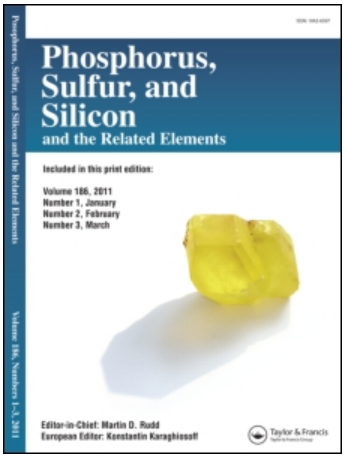

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"DRY MEDIA PROCESS": AN EFFICIENT TECHNIQUE FOR FAST REGIOSPECIFIC SYNTHESES OF SPIRANIC CYCLOPHOSPHAZENE CRYPTANDS

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"DRY MEDIA PROCESS": AN EFFICIENT TECHNIQUE FOR FAST REGIOSPECIFIC SYNTHESES OF SPIRANIC CYCLOPHOSPHAZENE CRYPTANDS

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The aminolysis of the hexachlorocyclotriphosphazene, $N_3P_3Cl_6$ **1**, by the oxodiamines H_2N-$(CH_2)_3$-O-$(CH_2)_2$-O-$(CH_2)_3$-NH_2 **2** and H_2N-$(CH_2)_3$-O-$(CH_2)_6$-O-$(CH_2)_3$-NH_2 **3** occurs immediately and regiospecifically in dry media leading to the corresponding spiranic cryptands **4** and **5**, respectively. This process is an actual improvement (time, selectivity and workup) on the standard reactions.

Key words: Cyclotriphosphazene; regiospecific aminolysis; dry media; alumina supported reaction.

Reactions of long oxodiamines, H_2N-$(CH_2)_n$-O-$(CH_2)_m$-O-$(CH_2)_n$-NH_2, with hexachlorocyclotriphosphazene ($N_3P_3Cl_6$) were investigated since 1989 with the aim of designing highly selective antitumoral drugs with acceptable solubility in physiological serum.[1,2] These reactions lead to macrocyclic host molecules, the conformation, the cavity size and the number of coordination sites of which depend drastically on experimental conditions.[3–11] Most of these attractive one- and two-ring architectures were unambiguously evidenced by x-ray investigations[6–11] and only four configurations were ever observed up to now (Figure 1):

(i) the SPIRO configuration (in which the oxodiamino ligand is grafted as a SPIRO loop onto one phosphorus atom of one N_3P_3 ring),
(ii) the cis-ANSA configuration (in which the oxodiamino ligand is grafted on one side of one N_3P_3 ring as an ANSA arch onto two different phosphorus atoms),
(iii) the trans-ANSA configuration (in which the oxodiamino ligand is grafted on both sides of one N_3P_3 ring as an ANSA arch onto two different phosphorus atoms) and
(iv) the BINO configuration (in which the oxodiamino ligand bridges two different N_3P_3 rings).

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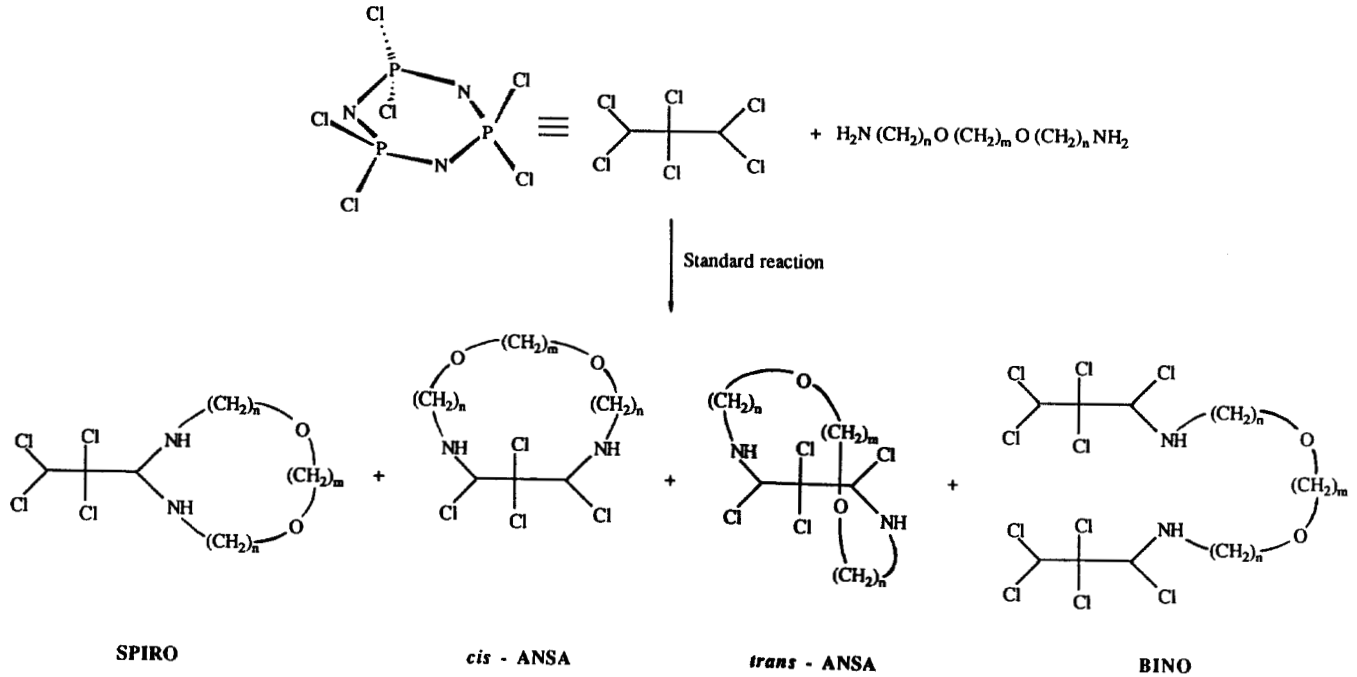

FIGURE 1 The four configurations obtained upon aminolysis of hexachlorocyclotriphosphazene **1** by oxodiamines.

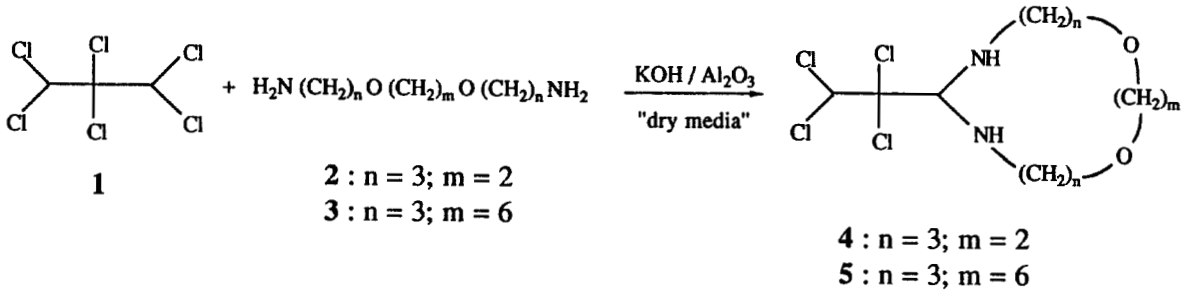

FIGURE 2 Regiospecific synthesis of **4**–**5** in "dry media."

However, such syntheses are not, strictly speaking, regioselective, every configuration being currently obtained with some others as by-products, and they need 48 hours at least to be achieved when performed at room temperature.

According to the capacity of these macrocyclic host cyclophosphazenes to bind metallic moieties and to yield so new cryptates for further applications,[12] it was of interest to attempt at the production of such "cages" in a more regioselective and less time-and-money consuming way. The present contribution reports on the improvements we got by using "dry media techniques".

It is well-known indeed that a wide variety of chemical reactions can be promoted in heterogeneous media thanks to the acidic and/or basic sites located on the surface of suitable solids such as alumina, clay, silica gel, talc and others.[13] The significant advantages of such "dry media" reactions relatively to the corresponding homogeneous reactions are the milder conditions, the more specific (chemospecific, regiospecific and stereospecific) transformations and the easier isolation of final pure products.

Syntheses of SPIRO cryptands from oxodiamines were extensively reported[2]: they were carried out in an heterogeneous liquid/liquid medium (saturated aq. Na_2CO_3/toluene) at room temperature for 48 hours. The completion of the reactions was followed by ^{31}P NMR spectroscopy and the percentage of each component in the final crude product was estimated by NMR. Thus, starting from **2**, the latter contains the expected SPIRO moiety **4** (80%) as the major product with 5% of BINO, 10% of unidentified by-products and 5% of unreacted $N_3P_3Cl_6$ **1**. Incidentally, the same situation occurs for most of other oxodiamines, except for **3** where the corresponding SPIRO **5** is no more obtained as the major product (5% only), its trans-ANSA isomer being here the main component of the crude final mixture (50%) with 10% of BINO, 30% of unidentified by-products and 5% of unreacted $N_3P_3Cl_6$ **1**. These reactions occur slowly on interface between the two liquid systems and require the use of important quantities of solvents (toxicity and workup problems).

These syntheses were repeated on impregnated alumina or talc in the absence of solvent ("dry media process") (Figure 2) and the desired SPIRO derivatives [**4** as well as **5**] were so obtained in ≥90% yield (see experimental section).

Many solid mineral supports (neutral or activated basic alumina, lamellar structures such as talcs) were tested. The influence of the nature of the basic system (potassium fluoride, potassium hydroxide, sodium carbonate or oxodiamine supported on the inorganic solid) was examined. Commercial basic alumina or sodium carbonate are not efficient conversely to the more basic potassium hydroxide supported on alumina. The amount of water is a critical parameter since the selectivity of the reaction depends drastically on the degree of dryness of basic supports (for example, 90% **5** were obtained from the alumina-supported KOH when dried at 70°C for 24 h in oven).

Acetone as the eluent has to be definitely preferred concerning the regioselectivity of the reaction. Indeed, a decrease of this selectivity is observed when elution is performed with other polar solvents such as acetonitrile.

Then, the use of alumina or alumina-supported KOH as mineral support and acetone as eluent makes syntheses of SPIRO cyclophosphazenic cryptands fast and regiospecific. Other inorganic supports will be tested with the aim of obtaining cis-

ANSA, trans-ANSA and BINO entities in such a time-and-money non-consuming way.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AC 200 spectrometer with H_3PO_4 85% as external reference.

Hexachlorocyclotriphosphazene **1** was generously provided to us (degree of purity ≥99,8%) by SHIN NISSO KAKO Co, subsidiary company of NIPPON SODA Co. BASF and TEXACO supplied us with the oxodiamines **2** and **3** (degree of purity ≥98%).

Alumina-supported potassium hydroxide: Potassium hydroxide (Prolabo Rectapur, 11 g) in H_2O (250 ml) was mixed with neutral chromatographic alumina (Fluka, type 207 C, 90–110 μ, 50 g). After stirring for 5 min, the water was removed under reduced pressure. The resulting powder was further dried at 70°C for 24 h in oven. This reagent may be kept in a dessicator without loss of activity during several weeks.

Talc-supported sodium carbonate: Sodium carbonate (Prolabo, 27 g) is dissolved in H_2O (250 ml) and talc (Prolabo Rectapur, 50 g) is added under stirring. The water is removed in vacuo. The impregnated talc is then dried in a drying oven (80°C—2 days) and stored without loss of activity during several weeks.

General method for the preparation of spiranic cyclophosphazene cryptands **4** *and* **5**: A mixture of **1** (0.40 g; 1.1 mmol) and the dioxodiamine **2** or **3** (1 eq.; 1.1 mmol) in toluene (20 ml) was added to solid support (Na_2CO_3/talc or KOH/alumina) (3.5 g. corresponding to 10 eq. of base). The solvent was immediately removed under reduced pressure at room temperature and the resulting powder was eluted with an organic solvent. The unreacted **1** was extracted with *n*-hexane and a second extraction with acetone gives the spiranic compounds **4** and **5** as pure form in ≥90% yield. The analytical parameters of **4–5** are in good agreement with the literature data.[2,10–11]

Remark: The stoichiometry of **1/2** or **3** was modified from 1/1 to 1/2 if neutral alumina was used as solid support, the excess of the oxodiamine operating as a base.

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