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Phosphorus–nitrogen compounds. Part 23: Syntheses, structural investigations, biological activities, and DNA interactions of new N/O spirocyclotriphosphazenes

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ABSTRACT

The Schiff base compounds (**1** and **2**) are synthesized by the condensation reactions of 2-furan-2-yl-methylamine with 2-hydroxy-3-methoxy- and 2-hydroxy-5-methoxy-benzaldehydes and reduced with $NaBH_4$ to give the new N/O-donor-type ligands (**3** and **4**). The monospirocyclotriphosphazenes containing 1,3,2-oxazaphosphorine rings (**5** and **6**) are prepared from the reactions of $N_3P_3Cl_6$ with **3** and **4**, respectively. The reactions of **5** and **6** with excess pyrrolidine, morpholine, and 1,4-dioxa-8-azaspiro [4,5] decane (DASD) produce tetrapyrrolidino (**5a** and **6a**), morpholino (**5b** and **6b**), and 1,4-dioxa-8-azaspiro [4,5] deca (**5c** and **6c**) spirocyclotriphosphazenes. The structural investigations of the compounds are examined by ^1H, ^{13}C, ^{31}P NMR, DEPT, HSQC, and HMBC techniques. The solid-state structures of **5**, **5a**, and **6** are determined using X-ray crystallography. The compounds **5a**, **5b**, **5c**, **6a**, **6b**, and **6c** are subjected to antimicrobial activity against six patojen bacteria and two yeast strains. In addition, interactions between these compounds and pBR322 plasmid DNA are presented by agarose gel electrophoresis.

1. Introduction

Organocyclophosphazenes $(NPR_2)_n$ ($n = 3, 4, \ldots$), all of which contain phosphorus and nitrogen atoms bonded alternately, are borderline in inorganic and organic chemistry and an important family of inorganic ring systems [1–4]. A large number of the phosphazene derivatives have been prepared by nucleophilic substitution reactions on hexachlorocyclotriphosphazene, $N_3P_3Cl_6$, introducing easily a wide variety of different mono [5,6] and difunctional organic groups onto P atoms [7–9]. A scan of the literature shows that the involvement of bifunctional ligands with the cyclophosphazene ring is considerably limited to monofunctional reagents. The condensation reactions of bifunctional ligands with $N_3P_3Cl_6$ may lead to spiro, ansa, bino, dispiro, diansa, spiro-ansa, spiro-bino, and trispirocyclophosphazene derivatives [10–13]. On the other hand, the next oligomer octachlorocyclotetraphosphazene, $N_4P_4Cl_8$, gives also similar products with bifunctional ligands [14–16].

As known, there are five possible reaction pathways for the reactions of $N_3P_3Cl_6$ with bidentate ligands: both functional groups of the ligand may replace with two chlorine atoms: (i) in cis nongeminal route to give ansa derivatives and/or (ii) in geminal route to give spiro derivatives, (iii) the replacement of one chlorine atom with one of the two functional groups of the ligand to produce open-chain (dangling) compounds, (iv) intermolecular reactions between Cl atoms on two different phosphazene rings to form bridged (bino) phosphazene derivatives, and (v) intermolecular condensation reactions to give cyclolinear or cyclomatrix polymers [17,18]. Moreover, the distribution of these phosphazene derivatives may depend on many factors, e.g. reaction time, solvent polarities, temperature, size of the phosphazene ring and the properties of the bifunctional ligands [19]. It has been observed that, when the reactions are carried out with N/O donor-type bidentate ligands and $N_3P_3Cl_6$, the major product is generally spiro derivative in tetrahydrofuran [20].

Recently, phosphazene derivatives have drawn considerable attention for the further design of highly selective anticancer agents [21] and antimicrobial [22] reagents. Aziridine-crown substituted cyclotriphosphazene derivatives cleave the DNA and halt the growth of cancer cells [23]. The Cu^{+2} complex of fully-phenoxy-substituted star-branched cyclotetraphosphazene derivative is also found to be active in the oxidative cleavage of DNA [24]. On the other hand, cyclophosphazenes have found industrial applications such as in the production of ionic liquids [25], liquid crystals [26], dendrimers having chiral ligands for asymmetric catalysis [27], flame retardants [28–30], advanced elastomers

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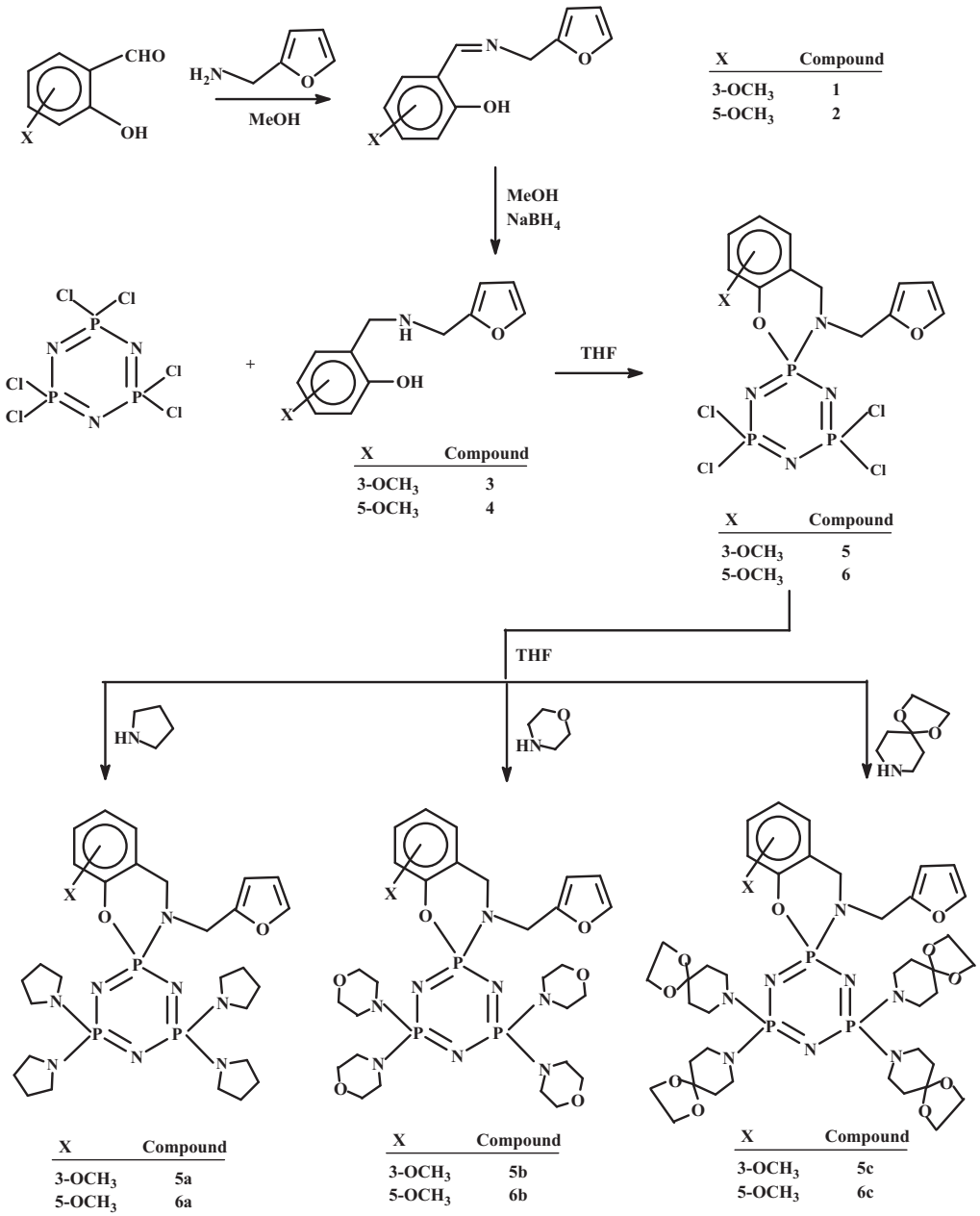

Scheme 1. The reaction pathway for the phosphazene derivatives.

[31,32], rechargeable batteries [33,34], and biomedical materials [35,36].

As a particular interest in our ongoing studies about N/O spirocyclic phosphazene derivatives, we report here in detail: (i) the synthesis of new N-(furan-2-yl-methyl)-3 and 5-methoxy-2-hydroxybenzylamines (**3** and **4**), (ii) the preparation of new tetrachloro (**5** and **6**), tetrapyrrolidino (**5a** and **6a**), tetramorpholino (**5b** and **6b**), and tetra(1,4-dioxa-8-azaspiro [4,5] deca) (**5c** and **6c**) monospirocyclotriphosphazenes (Scheme 1), (iii) investigations of antibacterial and antifungal activity of **5a**, **5b**, **5c**, **6a**, **6b**, and **6c**, and (iv) interactions between these compounds and pBR322 plasmid DNA examined by agarose gel electrophoresis. The determination of the structures of the compounds have been made using elemental analyses, mass spectrometry (MS), Fourier transform (FTIR), one-dimensional (1D) ^{1}H, ^{13}C, and ^{31}P NMR, distortionless enhancement by polarization transfer (DEPT), two-dimensional (2D) heteronuclear single quantum coherence (HSQC), and heteronuclear multiple-bond correlation (HMBC) techniques. Moreover, the molecular and solid-state structures of **5**, **5a**, and **6** have been established by X-ray diffraction techniques.

2. Experimental

2.1. General methods

Hexachlorocyclotriphosphazatriene (Aldrich), 2-hydroxy-3-methoxy- and 2-hydroxy-5-methoxy-benzaldehydes (Aldrich), 2-furan-2-yl-methylamine (Acros Organics), pyrrolidine (Fluka), morpholine (Fluka), and 1,4-dioxa-8-azaspiro [4,5] decane (Fluka) were purchased and used without further purification. All reactions were monitored using thin-layer chromatography in different solvents and chromatographed using silica gel. All experiments were carried out in an argon atmosphere. The ^{1}H, ^{13}C, and ^{31}P NMR, DEPT, HSQC, and HMBC spectra were recorded on a Bruker