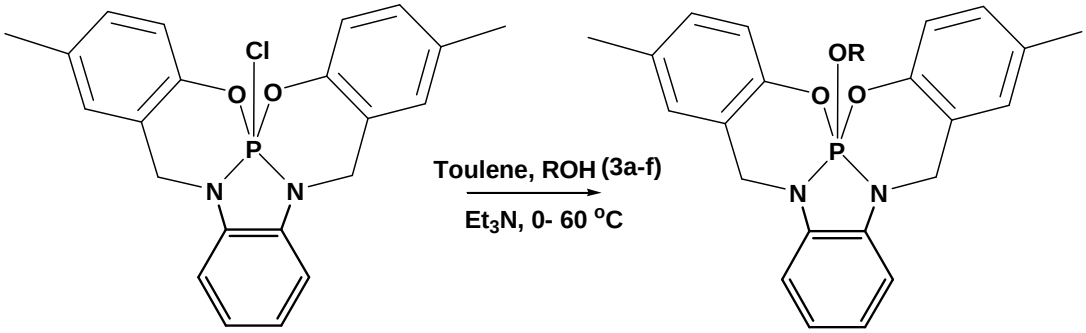

2 **4a-f**

Compd	R	Compd	R
3a & 4a	-C_6H_5	3f & 4f	-$C_6H_5Br(4)$
3b & 4b	-$C_6H_4F(4)$	3g & 4g	-$C_6H_5NO_2(4)$
3c & 4c	-$C_6H_4CH_3(4)$	3h & 4h	-$C_6H_5Cl_2(2,4)$
3d & 4d	-$C_6H_4OCH_3(4)$	3i & 4i	-$C_6H_5(CH_3)_2(2,4)$
3e & 4e	-$C_6H_4Cl(4)$	3j & 4ja	-$C_6H_5Cl(3)CH_3(4)$

Scheme – 1

4-methoxyphenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5-phospha-3-mehyl benzo [*b*] naphtho-[2,3-*l*] fluoren-5-yl) ether (4d): Yield 67 %, mp 189-191 °C IR (KBr) cm^{-1}: 1123 (O-C), 924 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.35-7.69 (14H, m, Ar-H), 4.59-4.92 (4H, m, -CH_2), 3.82 (3H, s, OCH_3), 2.39-2.55 (6H, m, 2CH_3); ^{13}C-NMR data: 29.4 (CH_3 (C-6&12)), 50.5 (C-4 and C-14), 57.6 (OCH_3), 128.0 (C-4a and C-13a), 132.6 (C-5 and C-13), 121.9 (C-6 and C-12), 129.6 (C-7 and C-11), 121.0 (C-8 and C-10), 149.5 (C-8a and C-9a), 128.3 (C-16 and C-21), 112.0 (C-17 and C-20), 117.1 (C-18 and C-19), 145.2 (C-1'), 116.7 (C-2' and C-6'), 114.4 (C-3' and C-5'),

153.3 (C-4'); ^{31}P NMR data: δ 31.13; FAB-MS m/z: 498 (M+H); Anal. Calcd. for $C_{27}H_{23}N_2O_4P$: C, 69.87; H, 5.46; N, 5.62. Found C, 69.80; H, 5.41; N, 5.55.

2,4-dimethylphenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3- methylbenzo - [*b*] naphtho[2,3-*l*]fluoren-5-yl) ether (4e): Yield 62 %, mp 219-221 °C IR (KBr) cm^{-1}: 1140 (O-C), 921 (P-O); ^{1}H NMR (DMSO-*d*6): δ 6.57 - 7.49 (13H, m, Ar-H), 4.55-4.82 (4H, m, -CH_2-), 2.31-2.78 (12H, m, Ar-CH_3); ^{31}P NMR data: δ 32.27; Anal. Calcd. for $C_{30}H_{29}N_2O_3P$: C, 72.57; H, 5.89; N, 5.64. Found C, 72.49; H, 5.81; N, 5.56.

4-chlorophenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3-methylbenzo [*b*] naphtho - [2,3-*l*] fluoren-5-yl) ether (4f): Yield 60 %, mp 214-26 °C IR (KBr) cm^{-1}: 1120 (O-C), 915 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.66-7.72 (14H, m, Ar-H), 4.37- 4.67 (4H, m, -CH_2), 2.41-2.72 (6H, m, Ar-CH_3); ^{31}PNMR data: δ 38.50; Anal. Calcd. for $C_{28}H_{24}N_2O_3PCl$: C, 66.87; H, 4.81; N, 7.05. Found C, 66.78; H, 4.73; N, 6.98.

4-bromophenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phosphabenzo[*b*] naphtha - [2,3-*l*] fluoren-5-yl) ether (4g): Yield 61 %, mp 191-193 °C IR (KBr) cm^{-1}: 1115 (O-C), 922 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.56-7.73 (14H, m, Ar-H), 4.49- 4.76 (4H, m, -CH_2-), 2.37-2.65 (6H, m, Ar-CH_3); ^{31}P NMR data: δ 31.30; Anal. Calcd. for $C_{28}H_{24}BrN_2O_3P$: C, 61.44; H, 4.42; N, 5.12. Found C, 61.38; H, 4.36; N, 5.05.

4-nitrophenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3-methylbenzo [*b*]naphtho [2,3-*l*]fluoren-5-yl) ether (4h): Yield 67 %, mp 206-208 °C IR (KBr) cm^{-1}: 1133 (O-C), 940 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.58-7.59 (14H, m, Ar-H), 4.85-5.10 (4H, m, -CH_2-), 2.29-2.51 (6H, m, Ar-CH_3) ; ^{31}P NMR data: δ 35.19; Anal. Calcd. for $C_{28}H_{24}N_3O_5P$: C, 65.49; H, 4.71; N, 8.18. Found C, 65.41; H, 4.64; N, 8.11.

2,4-dichlorophenyl(11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3-methylbenzo -[*b*] naphtho[2,3-l] fluoren-5-yl) ether (4i): Yield 65%, mp 224-226 °C IR (KBr) cm^{-1}:1120 (O-C), 935 (P-O); ^{1}H NMR (DMSO-d_6):δ 6.68-7.79 (14H, m, Ar-H), 4.35-4.80 (4H, m, -CH_2-), 2.40-2.69 (6H, m, Ar-CH_3); ^{31}P NMR data: δ 33.15; Anal. Calcd. for $C_{28}H_{23}Cl_2N_2O_3P$: C, 62.58; H, 4.31; N, 5.27. Found C, 62.51; H, 4.23; N, 5.18.

3-chloro-4-methylphenyl (11*H*,16*H*-5,6-dioxa-11a,15b-diaza-5aλ^5 - phospha-3-methylbenzo [*b*] naphtho [2,3-*l*]fluoren-5-yl) ether (4j) Yield 63%, mp 221-223 °C IR (KBr) cm^{-1}: 1125 (O-C), 935 (P-O); ^{1}H NMR (DMSO-d_6): δ 6.42-7.59 (13H, m, Ar-H), 4.65-4.97 (4H, m, -CH_2-), 2.38-2.65 (9H, m, Ar-CH_3); ^{31}P NMR data: δ 29.22; Anal. Calcd. for $C_{29}H_{26}ClN_2O_3P$: C, 67.38; H, 5.07; N, 5.42. Found C, 67.31; H, 4.99; N, 5.36.

RESULTS AND DISCUSSION

A new class of novel 4-substituted phenyl (11*H*, 16H-5, 6-dioxa-11a, 15b-diaza-5aλ^5-Phosphabenzo [*b*]naphtha-[2, 3-*l*] fluoren-5-yl) ether (**4a-j**) have been synthesized in a two step process. In the first step the intermediate monochloride (**2**) was prepared by the cyclocondensation of 2, 2'-(1, 2-phenylene bis (azenedily) bis methane) (**1**) with phosphorus pentachloride in presence of triethylamine in anhydrous tetrahydrofuran (THF) at 60 °C for 3h.In

the second step the intermediate monochloride was further reacted with various phenols in presence of triethylamine in anhydrous tetrahydrofuran at 60 °C for 2h. Progress of the reaction was monitored by TLC analysis. IR absorption bands for (P-O-$C_{aromatic}$) C-O and P-O in the region[6] 1115-1140, 910-940 cm^{-1} respectively were observed for compounds **4a-j**. The aromatic hydrogens of compounds **4a-j** gave multiplets in the region δ 6.25-7.85. The bridged methylene protons signals appeared as multiplets in the region δ 4.39-5.02 indicating their non-equivalence[7] and coupling with phosphorus. The ^{13}C NMR spectral data for **4a-d** are given in the experimental section. The methylene carbons (C-4&C-14) resonated as singlets[8] in the region of 50.5 - 54.6 ppm. The remaining carbon signals were observed in their expected regions. The compounds **4a-j** were exhibited a singlet[9] in their ^{31}P NMR spectra in the region 24.29 – 38.50 ppm. FAB mass of **4a-d** gave molecular ions at their expected m/z values.

Antimicrobial Activity of Compounds 4a-j

Antibacterial Activity

Antibacterial activity of all the title compounds (**4a-j)** was evaluated against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve) at different concentrations[10] (100, 50, 25 ppm) **Table 1**. All the compounds are less active against both the bacteria when compared to the reference compound Penicillin.

Antifungal Activity

The antifungal activity[11] of compounds (**4a-j**) was tested against the growth of *Aspergillus Niger* and *Curvularia lunata* at various concentrations (100, 50, 25 ppm) and the results were presented in **Table 2** and Griseofulvin was used as the standard reference compound. Majority of the title compounds showed low antifungal activity against both the fungi.

Table 1: Antibacterial Activity of Compounds 4a-j

Compound	*Zone Of Inhibition (%)*					
	Escherichia coli			*Staphylococcus aureus*		
	100	50	25	100	50	25
4a	08	05	02	09	05	01
4b	07	05	03	09	04	02
4c	09	04	-	08	04	-
4d	05	03	01	07	04	-
4e	09	04	-	06	05	-
4f	08	05	03	10	06	02
4g	08	04	-	09	04	01
4h	08	05	-	08	05	02
4i	08	05	01	06	03	-
4j	05	02	-	07	03	-
Pencillin	12	07	-	11	08	-

Table 2: Antifungal activity of compounds 4a-j

Compound	*Zone Of Inhibition (%)*					
	Aspergillus Niger			*Helmenthosphorium oryzae*		
	100	50	25	100	50	25
4a	07	05	03	10	06	03
4b	07	05	03	08	05	02
4c	09	06	02	09	05	03
4d	05	03	01	07	04	-
4e	09	04	-	06	05	-
4f	08	05	03	10	06	02
4g	08	04	-	09	04	01
4h	09	04	-	08	04	-
4i	08	05	02	09	05	01
4j	07	03	-	08	04	01
Griseo –fulvin	11	08	06	13	08	06

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