Polyhedron 117 (2016) 394–403

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Synthesis and characterization of cyclotriphosphazene derivatives bearing azole groups

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ARTICLE INFO

Article history:
Received 3 May 2016
Accepted 7 June 2016
Available online 18 June 2016

Keywords:
Phosphazene
Azole
Heterocyclic
Osiris
Molinspiration

ABSTRACT

A series of new cyclophosphazene derivatives were obtained from the reactions of morpholino or propandioxy derivatives of cyclotriphosphazenes with imidazole, benzimidazole and pyrazole. Reported compounds $[N_3P_3Cl_5(NC_4H_8O)]$ (**1**), *cis*-$[N_3P_3Cl_4(NC_4H_8O)_2]$ (**2**), *trans*-$[N_3P_3Cl_4(NC_4H_8O)_2]$ (**3**), *trans*-$[N_3P_3(NC_4H_8O)_2(R)_4]$ [R = imidazole (**4**); benzimidazole (**5**); pyrazole (**6**)], spiro-$[N_3P_3(OC_3H_6O)(R)_4]$ [R = imidazole (**8**); benzimidazole (**9**); pyrazole (**10**)] were characterized using spectroscopic methods, elemental analysis and X-ray crystallography. Stereogenic properties of compounds having chiral centers were discussed. The physicochemical parameters and the toxicity risk assessment of the synthesized compounds were estimated using Molinspiration and Osiris property calculation methods.

1. Introduction

Heterocycles having importance biologically and industrially constitute one of the largest classes of organic chemistry and are important sources for the discovery of new compounds with diverse biological activity [1,2]. They form the majority of pharmaceuticals and biologically active agrochemicals and more than 90% of new drugs contain heterocyclic compounds [1,2]. Therefore, it can be valuable to make extensive efforts to synthesize new compounds which contain heterocyclic components. Azoles are an important class of nitrogen heterocycles and are of wide interest because of their diverse biological activity [3,4]. Their derivatives play an important role in medicinal chemistry due to their antibacterial and antifungal properties [3,4]. Morpholine which presents in many bioactive compounds is another heterocyclic group and their derivatives show biological properties [5–8].

Chlorocyclophosphazenes are an important class of inorganic phosphorus-nitrogen compounds which have the ability to undergo nucleophilic substitution reactions via the chlorine atoms attached to phosphorus atoms. They can be easily substituted with a wide variety of organic groups and new derivatives having different properties can be obtained depending on the characteristics of the substituted groups [9]. Additionally, they can be used as a model or starting material for the phosphazene polymers [9]. Recent developments in phosphazene chemistry have been mostly focused on the synthesis of new types of linear, cyclic or polymeric such derivatives and on their application as precursors for obtaining materials with special properties. Therefore the design and synthesis of new types of phosphazene derivatives are important and are expected to open new research areas [10–16]. Cyclophosphazene derivatives containing heterocyclic groups are attractive molecules because of their tendency to exhibit biological activity [17–23].

The aim of this work was to design and synthesize new cyclotriphosphazenes containing azole side groups and morpholino or propandioxy moieties as cosubstituent groups. New cyclophosphazene derivatives were characterized using mass, ^{31}P and ^{1}H NMR spectroscopies and elemental analysis. Compounds **1**–**3**, **5**, **6**, **8** and **10** were determined structurally by using X-ray crystallography. The physicochemical parameters and the toxicity risk assessment of the synthesized compounds (**4**–**6** and **8**–**10**) were also calculated using Molinspiration and Osiris programs.

2. Experimental

2.1. Materials

The chemicals were obtained commercially and used as received; morpholine (>98%), benzimidazole (99%), pyrazole (99%), *n*-hexane (>96%), tetrahydrofuran (⩾99%), 1,3-propandiol (>98%), dichloromethane (⩾99.0%), triethylamine (>99%), deuterated chloroform (for NMR spectroscopy) from Merck, Imidazole (99%) from Alfa Aesar. Hexachlorocyclotriphosphazene which was purified by crystallisation from *n*-hexane was obtained from Aldrich. Thin layer chromatography (TLC) and column

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http://dx.doi.org/10.1016/j.poly.2016.06.009
0277-5387/

chromatography were carried out on Merck silica gel plates (Kieselgel 60, F_{254} indicator, 0.25 mm) and silica gel (Kieselgel 60, 70–230 mesh) respectively.

2.2. Equipment

Elementar Vario MICRO Cube Instrument and Bruker Daltonics Microflex LT MALDI-TOF mass spectrometers were used to obtain elemental analyses and mass spectra respectively. NMR (^{31}P, ^{1}H) spectra were recorded on a Varian INOVA 500 MHz spectrometer in $CDCl_3$ solutions using 85% H_3PO_4 as external reference for ^{31}P and TMS as internal reference for ^{1}H.

2.3. Syntheses

Spiro-propandioxycyclotriphosphazene $[N_3P_3Cl_4(OC_3H_6O)]$ (**7**), was prepared as described in the literature [24].

2.3.1. $[N_3P_3Cl_5(NC_4H_8O)]$ (**1**), cis-$[N_3P_3Cl_4(NC_4H_8O)_2]$ (**2**) and trans-$[N_3P_3Cl_4(NC_4H_8O)_2]$ (**3**)

To a stirred solution of hexachlorocyclotriphosphazene (2.0 g, 5.75 mmol) in 50 mL tetrahydrofuran (THF) was added triethylamine (1.60 ml, 11.50 mmol) under an argon atmosphere. The solution was cooled to 0 °C using an ice-bath, morpholine (0.85 g, 9.76 mmol) in 30 mL THF was then added dropwise to the stirred mixture under an argon atmosphere. The mixture was stirred for 24 h at room temperature, then the triethylamine hydrochloride salt formed was filtered off and the solvent was removed under reduced pressure. From the crude mixture, compounds (**1**–**3**) were isolated by column chromatography using ethyl acetate/*n*-hexane (6:1) as the mobile phase. Compounds **1**–**3** were crystallized from dichloromethane/*n*-hexane (2:1); **1**, 0.18 g, 8%, mp 94 °C; **2**, 0.06 g, 2%, mp 198 °C; **3**, 1.52 g, 59%, mp 108 °C.

2.3.2. trans-$[N_3P_3(NC_4H_8O)_2(C_3H_3N_2)_4]$ (**4**)

Compound **3**, (0.50 g, 1.11 mmol) was dissolved in THF (20 ml) and triethylamine (0.62 ml, 4.44 mmol) was added under an argon atmosphere. Imidazole (0.30 g, 4.44 mmol) dissolved in 15 mL THF was then added dropwise to the stirred solution of compound **3** under an argon atmosphere. The mixture was refluxed until TLC indicated complete consumption of the starting compound **3**. After refluxing for 21 h, the mixture was cooled to ambient temperature, the precipitate filtered and the solvent removed under reduced pressure. From the crude mixture, compound **4** was isolated using column chromatography with THF as the mobile phase; **4**, 0.40 g, 63%, mp 174 °C.

2.3.3. trans-$[N_3P_3(NC_4H_8O)_2(C_7H_5N_2)_4]$ (**5**)

Compound **3** (0.50 g, 1.11 mmol) was dissolved in THF (20 ml) and triethylamine (0.62 ml, 4.44 mmol) was added under argon atmosphere. Benzimidazole (0.52 g, 4.44 mmol) dissolved in 20 mL THF was then added dropwise to the stirred solution of compound **3** under an argon atmosphere. The reaction mixture was refluxed until TLC indicated complete consumption of the starting compound **3**. After 4 days, the mixture was cooled to ambient temperature, the precipitate filtered and the solvent removed under reduced pressure. From the crude mixture, compound **5** was isolated using column chromatography with THF/*n*-hexane (2:1) as the mobile phase. Compound **5** was crystallized from dichloromethane/THF (1:1); **5**, 0.73 g, 85%, mp 151 °C.

2.3.4. trans-$[N_3P_3(NC_4H_8O)_2(C_3H_3N_2)_4]$ (**6**)

Compound **3**, (0.50 g, 1.11 mmol) was dissolved in THF (20 ml) and triethylamine (0.62 ml, 4.44 mmol) was added under argon atmosphere. Pyrazole (0.30 g, 4.44 mmol) in 15 mL THF was then added dropwise to the stirred solution of compound **3** under an argon atmosphere. The reaction mixture was refluxed until TLC indicated complete consumption of the starting compound **3**. After 7 days, the mixture was cooled to ambient temperature, the precipitate filtered and the solvent removed under reduced pressure. From the crude mixture, compound **6** was isolated using column chromatography with THF/*n*-hexane (1:1) as the mobile phase and crystallized from dichloromethane/THF (1:1); **6**, 0.40 g, 63%, mp 174 °C.

2.3.5. spiro-$[N_3P_3(OC_3H_6O)(C_3H_3N_2)_4]$ (**8**)

Compound **7** (0.60 g, 1.71 mmol) was dissolved in THF (20 ml) and triethylamine (0.95 ml, 6.84 mmol) was added under argon atmosphere. Imidazole (0.47 g, 6.84 mmol) dissolved in 20 mL THF was then added dropwise to the stirred solution of compound **7** under an argon atmosphere. The reaction mixture was refluxed until TLC indicated complete consumption of the starting compound **7**. After 24 h, the reaction mixture was cooled to ambient temperature, the precipitate filtered and the solvent removed under reduced pressure. The residue was treated with water and extracted with dichloromethane three times. The residue was crystallized from dichloromethane to afford compound **8**, 0.49 g, 60%, mp 143 °C.

2.3.6. spiro-$[N_3P_3(OC_3H_6O)(C_7H_5N_2)_4]$ (**9**)

Compound **7** (0.40 g, 1.14 mmol) was dissolved in THF (20 ml) and triethylamine (0.64 ml 4.56 mmol) was added under argon atmosphere. Benzimidazole (0.54 g, 4.56 mmol) dissolved in 20 mL THF was then added dropwise to the stirred solution of compound **7** under an argon atmosphere. The reaction mixture was refluxed until TLC indicated complete consumption of the starting compound **7**. After 2 days, the mixture was cooled to ambient temperature, the precipitate filtered and the solvent removed under reduced pressure. Compound **9** was isolated as oily using column chromatography with THF/*n*-hexane (6:1). **9**, 0.66 g, 85%.

2.3.7. spiro-$[N_3P_3(OC_3H_6O)(C_3H_3N_2)_4]$ (**10**)

Compound **7** (0.4 g, 1.14 mmol) was dissolved in THF (20 ml) and triethylamine (0.64 ml 4.56 mmol) was added under argon atmosphere. Pyrazole (0.31 g, 4.56 mmol) dissolved in 15 mL THF was then added dropwise to the stirred solution of compound **7** under an argon atmosphere. The reaction mixture was refluxed until TLC indicated complete consumption of the starting compound **7**. After 7 days, the mixture was cooled to ambient temperature, the precipitate filtered and the solvent removed under reduced pressure. The residue was treated with water and extracted with dichloromethane three times. The residue was crystallized from dichloromethane/*n*-hexane (1:1); **10**, 0.38 g, 70%, mp 214 °C.

2.4. X-ray crystallography

X-ray crystallographic data was collected with a Bruker APEX II QUAZAR system equipped with diffractometer using Mo Kα radiation (λ = 0.71073 Å). Absorption correction was performed by the multi-scan method implemented in SADABS [25] and space groups were determined using XPREP implemented in APEX2 [26]. Structures were determined using the direct methods procedure in SHELXS-97 and refined by full-matrix least squares on F^2 using SHELXL-97 [27]. All non-H atoms were refined anisotropically, while H atoms were generally fixed in idealized positions with their displacement parameters riding on the values of their parent atoms. Further data collection and for crystal structure and refinement details for compounds (**1**–**3**, **5**, **6**, **8**, **10**) are provided in Table 6. The general-purpose crystallographic tool PLATON [28] was used