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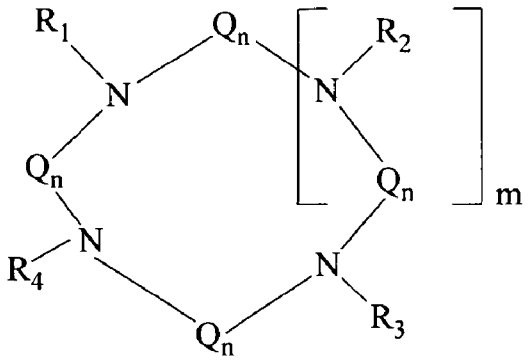
(54) Title: PROCESS FOR THE PREPARATION OF SUBSTITUTED POLYAZAMACROCYCLES



(I)

(57) Abstract: Process for the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group comprising reacting at least one unsubstituted polyazamacrocycle with at least one halogenated aryl or heteroaryl compound. Said polyazamacrocycle substituted with at least one aryl or heteroaryl group may advantageously be used in the synthesis of anionic or cationic complexes and/or of supramolecular adducts useful in the construction of luminescent solar concentrators (LSCs), which in their turn may advantageously be used together, for example, with photovoltaic cells (or solar cells), or with photoelectrolytic cells, in solar devices (i.e. devices for exploiting solar energy). Moreover, said polyazamacrocycle may be used in other fields such as, for example, the analytical field, the medical or biomedical field, the biological field, the field of detergents (both for household use and for personal care use). Formula I

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PROCESS FOR THE PREPARATION OF SUBSTITUTED POLYAZAMACROCYCLES

DESCRIPTION

The present invention relates to a process for the preparation of a substituted polyazamacrocycle.

More particularly, the present invention relates to a process for the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group comprising reacting at least one unsubstituted polyazamacrocycle with at least one halogenated aryl or heteroaryl compound.

Said polyazamacrocycle substituted with at least one aryl or heteroaryl group may advantageously be used in the synthesis of anionic or cationic complexes and/or of supramolecular adducts useful in the construction of luminescent solar concentrators (LSCs), which in their turn may advantageously be used together, for example, with photovoltaic cells (or solar cells), or with photoelectrolytic cells, in solar devices (i.e. devices for exploiting solar energy). Moreover, said polyazamacrocycle may be used in other fields such as, for example, the analytical field, the medical or biomedical field, the biological field, the field of detergents (both for household use and for personal care use).

Polyazamacrocycles and processes for the preparation thereof are known in the art.

For example, American patent US 5,587,451 discloses a process for the preparation of polyazamacrocycles using a nucleophilic imidazoline with:

(A) an ethylene oxide or an ethylene carbonate, in an aprotic solvent, followed by intramolecular amination, and then either by basic or acidic hydrolysis; or

(B) an electrophilic substrate, in a polar solvent, optionally in the presence of a non-nucleophilic base, to form an intermediate, followed by basic hydrolysis; or

(C) an electrophilic substrate, in a polar solvent, optionally in the presence of a non-

nucleophilic base, followed by prolonged heating in a polar solvent or by treatment with a peroxide solution, followed by basic hydrolysis to form urea, then by basic hydrolysis under pressure; and

then separating the desired polyazamacrocycle. The polyazamacrocycles so obtained are useful in pharmaceutical applications.

Tripier R. et al., in "From new tricyclic bisaminal derivatives to *trans-N,N'*-disubstituted cyclams", "*Chemical Communication*" (2001), pp. 2728-2729, describe the reactivity of cyclam (i.e. 1,4,8,11-tetraazacyclotetradecane) towards different aldehydes such as formaldehyde, benzaldehyde, pyridinaldehyde.

Alternatively, polyazamacrocycles may be obtained by arylation reactions in the presence of palladium-based catalysts, as disclosed for example by: Averin A. D. et al. in "Synthesis of 1,3-Bis(trimethylcyclam) and 1,3-Bis(trimethylcyclen) Substituted Benzene", "*Macroheterocycles*" (2009), Vol. 2(3-4), pp. 281-285; Beletskaya I. P. et al. in "Palladium-Catalyzed Arylation of Linear and Cyclic Polyamines", "*European Journal of Organic Chemistry*" (2005), pp. 261-280.

However, the aforementioned process may have some drawbacks, such as, for example:

- lots of steps and therefore higher preparation and waste disposal costs;
- use of compounds such as ethylene oxide, ethylene carbonate, peroxides, which lead to toxicity problems in relation to both the environment and the health of the operators, as well as problems resulting from the disposal thereof which often involves high costs, with resulting higher preparation and waste disposal costs;
- use of palladium-based catalysts, which is expensive, with resulting higher preparation costs;
- separation of the compounds of interest by chromatographic techniques, which often have high costs, with resulting higher preparation costs.

The Applicant has therefore taken on the problem of finding a process for the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group which can overcome the aforementioned drawbacks.

The Applicant has now found that the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group can be implemented by way of a process comprising reacting at least one unsubstituted polyazamacrocycle with at least one halogenated aryl or heteroaryl compound.

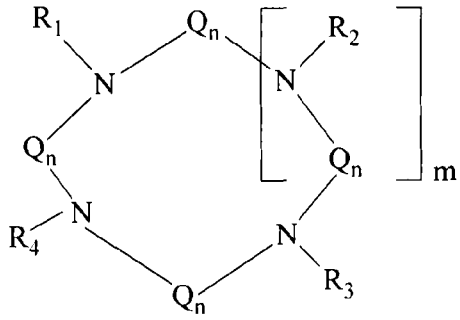
Many advantages are achieved by working in accordance with the aforementioned process such as, for example:

- simpler synthesis, and therefore lower preparation and waste disposal costs;
- avoiding the use of palladium-based catalysts and use of solid copper-based catalysts which, aside from being cheaper, are easily separable from the reaction mixture by filtration and reusable for several production cycles;
- increased yields (i.e. yields greater than or equal to 70%);
- obtaining polyazamacrocycles substantially free from metal ions, which do not require further purification or solvolysis processes of the complexes possibly formed;
- use of compounds which result in few or even no toxicity problems in relation to both the environment and the health of the operators, as well as problems resulting from the disposal thereof which often involves high costs, with resulting higher preparation and waste disposal costs;
- use of cheap, recyclable solvents, such as xylene, toluene and the like.

Said polyazamacrocycle substituted with at least one aryl or heteroaryl group may advantageously be used in the synthesis of anionic or cationic complexes and/or of supramolecular adducts useful in the construction of luminescent solar concentrators

(LSCs), which in their turn may advantageously be used together, for example, with photovoltaic cells (or solar cells), or with photoelectrolytic cells, in solar devices (i.e. devices for exploiting solar energy). Moreover, said polyazamacrocycle may be used in other fields such as, for example, the analytical field, the medical or biomedical field, the biological field, the field of detergents (both for household use and for personal care use).

The present invention therefore relates to a process for the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group having general formula (I):



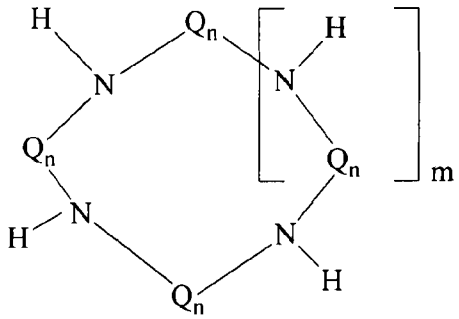
(I)

in which:

- Q represents a $-CH_2-$ group; a -C(O)- group; a $-CHR_5$ group in which R_5 represents a hydrogen atom, or a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; a $-CO_2R_6$ group in which R_6 represents a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; an optionally substituted aryl group;
- n, identical or different from one another, are an integer ranging from 1 to 3;
- m is 0, or an integer ranging from 1 to 9;
- R_1, R_2, R_3 and R_4, identical or different from one another, represent a hydrogen atom; or represent a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; an optionally

substituted cycloalkyl group; an optionally substituted aryl group; an optionally substituted heteroaryl group; with the proviso that at least one of R_1, R_2, R_3 and R_4, is an optionally substituted aryl group or an optionally substituted heteroaryl group;

said process comprising reacting at least one polyazamacrocycle having general formula (II):



(II)

in which Q, n and m, have the same meanings as described above;

with at least one halogenated aryl or heteroaryl compound having general formula (III):

Ar-X (III)

in which Ar represents an optionally substituted aryl group, or an optionally substituted heteroaryl group, X represents a halogen atom selected from fluorine, chlorine, bromine, iodine, preferably bromine;

in the presence of at least one strong base, at least one anhydrous aprotic organic solvent and at least one catalyst containing copper in oxidation state +1 having general formula (IV):

Cu_pX_1 (IV)

in which X_1 represents an oxygen atom, or a halogen atom selected from chlorine, bromine, iodine, preferably an oxygen atom, and p is 1 in the case wherein X_1 represents a halogen atom, or 2 in the case wherein X_1 represents an oxygen atom.

For the purpose of the present description and of the following claims, the definitions of numerical ranges always include the extremes unless stated otherwise.

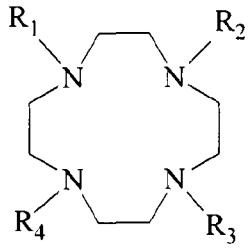
For the purpose of the present description and of the following claims, the term "comprising" also includes the terms "consisting essentially of" or "consisting of".

As stated above, the process according to the present invention makes it possible to obtain polyazamacrocycles substantially free of metal ions.

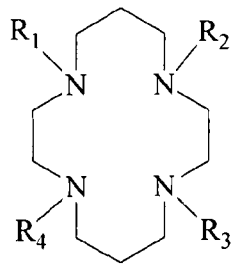
In a preferred embodiment of the present invention, said process relates to the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group having general formula (I) substantially free of metal ions.

For the purpose of the present description and of the following claims, the term "substantially free of metal ions" means that, when present, said metal ions are present in a quantity of less than 1% per individual metal ion.

In a preferred embodiment of the present invention, said process relates to the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group having general formula (Ia) or (Ib):



(Ia)



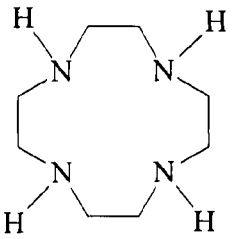
(Ib)

in which:

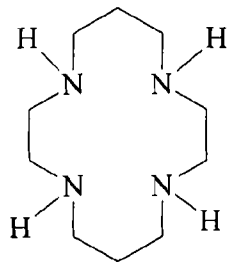
- R_1, R_2, R_3 and R_4, identical or different from one another, represent a hydrogen atom; or represent a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; an optionally

substituted cycloalkyl group; an optionally substituted aryl group; an optionally substituted heteroaryl group; with the proviso that at least one of R_1, R_2, R_3 and R_4, is an optionally substituted aryl group or an optionally substituted heteroaryl group; preferably an aryl group, still more preferably a phenyl;

said process comprising reacting at least one polyazamacrocycle having general formula (IIa) or (IIb):



(IIa)



(IIb)

with at least one halogenated aryl or heteroaryl compound having general formula (III):

Ar-X (III)

in which Ar represents an optionally substituted aryl group, or an optionally substituted heteroaryl group, preferably an aryl group, still more preferably a phenyl, X represents a halogen atom selected from fluorine, chlorine, bromine, iodine, preferably bromine;

in the presence of at least one strong base, at least one anhydrous aprotic organic solvent and at least one catalyst containing copper in oxidation state +1 having general formula (IV):

Cu_pX_1 (IV)

in which X_1 represents an oxygen atom, or a halogen atom selected from chlorine, bromine, iodine, preferably an oxygen atom, and p is 1 in the case wherein X_1 represents

a halogen atom, or 2 in the case wherein X_1 represents an oxygen atom.

The term "C_1-C_{20} alkyl group" refers to an alkyl group having from 1 to 20 carbon atoms, linear or branched, saturated or unsaturated. Specific examples of C_1-C_{20} alkyl groups are: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *t*-butyl, pentyl, ethyl-hexyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl.

The term "C_1-C_{20} alkyl group optionally containing heteroatoms" refers to an alkyl group having from 1 to 20 carbon atoms, linear or branched, saturated or unsaturated, in which at least one of the hydrogen atoms is substituted with a heteroatom selected from: halogens such as, for example, fluorine, chlorine, bromine, preferably fluorine; nitrogen; sulphur; oxygen. Specific examples of C_1-C_{20} alkyl groups optionally containing heteroatoms are: fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, perfluoropentyl, perfluorooctyl, perfluorodecyl, oxymethyl, thiomethyl, thioethyl, dimethylamino, propylamino, dioctylamino.

The term "cycloaklyl group" refers to a cycloalkyl group having from 3 to 10 carbon atoms. Said cycloalkyl group may optionally be substituted with one or more groups, identical or different from one another, selected from: halogen atoms such as, for example, fluorine, chlorine, preferably fluorine; hydroxyl groups; C_1-C_{20} alkyl groups; C_1-C_{20} alkoxyl groups; cyano groups; amino groups; nitro groups. Specific examples of cycloalkyl groups are: cyclopropyl, 2,2-difluorocyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, methoxycyclohexyl, fluorocyclohexyl, phenylcyclohexyl.

The term "aryl group" refers to an aromatic carbocyclic group containing from 5 to 60 carbon atoms. Said aryl group may optionally be substituted with one or more groups, identical or different from one another, selected from: halogen atoms such as, for example, fluorine, chlorine, bromine, preferably fluorine; hydroxyl groups; C_1-C_{12} alkyl

groups; C_1-C_{12} alkoxyl groups; C_1-C_{12} thioalkoxyl groups; C_3-C_{24} tri-alkylsilyl groups; polyethyleneoxyl groups; cyano groups; amino groups; C_1-C_{12} mono- or di-alkylamino groups; nitro groups. Specific examples of aryl groups are: phenyl, methylphenyl, trimethylphenyl, methoxyphenyl, trimethoxyphenyl, hydroxyphenyl, phenyloxyphenyl, fluorophenyl, pentafluorophenyl, chlorophenyl, bromophenyl, nitrophenyl, dimethylaminophenyl, naphthyl, phenylnaphthyl, phenanthrenyl, anthracenyl, 1-fluoro-4-nitrophenyl, biphenyl, perylenyl, pyranyl, coronenyl.

The term "heteroaryl group" refers to an aromatic heterocyclic group, penta-atomic or hexa-atomic, including benzocondensed or heterobicyclic, containing from 1 to 60 carbon atoms and from 1 to 4 heteroatoms selected from nitrogen, oxygen, sulphur, silicon, selenium, phosphorus. Said heteroaryl group may optionally be substituted with one or more groups, identical or different from one another, selected from: halogen atoms such as, for example, fluorine, chlorine, bromine, preferably fluorine, hydroxyl groups; C_1-C_{12} alkyl groups; C_1-C_{12} alkoxyl groups; C_1-C_{12} thioalkoxyl groups; C_3-C_{24} tri-alkylsilyl groups; polyethyleneoxyl groups; cyano groups; amino groups; C_1-C_{12} mono- or di-alkylamino groups; nitro groups. Specific examples of heteroaryl groups are: pyridyl, methylpyridyl, methoxypyridyl, phenylpyridyl, fluoropyridyl, pyrimidyl, pyridazyl, pyrazyl, triazyl, tetrazyl, quinolyl, quinoxalyl, quinazolyl, furanyl, thiophenyl, hexylthiophenyl, bromothiophenyl, dibromothiophenyl, pyrrolyl, oxazolyl, thiazolyl, isooxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, indolyl, benzofuranyl, benzothiophenyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, benzothiadiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, triazolopyridyl, triazolopyrimidyl, cumaryl.

In a preferred embodiment of the present invention, said polyazamacrocycle having general formula (II) and said halogenated aryl or heteroaryl compound having general formula (III) may be used in molar ratios ranging from 1:1 to 1:2 for each substituent to be

introduced, preferably ranging from 1:1 to 1:1.9 for each substituent to be introduced.

For the purpose of the present description and of the following claims, the term "strong base" refers to any base of which the conjugate acid has a pKa in dimethylsulphoxide (DMSO) greater than or equal to 32.

In a preferred embodiment of the present invention, said strong base may be selected, for example, from: alkali metal alkoxides such as, for example, lithium *t*-butoxide, sodium *t*-butoxide, potassium *t*-butoxide, cesium *t*-butoxide, rubidium *t*-butoxide, or mixtures thereof; alkali metal amides such as, for example, lithium amide, sodium amide, potassium amide, cesium amide, rubidium amide, or mixtures thereof; or mixtures thereof. Preferably, said strong base is potassium *t*-butoxide.

In a preferred embodiment of the present invention, said polyazamacrocycle having general formula (II) and said strong base may be used in molar ratios ranging from 1:1 to 1:6 for each substituent to be introduced, preferably ranging from 1:4 to 1:5.9 for each substituent to be introduced.

In a preferred embodiment of the present invention, said aprotic organic solvent may be selected, for example, from: anhydrous *N,N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), *N,N*-dimethylacetamide (DMAc), toluene, xylene, benzonitrile (PhCN), or mixtures thereof. Preferably, said anhydrous aprotic organic solvent may be selected from *N*-methyl-2-pyrrolidone (NMP), toluene, xylene.

In a preferred embodiment of the present invention, said polyazamacrocycle having general formula (II) may be used in said anhydrous aprotic organic solvent in such a quantity so as to have a molar concentration in said solvent ranging from 5.0×10^{-2} M to 8.0×10^{-2} M, preferably ranging from 6.0×10^{-2} M to 7.5×10^{-2} M.

To avoid parallel reactions such as, for example, reactions of the halogenated aryl or heteroaryl compound having general formula (III) with itself, the process according to the

present invention may be carried out in the presence of at least one anhydrous zinc salt.

In a preferred embodiment of the present invention, said process may be carried out in the presence of at least one anhydrous zinc salt which may be selected, for example, from: zinc acetate, zinc chloride, zinc tetrafluoroborate. Preferably, said anhydrous zinc salt is zinc acetate.

In a preferred embodiment of the present invention, said polyazamacrocycle having general formula (II) and said anhydrous zinc salt may be used in molar ratios ranging from 1:1 to 1:1.5, preferably ranging from 1:1 to 1:1.2.

In a preferred embodiment of the present invention, said process may be carried out at a temperature ranging from 50°C to 150°C, preferably ranging from 100°C to 130°C.

In a preferred embodiment of the present invention, said process may be carried out for a time ranging from 1 hour to 36 hours, preferably ranging from 10 hours to 30 hours.

The polyazamacrocycle having general formula (II) and the halogenated aryl or heteroaryl compound having general formula (III) are readily commercially available.

For the purpose of better understanding the present invention and for putting it into practice, some illustrative, non-limiting examples are given in the following.

The following characterization methods are used in the following examples.

Inductively Coupled Plasma Mass Spectrometry (ICP/MS)

The analysis of traces of contaminant elements present in the compounds obtained was carried out using a Perkin Elmer automatic spectrometer, model Elan DRC-e, by Inductively Coupled Plasma Mass Spectrometry (ICP/MS), prior to acid mineralisation carried out in an ETHOS ONE digestion system from Milestone.

For this purpose, approximately 15 mg of the compound to be analysed were weighed into the appropriate quartz container and 5 ml of concentrated nitric acid [$HNO_{3(conc.)}$] were added thereto: the mixture obtained was then subjected to a heating phase to 220°C, with

a temperature increase ramp for 10 minutes and 15 minutes of isotherm. Subsequently, the mixture was cooled to room temperature (25°C), transferred into polypropylene (PP) containers, and diluted in accordance with the analytical requirements, which provided for a first semiquantitative analysis and a subsequent quantitative analysis for the elements of interest using the aforementioned spectrometer.

Mass spectra (DCI/MS)

The mass spectra (DCI/MS) of the compounds obtained were carried out using a Finnigan Mat 95S inverse-geometry, dual-focus magnetic mass spectrometer by DCI (Desorption Chemical Ionization) with *iso*-butane as the reagent gas in positive ion mode. For this purpose, a drop of a solution of the compound to be analysed in toluene, previously subjected to a vacuum in order to evaporate the excess solvent, was loaded onto a tungsten emitter placed on a probe which was subsequently introduced into the source of the aforementioned mass spectrometer. A reaction gas suitable for ionizing the components of the compound to be analysed (i.e. *iso*-butane) was flushed into said source.

The following working conditions were adopted:

- filament current: 0.2 mA;
- acceleration potential: 5 kV;
- dynode current: 2 V;
- reagent gas: *iso*-butane;
- scanning: 100 amu/e – 1000 amu/e.

High-Resolution-Mass Spectrometry (HRMS)

Samples of the compounds obtained were analyzed by High-Resolution-Mass Spectrometry (HRMS) using a Thermo LTQ FT-ICR spectrometer, working by direct injection of the sample to be analysed by means of syringe-pump and using the

"electrospray" (ESI) source. The working conditions used are given below.

"API" (Atmospheric Pressure Ionization) source

- Source Voltage: 4.5 kV;
- Sheath Gas Flow Rate (arbitrary units): 10.0;
- Aux Gas Flow Rate (arbitrary units): 5.0;
- capillary voltage: 12.0 V;
- capillary temperature: 275.0°C;
- tube lens voltage: 70.0 V.

ION DETECTION SYSTEM

- dynode voltage: -14.8 kV;
- multiplier 1: -1323.9 V;
- Resolution Power (RP): 400000.

ELEMENTAL ANALYSIS

Carbon, hydrogen, nitrogen, sulphur and oxygen determination

In the compounds obtained, the carbon, hydrogen, nitrogen and sulphur, were determined using a Thermo Fisher automatic analyser, model Flash 2000, whilst the oxygen was determined using a Thermo Fisher automatic analyser, model EA 1100.

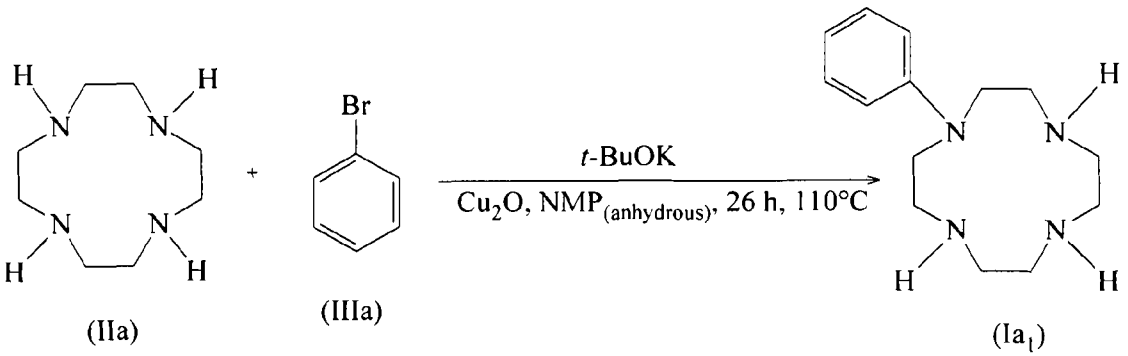
^{1}H-NMR spectra

The ^{1}H-NMR spectra of the compounds obtained were carried out using an NMR Bruker Avance 400 spectrometer.

For this purpose, approximately 10 mg of the compound to be analysed were dissolved in approximately 0.75 ml of dimethylsulphoxide hexadeuterate ($DMSO_{d6}$) from Aldrich, directly in the glass tube used for the measurement. The scale of the chemical shifts was calibrated in relation to the tetramethylsilane (TMS) signal at 0 ppm.

EXAMPLE 1

Synthesis of 1-phenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_1)



(IIa) (IIIa) (Ia_1)

All glassware used was previously furnace-dried at 130°C under vacuum for one night, rapidly assembled under heating, and cooled to room temperature (25°C), under argon flow (Ar).

Into a 50 ml long-necked test tube, provided with a magnetic stir bar and a tap, were introduced, under argon (Ar) flow, 230 mg (1.33×10^{-3} mol) of 1,4,7,10-tetraazacyclododecane (Aldrich) having formula (IIa), 764 mg (6.81×10^{-3} mol) of potassium *t*-butoxide (*t*-BuOK) (Aldrich), 262 µl (2.50×10^{-3} mol) of bromobenzene (Aldrich) having formula (IIIa), 249 mg (1.74×10^{-3} mol) of cuprous oxide (Cu_2O) (Aldrich) and 20.0 ml of anhydrous *N*-methyl-2-pyrrolidone [$NMP_{(anhydrous)}$] (Aldrich).

The long-necked test tube was subsequently immersed in a bath which had been preheated to 110°C, and the whole was left under stirring (700 rpm) for 26 hours, working as follows: when 110°C was reached, the long-necked test tube was allowed to vent by opening the tap, still under argon (Ar) flow, for approximately 2 seconds, so as to avoid the pressure increase resulting from the temperature increase, and subsequently the tap was closed again and the long-necked test tube was kept at said temperature for 26 hours. At the end, the progress of the reaction was controlled, working as follows: 0.1 ml of reaction mixture were removed from the long-necked test tube and placed in a test tube containing 1 ml of diethylether [$(CH_3CH_2)_2O$] (Aldrich) and 2 ml of an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$], and the whole

was left under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and subjected to Thin Layer Chromatography (TLC) on neutral alumina, using a methanol [CH_3OH] (Aldrich)/dichloromethane [CH_2Cl_2] (Aldrich) mixture (1/1, v/v) as eluent and a 254 nm ultraviolet (UV) lamp as detector: said analysis indicated that 1-phenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_1) had been formed.

The reaction mixture was subsequently submerged in a separating funnel containing diethyl ether [$(CH_3CH_2)_2O$] (Aldrich) and an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the whole was put under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and extracted three times using an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the aqueous phases obtained were put together, and extracted twice using diethyl ether [$(CH_3CH_2)_2O$] (Aldrich). The organic phases obtained at the end of the extractions were put together and dried using a rotary evaporator, and the resulting oil was treated using an oil pump so as to eliminate the traces of solvent still present, to obtain a residue which was dissolved in the minimum possible volume of dichloromethane (CH_2Cl_2) (Aldrich); subsequently 2 g of basic alumina (Aldrich) were added thereto and subsequently it was dried again using a rotary evaporator.

The powder obtained was placed over a basic alumina panel (Aldrich) so in order to be filtered, initially, using *n*-heptane (Aldrich), so as to remove all the low-polarity impurities, and subsequently, working in gradient elution towards a methanol [CH_3OH] (Aldrich)/dichloromethane [CH_2Cl_2] (Aldrich) mixture (1/1, v/v), so as to elute the 1-phenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_1). The filtrate obtained was evaporated until dry using a rotary evaporator to obtain 267 mg of a white solid of pure 1-

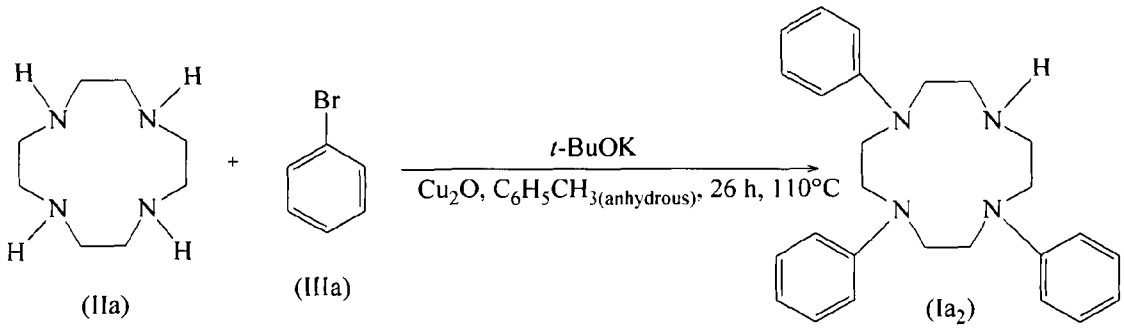
phenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_1) (81% yield), which was subjected to the following characterizations.

DCI/MS (m/z): $[M+H]^+$: 249.2 (100%); $[M+H+gas]^+$: 305.2 (21%).

Elemental analysis [found (calculated)]: C: 68.00% (67.70%); H: 9.81% (9.74%); N: 22.49% (22.56%).

EXAMPLE 2

Synthesis of 1,4,7-triphenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_2)



All glassware used was previously furnace-dried at 130°C under vacuum for one night, rapidly assembled under heating, and cooled to room temperature (25°C), under argon flow (Ar).

Into a 50 ml long-necked test tube, provided with a magnetic stir bar and a tap, were introduced, under argon (Ar) flow, 230 mg (1.33×10^{-3} mol) of 1,4,7,10-tetraazacyclododecane (Aldrich) having formula (IIa), 2.60 g (2.32×10^{-2} mol) of potassium *t*-butoxide (*t*-BuOK) (Aldrich), 431 µl (4.10×10^{-3} mol) of bromobenzene (Aldrich) having formula (IIIa), 249 mg (1.74×10^{-3} mol) of cuprous oxide (Cu_2O) (Aldrich) and 20.0 ml of anhydrous toluene [$C_6H_5CH_{3(anhydrous)}$] (Aldrich).

The long-necked test tube was subsequently immersed in a bath which had been preheated to 110°C, and the whole was left under stirring (700 rpm) for 26 hours, working as follows: when 110°C was reached, the long-necked test tube was allowed to vent by opening the tap, still under argon (Ar) flow, for approximately 2 seconds, so as to avoid

the pressure increase resulting from the temperature increase, and subsequently the tap was closed again and the long-necked test tube was kept at said temperature for 26 hours. At the end, the progress of the reaction was controlled, working as follows: 0.1 ml of reaction mixture were removed from the long-necked test tube and placed in a test tube containing 1 ml of toluene [$C_6H_5CH_3$] (Aldrich) and 2 ml of an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$], and the whole was left under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and subjected to Thin Layer Chromatography (TLC) on neutral alumina, using dichloromethane [CH_2Cl_2] (Aldrich) as eluent and a 254 nm ultraviolet (UV) lamp as detector: said analysis indicated that 1,4,7-triphenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_2) had been formed.

The reaction mixture was subsequently submerged in a separating funnel containing toluene [$C_6H_5CH_3$] (Aldrich) and an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the whole was put under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and extracted three times using an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the aqueous phases obtained were put together, and extracted twice using toluene [$C_6H_5CH_3$] (Aldrich). The organic phases obtained at the end of the extractions were put together and dried using a rotary evaporator, and the resulting residue was dissolved in the minimum possible volume of dichloromethane (CH_2Cl_2) (Aldrich); subsequently 2 g of basic alumina (Aldrich) were added thereto and subsequently it was dried again using a rotary evaporator.

The powder obtained was placed over a basic alumina panel (Aldrich) in order to be

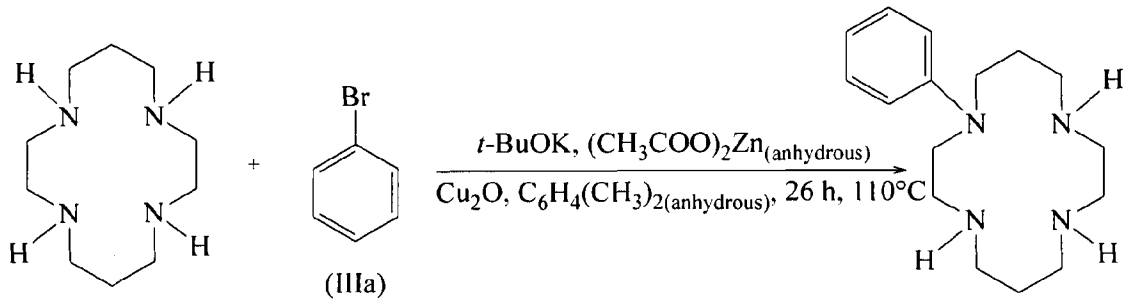
filtered, initially, using *n*-heptane (Aldrich), so as to remove all the low-polarity impurities, and subsequently, working in gradient elution towards dichloromethane [CH_2Cl_2] (Aldrich), so as to elute the 1,4,7-triphenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_2). The filtrate obtained was evaporated until dry using a rotary evaporator to obtain 469 mg of a white solid of pure 1,4,7-triphenyl-1,4,7,10-tetraazacyclododecane having formula (Ia_2) (88% yield), which was subjected to the following characterizations.

DCI/MS (m/z): $[M+H]^+$: 401.3 (100%); $[M+H+gas]^+$ 457.3 (27%).

Elemental analysis [found (calculated)]: C: 77.90% (77.96%); H: 8.08% (8.05%); N: 14.02% (13.99%).

EXAMPLE 3

Synthesis of 1-phenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_1)



(IIb) (IIIa) (Ib_1)

All glassware used was previously furnace-dried at 130°C under vacuum for one night, rapidly assembled under heating, and cooled to room temperature (25°C), under argon flow (Ar).

Into a 50 ml long-necked test tube, provided with a magnetic stir bar and a tap, were introduced, under argon (Ar) flow, 255 mg (1.27×10^{-3} mol) of 1,4,8,11-tetraazacyclotetradecane (Aldrich) having formula (IIb), 250 mg (1.36×10^{-3} mol) of anhydrous zinc acetate [$(CH_3COO)_2Zn_{(anhydrous)}$] and 10.0 ml of anhydrous xylene [$C_6H_4(CH_3)_{2(anhydrous)}$] (Aldrich).

The long-necked test tube was subsequently immersed in a bath which had been

preheated to 110°C, and the whole was left under stirring (700 rpm) for 10 minutes. The long-necked test tube was subsequently removed from the heating bath and brought to room temperature (25°C) using compressed air, and subsequently, under argon flow (Ar), 320 mg (2.24×10^{-2} mol) of cuprous oxide (Cu_2O) (Aldrich), 747 mg (6.66×10^{-3} mol) of potassium *t*-butoxide (*t*-BuOK) (Aldrich), 147 µl (1.40×10^{-3} mol) of bromobenzene (Aldrich) having formula (IIIa), and a further 10.0 ml of anhydrous xylene [$C_6H_4(CH_3)_{2(anhydrous)}$] (Aldrich) were added.

The long-necked test tube was subsequently again immersed in a bath which had been preheated to 110°C, and the whole was left under stirring (700 rpm) for 26 hours, working as follows: when 110°C was reached, the long-necked test tube was allowed to vent by opening the tap, still under argon (Ar) flow, for approximately 2 seconds, so as to avoid the pressure increase resulting from the temperature increase, and subsequently the tap was closed again and the long-necked test tube was kept at said temperature for 26 hours. At the end, the progress of the reaction was controlled, working as follows: 0.1 ml of reaction mixture were removed from the long-necked test tube and placed in a test tube containing 1 ml of toluene [$C_6H_5CH_3$] (Aldrich) and 2 ml of an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$], and the whole was put under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and subjected to Thin Layer Chromatography (TLC) on neutral alumina, using a methanol [CH_3OH] (Aldrich)/dichloromethane [CH_2Cl_2] (Aldrich) mixture (1/1, v/v) as eluent and a 254 nm ultraviolet (UV) lamp as detector: said analysis indicated that 1-phenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_1) had been formed.

The reaction mixture was subsequently submerged in a separating funnel containing toluene [$C_6H_5CH_3$] (Aldrich) and an aqueous solution at pH 14 prepared using potassium

hydroxide (Aldrich) [$KOH_{(aq.)}$]: the whole was left under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and extracted three times using an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the aqueous phases obtained were put together, and extracted twice using toluene [$C_6H_5CH_3$] (Aldrich). The organic phases obtained at the end of the extractions were put together and dried using a rotary evaporator, and the resulting residue was dissolved in the minimum possible volume of dichloromethane (CH_2Cl_2) (Aldrich); subsequently 2 g of basic alumina (Aldrich) were added thereto and subsequently it was dried again using a rotary evaporator.

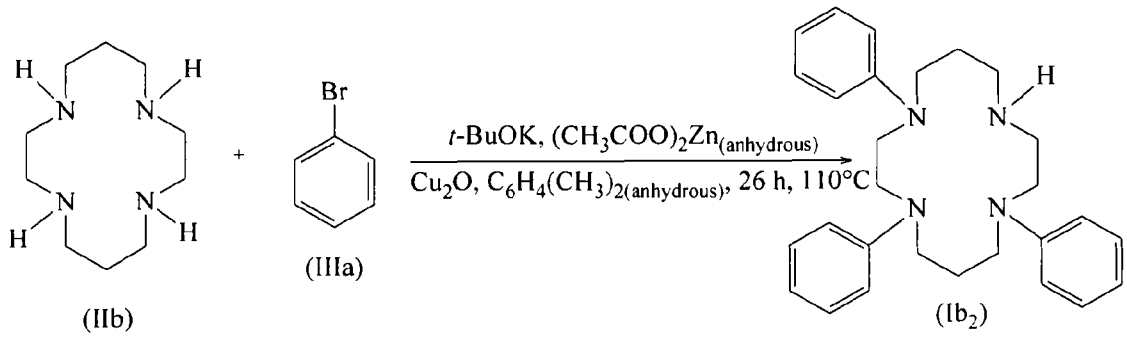
The powder obtained was placed over a basic alumina panel (Aldrich) in order to be filtered, initially, using *n*-heptane (Aldrich), so as to remove all the low-polarity impurities, and subsequently, working in gradient elution towards a methanol [CH_3OH] (Aldrich)/dichloromethane [CH_2Cl_2] (Aldrich) mixture (1/1, v/v), so as to elute the 1-phenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_1). The filtrate obtained was evaporated until dry using a rotary evaporator to obtain 281 mg of a white solid of pure 1-phenyl-1,4,8,11-tetraazacyclododecane having formula (Ib_1) (80% yield), which was subjected to the following characterizations.

DCI/MS (m/z): $[M+H]^+$: 277.2 (100%); $[M+H+gas]^+$: 333.3 (18%).

Elemental analysis [found (calculated)]: C: 69.60% (69.52%); H: 10.12 (10.21%); N: 20.30% (20.27%).

EXAMPLE 4

Synthesis of 1,4,8-triphenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_2)



(IIb) (IIIa) (Ib_2)

All glassware used was previously furnace-dried at 130°C under vacuum for one night, rapidly assembled under heating, and cooled to room temperature (25°C), under argon flow (Ar).

Into a 50 ml long-necked test tube, provided with a magnetic stir bar and a tap, were introduced, under argon (Ar) flow, 250 mg (1.25×10^{-3} mol) of 1,4,8,11-tetraazacyclotetradecane (Aldrich) having formula (IIb), 247 mg (1.35×10^{-3} mol) of anhydrous zinc acetate [$(CH_3COO)_2Zn_{(anhydrous)}$] and 10.0 ml of anhydrous xylene [$C_6H_4(CH_3)_{2(anhydrous)}$] (Aldrich).

The long-necked test tube was subsequently immersed in a bath which had been preheated to 110°C, and the whole was left under stirring (700 rpm) for 10 minutes. The long-necked test tube was subsequently removed from the heating bath and brought to room temperature (25°C) using compressed air, and subsequently, under argon flow (Ar), 289 mg (2.02×10^{-3} mol) of cuprous oxide (Cu_2O) (Aldrich), 1.82 g (1.62×10^{-2} mol) of potassium *t*-butoxide (*t*-BuOK) (Aldrich), 421 µl (4.01×10^{-3} mol) of bromobenzene (Aldrich) having formula (IIIa), and a further 10.0 ml of anhydrous xylene [$C_6H_4(CH_3)_{2(anhydrous)}$] (Aldrich) were added.

The long-necked test tube was subsequently again immersed in a bath which had been preheated to 110°C, and the whole was left under stirring (700 rpm) for 26 hours, working as follows: when 110°C was reached, the long-necked test tube was allowed to vent by opening the tap, still under argon (Ar) flow, for approximately 2 seconds, so as to avoid

the pressure increase resulting from the temperature increase, and subsequently the tap was closed again and the long-necked test tube was kept at said temperature for 26 hours. At the end, the progress of the reaction was controlled, working as follows: 0.1 ml of reaction mixture were removed from the long-necked test tube and placed in a test tube containing 1 ml of toluene [$C_6H_5CH_3$] (Aldrich) and 2 ml of an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$], and the whole was left under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and subjected to Thin Layer Chromatography (TLC) on neutral alumina, using dichloromethane [CH_2Cl_2] (Aldrich) as eluent and a 254 nm ultraviolet (UV) lamp as detector: said analysis indicated that 1,4,8-triphenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_2) had been formed.

The reaction mixture was subsequently submerged in a separating funnel containing toluene [$C_6H_5CH_3$] (Aldrich) and an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the whole was put under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and extracted three times using an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the aqueous phases obtained were put together, and extracted twice using toluene [$C_6H_5CH_3$] (Aldrich). The organic phases obtained at the end of the extractions were put together and dried using a rotary evaporator, and the resulting residue was dissolved in the minimum possible volume of dichloromethane (CH_2Cl_2) (Aldrich); subsequently 2 g of basic alumina (Aldrich) were added thereto and subsequently it was dried again using a rotary evaporator.

The powder obtained was placed over a basic alumina panel (Aldrich) in order to be

filtered, initially, using *n*-heptane (Aldrich), so as to remove all the low-polarity impurities, and subsequently, working in gradient elution towards dichloromethane [CH_2Cl_2] (Aldrich), so as to elute the 1,4,8-triphenyl-1,4,8,11- tetraazacyclotetradecane having formula (Ib_2). The filtrate obtained was evaporated until dry using a rotary evaporator to obtain 423 mg of a white solid of pure 1,4,8-triphenyl-1,4,8,11- tetraazacyclotetradecane having formula (Ib_2) (79% yield), which was subjected to the following characterizations.

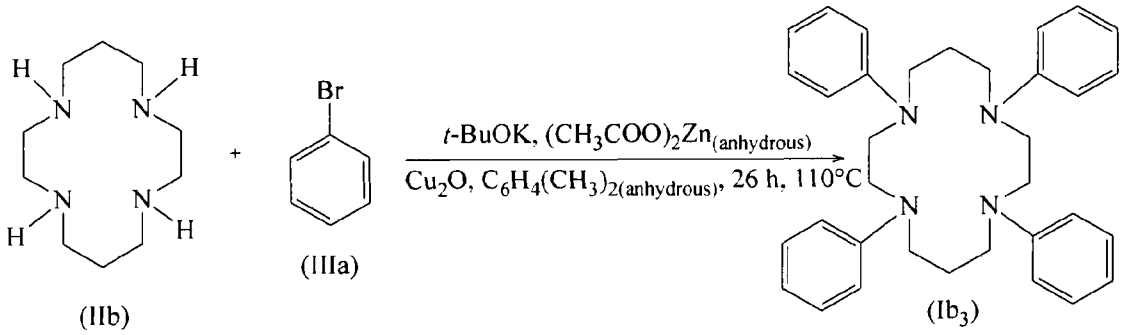
DCI/MS (m/z): $[M+H]^+$: 429.3 (100%); $[M+H+gas]^+$: 485.4 (18%).

HRMS (m/z): 429.3017±1.0029 ppm $[C_{28}H_{37}N_4]^+$.

Elemental analysis [found (calculated)]: C: 78.51% (78.46%); H: 8.50 (8.47%); N: 13.01% (13.07%).

EXAMPLE 5

Synthesis of 1,4,8,11-tetraphenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_3)



All glassware used was previously furnace-dried at 130°C under vacuum for one night, rapidly assembled under heating, and cooled to room temperature (25°C), under argon flow (Ar).

Into a 500 ml three-necked flask, provided with a magnetic stir bar, a thermometer having a ground glass joint, an insufflator having a tap, and a plug, were introduced, under argon (Ar) flow, 2.55 g (1.27×10^{-2} mol) of 1,4,8,11-tetraazacyclotetradecane (Aldrich) having formula (IIb), 2.49 g (1.36×10^{-2} mol) of anhydrous zinc acetate [$(CH_3COO)_2Zn_{(anhydrous)}$] and 100 ml of anhydrous xylene [$C_6H_4(CH_3)_{2(anhydrous)}$] (Aldrich).

The flask was subsequently immersed in a bath which had been preheated to 119°C, and the whole was left under stirring (700 rpm) for 10 minutes. The flask was subsequently removed from the heating bath and brought to room temperature (25°C) using compressed air, and subsequently, under argon flow (Ar), 3.10 g (2.17×10^{-2} mol) of cuprous oxide (Cu_2O) (Aldrich), 27.4 g (0.244 mol) of potassium *t*-butoxide (*t*-BuOK) (Aldrich), 5.60 ml (5.33×10^{-2} mol) of bromobenzene (Aldrich) having formula (IIIa), and a further 80.0 ml of anhydrous xylene [$C_6H_4(CH_3)_{2(anhydrous)}$] (Aldrich) were added.

The flask was subsequently again immersed in a bath which had been preheated to 119°C, and the whole was left under stirring (700 rpm) for 26 hours, working as follows: when 110°C was reached (as shown by the thermometer having a ground glass joint), the tap of the insufflator was opened, still under argon (Ar) flow, for approximately 5 seconds, so as to avoid the pressure increase resulting from the temperature increase, and subsequently the tap was closed again and the long-necked test tube was kept at said temperature for 26 hours.

At the end, the progress of the reaction was controlled, working as follows: 0.1 ml of reaction mixture were removed from the flask and placed in a test tube containing 1 ml of toluene [$C_6H_5CH_3$] (Aldrich) and 2 ml of an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$], and the whole was put under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and subjected to Thin Layer Chromatography (TLC) on neutral alumina, using dichloromethane [CH_2Cl_2] (Aldrich) as eluent and a 254 nm ultraviolet (UV) lamp as detector: said analysis indicated that 1,4,8,11-tetraphenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_3) had been formed.

The reaction mixture was subsequently submerged in a separating funnel containing

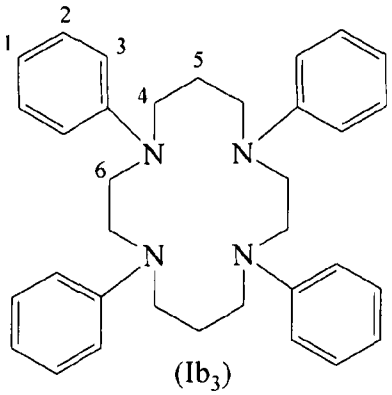
toluene [$C_6H_5CH_3$] (Aldrich) and an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the whole was put under stirring to obtain a biphasic system comprising a predominantly organic phase and a predominantly aqueous phase. The predominantly organic phase was separated and extracted three times using an aqueous solution at pH 14 prepared using potassium hydroxide (Aldrich) [$KOH_{(aq.)}$]: the aqueous phases obtained were put together, and extracted twice using toluene [$C_6H_5CH_3$] (Aldrich). The organic phases obtained at the end of the extractions were put together and dried using a rotary evaporator, and the resulting residue was dissolved in the minimum possible volume of dichloromethane (CH_2Cl_2) (Aldrich); subsequently 10 g of basic alumina (Aldrich) were added thereto and subsequently it was dried again using a rotary evaporator.

The powder obtained was placed over a basic alumina panel (Aldrich) in order to be filtered, initially, using *n*-heptane (Aldrich), so as to remove all the low-polarity impurities, and subsequently, working in gradient elution towards dichloromethane [CH_2Cl_2] (Aldrich), so as to elute the 1,4,8,11-tetraphenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_3). The filtrate obtained was evaporated until dry using a rotary evaporator to obtain 6.09 g of a white solid of pure 1,4,8,11-tetraphenyl-1,4,8,11-tetraazacyclotetradecane having formula (Ib_3) (95% yield), which was subjected to the following characterisations.

DCI/MS (m/z): $[M+H]^+$: 505.3 (100%); $[M+H+gas]^+$: 561.3 (18%).

HRMS (m/z): 505.3332±1.3196 ppm $[C_{34}H_{41}N_4]^+$.

Elemental analysis [found (calculated)]: C: 80.95% (80.91%); H: 8.05% (7.99%); N: 11.08% (11.10%).



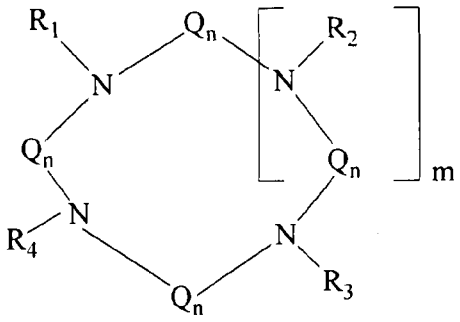
(Ib_3)

^{1}H-MNR (400 MHz, $DMSO_{d6}$,) δ (ppm): 7.20 (dd, $J_{2,1}$ = 7.3 Hz, $J_{2,3}$ = 8.0 Hz, 8H, H_2); 6.80 (d, $J_{3,2}$ = 8.0 Hz, 8H, H_3); 6.67 (t, $J_{1,2}$ = 7.3 Hz, 4H, H_1); 3.55 (s, 8H, H_6); 3.49 (br. t, $J_{4,5}$ = 6.7 Hz, 8H, H_4); 1.93 (br. m, $J_{5,4}$ = 6.7 Hz, 4H, H_5).

ICP (ppm): B < 30; Na = 20*10^2; Mg = 50; Al = 80*10^1; P < 20; K < 10*10^1; Sc < 5; Ti = 3; V < 10; Cr = 7; Mn = 0.4; Fe = 90; Ni < 30; Cu = 7.0; Zn < 10*10^1; As = 0.6; Sr = 1; Nb < 3; Mo < 5; Pd = 5; Sn < 1; Ba < 10*10^1; W < 5; Ir < 3; Pt < 3; Au < 5; Pb = 0,6; Bi < 1.

CLAIMS

1. Process for the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group having general formula (I):



(I)

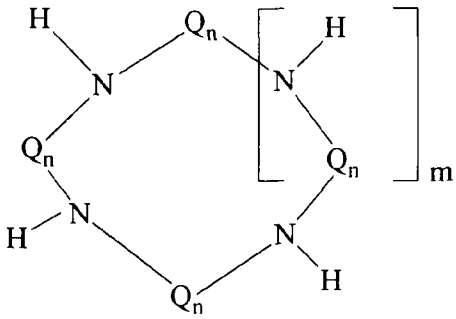
in which:

- Q represents a $-CH_2-$ group; a -C(O)- group; a $-CHR_5$ group in which R_5 represents a hydrogen atom, or a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; a $-CO_2R_6$ group in which R_6 represents a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; an optionally substituted aryl group;
- n, identical or different from one another, are an integer ranging from 1 to 3;
- m is 0, or an integer ranging from 1 to 9;
- R_1, R_2, R_3 and R_4, identical or different from one another, represent a hydrogen atom; or represent a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; an optionally substituted cycloalkyl group; an optionally substituted aryl group; an optionally substituted heteroaryl group; with the proviso that at least one of R_1, R_2, R_3 and R_4, is an optionally substituted aryl group or an optionally substituted heteroaryl group;

with the proviso that at least one of R_1, R_2, R_3 and R_4, is an optionally substituted

aryl group or an optionally substituted heteroaryl group;

said process comprising reacting at least one polyazamacrocycle having general formula (II):



(II)

in which Q, n and m, have the same meanings as described above;

with at least one halogenated aryl or heteroaryl compound having general formula (III):

Ar-X (III)

in which Ar represents an optionally substituted aryl group, or an optionally substituted heteroaryl group, X represents a halogen atom selected from fluorine, chlorine, bromine, iodine, preferably bromine;

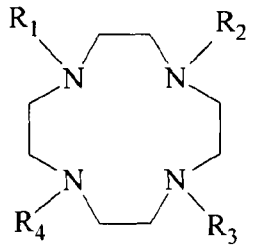
in the presence of at least one strong base, at least one anhydrous aprotic organic solvent and at least one catalyst containing copper in oxidation state +1 having general formula (IV):

Cu_pX_1 (IV)

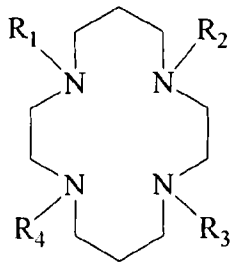
in which X_1 represents an oxygen atom, or a halogen atom selected from chlorine, bromine, iodine, preferably an oxygen atom, and p is 1 in the case wherein X_1 represents a halogen atom, or 2 in the case wherein X_1 represents an oxygen atom.

2. Process according to claim 1, wherein said process relates to the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group having general formula (I) substantially free of metal ions.

3. Process according to claim 1 or 2, wherein said process relates to the preparation of a polyazamacrocycle substituted with at least one aryl or heteroaryl group having general formula (Ia) or (Ib):



(Ia)

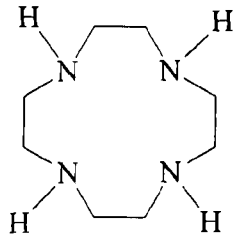


(Ib)

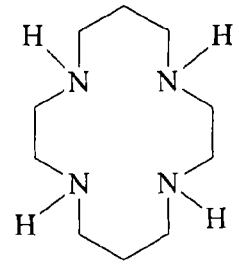
in which:

- R_1, R_2, R_3 and R_4, identical or different from one another, represent a hydrogen atom; or represent a C_1-C_{20} alkyl group, preferably C_1-C_{10}, linear or branched, saturated or unsaturated, optionally containing heteroatoms; an optionally substituted cycloalkyl group; an optionally substituted aryl group; an optionally substituted heteroaryl group; with the proviso that at least one of R_1, R_2, R_3 and R_4, is an optionally substituted aryl group or an optionally substituted heteroaryl group; preferably an aryl group, still more preferably a phenyl;

said process comprising reacting at least one polyazamacrocycle having general formula (IIa) or (IIb):



(IIa)



(IIb)

with at least one halogenated aryl or heteroaryl compound having general formula (III):

Ar-X (III)

in which Ar represents an optionally substituted aryl group, or an optionally substituted heteroaryl group, preferably an aryl group, still more preferably a phenyl, X represents a halogen atom selected from fluorine, chlorine, bromine, iodine, preferably bromine;

in the presence of at least one strong base, at least one anhydrous aprotic organic solvent and at least one catalyst containing copper in oxidation state +1 having general formula (IV):

Cu_pX_1 (IV)

in which X_1 represents an oxygen atom, or a halogen atom selected from chlorine, bromine, iodine, preferably an oxygen atom, and p is 1 in the case wherein X_1 represents a halogen atom, or 2 in the case wherein X_1 represents an oxygen atom.

4. Process according to any of the preceding claims, wherein said polyazamacrocycle having general formula (II) and said halogenated aryl or heteroaryl compound having general formula (III) are used in molar ratios ranging from 1:1 to 1:2 for each

substituent to be introduced, preferably ranging from 1:1 to 1:1.9 for each substituent to be introduced.

5. Process according to any of the preceding claims, wherein said strong base is selected from: alkali metal alkoxides such as lithium *t*-butoxide, sodium *t*-butoxide, potassium *t*-butoxide, cesium *t*-butoxide, rubidium *t*-butoxide, or mixtures thereof; alkali metal amides such as lithium amide, sodium amide, potassium amide, cesium amide, rubidium amide, or mixtures thereof; or mixtures thereof; preferably, said strong base is potassium *t*-butoxide.

6. Process according to any of the preceding claims, wherein said polyazamacrocycle having general formula (II) and said strong base are used in molar ratios ranging from 1:1 to 1:6 for each substituent to be introduced, preferably ranging from 1:4 to 1:5.9 for each substituent to be introduced.

7. Process according to any of the preceding claims, wherein said aprotic organic solvent is selected from anhydrous *N,N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), *N,N*-dimethylacetamide (DMAc), toluene, xylene, benzonitrile (PhCN), or mixtures thereof; preferably, said anhydrous aprotic organic solvent is selected from *N*-methyl-2-pyrrolidone (NMP), toluene, xylene.

8. Process according to any of the preceding claims, wherein said polyazamacrocycle having general formula (II) is used in said anhydrous aprotic organic solvent in such a quantity so as to have a molar concentration in said solvent ranging from 5.0×10^{-2} M to 8.0×10^{-2} M, preferably ranging from 6.0×10^{-2} M to 7.5×10^{-2} M.

9. Process according to any of the preceding claims, wherein said process is carried out in the presence of at least one anhydrous zinc salt selected from: zinc acetate, zinc chloride, zinc tetrafluoroborate; preferably, the anhydrous zinc salt is zinc acetate.

10. Process according to any of the preceding claims, wherein said polyazamacrocycle having general formula (II) and said anhydrous zinc salt are used in molar ratios ranging from 1:1 to 1:1.5, preferably ranging from 1:1 to 1:1.2.

11. Process according to any of the preceding claims, wherein said process is carried out at a temperature ranging from 50°C to 150 °C, preferably ranging from 100°C to 130°C.

12. Process according to any of the preceding claims, wherein said process is carried out for a time ranging from 1 hour to 36 hours, preferably ranging from 10 hours to 30 hours.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055120

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D257/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZYRYANOV ET AL.: "Synthesis of 1-amino-2,5-di(2-thienyl)benzenes as potential monomers for the preparation of hybrid polythiophene anionic sensors", RUSSIAN CHEMICAL BULLETIN, INTERNATIONAL EDITION, vol. 61, no. 2, 2012, pages 303-307, XP035146187, page 303 - page 306; table 1	1-12

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[X] Further documents are listed in the continuation of Box C.

[ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2015	01/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fazzi, Raffaella

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALEXEI D. AVERIN ET AL: "Synthesis of 1,3-Bis(trimethylcyclam) and 1,3-Bis(trimethylcyclen) Substituted Benzenes", MACROHETEROCYCLES, vol. 2, no. 3-4, 2009, pages 281-285, XP055152046, RU page 283	1-12
A	BELETSKAYA ET A L.: "Palladium-catalyzed arylation of linear and cyclic polyamines", EUR. J. ORG. CHEM., 2005, pages 261-280, XP002732547, DOI: 10.1002/ejoc.200400456 cited in the application page 265	1-12
A	BELETSKAYA I P ET AL: "Synthesis of 1,8-bis(cyclam) and 1,8-bis(azacrown) substituted anthracenes by palladium-catalyzed arylation of cyclam", TETRAHEDRON LETTERS, PERGAMON, GB, vol. 43, no. 7, 11 February 2002 (2002-02-11), pages 1193-1196, XP004333883, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(01)02356-5 page 1194	1-12
A	COLLINS ET AL.: "Effect of solvent polarity, pH, and metal complexation on the triple fluorescence of 4-(N-1,4,8,11-tetraazacyclotetradecyl)benzonitrile", J. AM. CHEM. SOC., vol. 120, 1998, pages 1474-1478, XP002732548, page 1475	1-12

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