

PROCESS FOR PREPARING INTERMEDIATES OF SARTAN ACTIVE COMPOUNDS

FIELD OF THE INVENTION

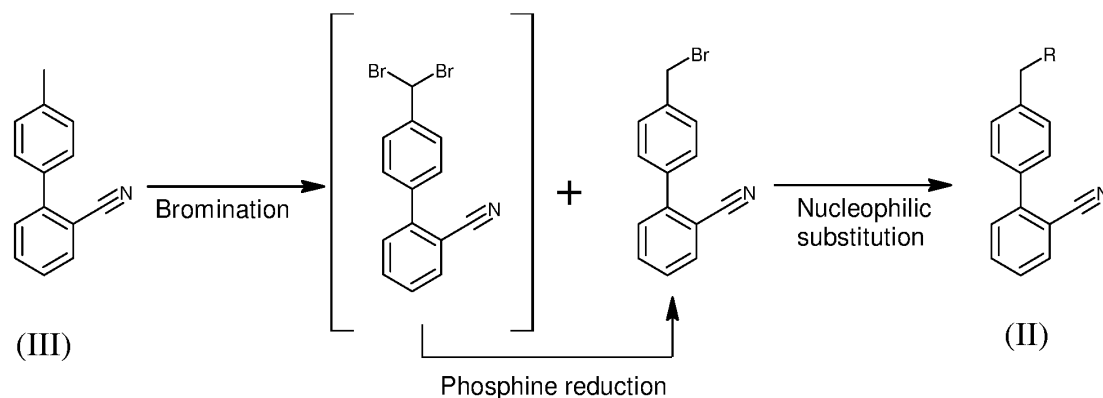
The invention belongs to the field of pharmacy, and particularly relates to a process for preparing intermediates used in the synthesis of sartan active compounds having a tetrazole ring.

BACKGROUND OF THE DISCLOSURE

Irbesartan, losartan, valsartan and candesartan are all prescription angiotensin receptor blocker (ARB) drugs, which are also known as “sartans” active compounds. “Sartans” are a class of drugs used to treat patients with high blood pressure to help prevent heart attacks and stroke. In particular, irbesartan is an antihypertensive drug that is an angiotensin II type I (AT1)-receptor antagonist for the treatment of hypertension. The drug is also the first major antihypertensive drug approved for the treatment of patients with hypertension, type 2 diabetes, and kidney disease.

A process for preparing intermediates hereafter compounds of formula (II), involved in the synthesis of sartan active compounds, is described in prior art and involves three steps, starting from o-tolylbenzonitrile hereafter compound of formula (III), as disclosed in the following scheme 1:

Scheme 1



R being selected from formulas (1), (2), (3), (4) and (5) as defined herein after.

In prior art, such as documents WO2023052309 and Manian Rajesh Kumar et al. Adv. Synth. Catal. 2010, 352, 3255-3266, the R group of the sartan active compounds is introduced by using a nucleophilic substitution of a compound RH or one of its salts in a second step, starting from a monobrominated compound, which presents several drawbacks.

5 Indeed, the bromination step, i.e. the first step of the scheme above, generates a considerable amount of bromide containing salts which have then to be treated as aqueous effluent. For example, one kilogram of bromide is used for the synthesis of one kilogram of irbesartan. Moreover, the bromination step is not very selective as it also generates di-brominated product. Thus, such step requires another step of treatment corresponding to a
10 phosphine reduction of the di-brominated product into the mono-brominated product, prior to the nucleophilic substitution. Moreover, the bromination step is performed in dichloromethane as a solvent being a hazardous volatile organic compound. Finally, brominated products are allergizing and thus can induce health issues.

Other prior art documents, such as David J Carini et al. J. Med. Chem. 1991, 34, 2525-
15 2547, involved mono-brominated intermediates also obtained thanks to a step of bromination which present the above-mentioned drawbacks.

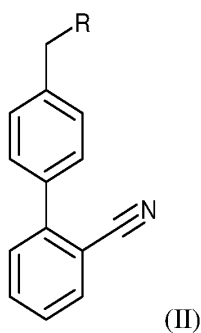
Other prior art documents, such as Lukas J. Goossen et al. J. org. Chem. 2007, 72, 7473-7476, disclose the synthesis of sartan precursor using a compound comprising an aldehyde group.

20 Furthermore, the mono-brominated product was identified as being a precursor to well-known hazardous benzylic azide impurities formed during the process to synthesize sartan active compounds, much more defined herein after.

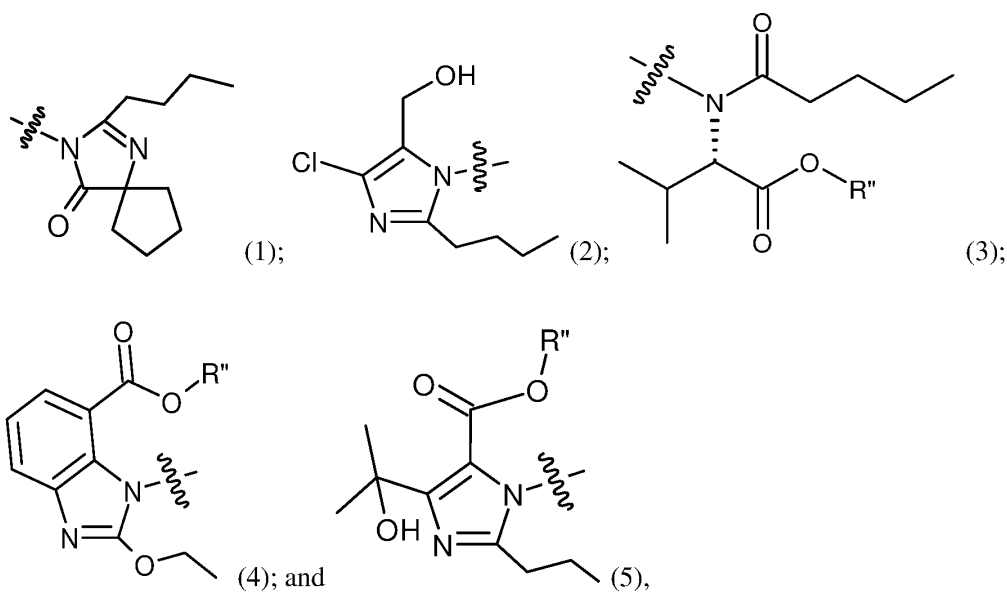
According to the herein above detailed drawbacks and in view of the industrial and environmental requirements, there is still a need to provide new routes for the synthesis of sartan
25 active compounds.

SUMMARY OF THE DISCLOSURE

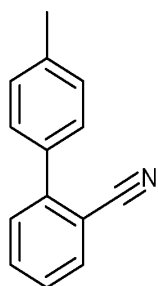
Disclosed herein is a novel process for preparing a compound of formula (II):



wherein R is selected from formulas (1), (2), (3), (4) and (5):



- 5 wherein R'' is selected from a hydrogen atom and a (C₁-C₃)alkyl group, comprising reacting a compound of formula (III)



with a compound RH or one of its salts, wherein R is as defined above, under metal catalyzed dehydrogenative amidation conditions.

Such process allows to provide a synthetic route to form compound of formula (II) as defined above with only one reaction step compared to the synthetic route of the prior art described in the above scheme 1 which comprises three reaction steps. Thus, a straightforward route thanks to fewer steps is obtained allowing atom economy. It implies, compared to known processes, that lower number of isolations, solvents and purification steps are implemented, which reduces the waste generated by process.

Typically, such process bypasses the mono-brominated product synthesis route described in scheme 1, which avoids hazardous intermediates in particular allergizing brominated products, hazardous solvent for example dichloromethane, as well as some effluent treatment for example aqueous effluent comprising bromide salts.

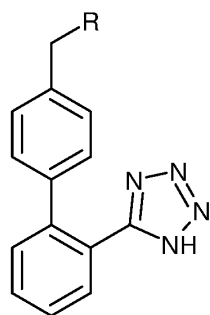
Furthermore, the process avoids hazardous intermediates by bypassing the mono-brominated product synthetic route, in particular allergizing brominated products which are also sources of hazardous benzylic azide impurities for example azido nitrile and azido tetrazole described in the paragraph "tetrazolylolation step" hereafter.

In addition, the process provides high yielding synthesis of compound of formula (II) as defined above, as well as robust and scalable conditions, which fulfills the current industrial requirements.

Moreover, such process is cost effective by lowering the number of steps but also by implementing for example a cheap catalyst as apparent in the paragraph "catalyst sources" described hereafter.

Finally, in view of the advantages hereabove, such process is in adequation with the green chemistry requirements.

Disclosed herein is also a novel process for preparing a sartan active compound of formula (I) or one of its pharmaceutically acceptable salts:

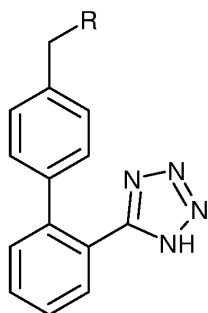


(I), wherein R is as defined above,

comprising a tetrazolylolation step reacting the compound of formula (II) as defined above as prepared by the process described above, in particular a tetrazolylolation step wherein it is

performed in a reactional medium with at least one azide derivative, wherein benzylic azide impurities formed during said tetrazolylolation are converted into aldehyde derivatives.

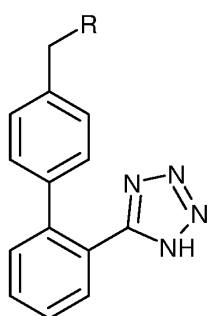
In other words, disclosed herein is also a novel process for preparing a sartan active compound of formula (I) or one of its pharmaceutically acceptable salts:



5 (I), wherein R is as defined above,

comprising a tetrazolylolation step reacting the compound of formula (II) as defined above prepared by the process described above, in particular a tetrazolylolation step wherein it is performed in a reactional medium with at least one azide derivative, wherein benzylic azide impurities formed during said tetrazolylolation are converted into aldehyde derivatives.

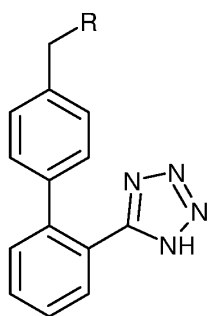
10 In other words, disclosed herein is a process for preparing a sartan active compound of formula (I) or one of its pharmaceutically acceptable salts:



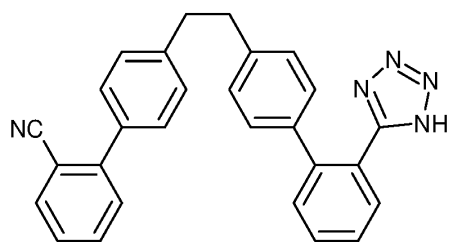
(I), wherein R is as defined above,

comprising a tetrazolylolation step reacting the compound of formula (II) as defined above and wherein the process comprises the step involving metal catalyzed dehydrogenative amidation conditions for the preparation of compound of formula (II),
15 in particular a tetrazolylolation step wherein it is performed in a reactional medium with at least one azide derivative, wherein benzylic azide impurities formed during said tetrazolylolation are converted into aldehyde derivatives.

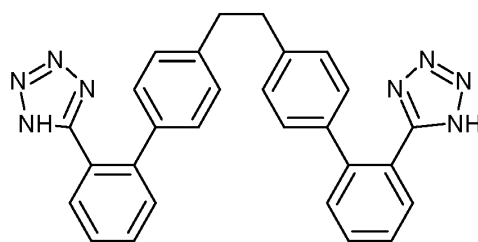
Disclosed herein is also a sartan active compound of formula (I), or one of their
20 pharmaceutically acceptable salts:



(I), wherein R is as defined above, obtainable by the novel process described above and followed by a tetrazolylolation step as defined above, comprising at least one of compounds of formula (V) and (VI):



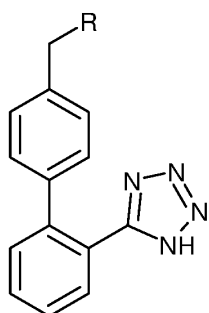
(V),



(VI).

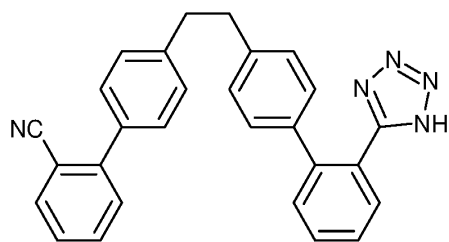
5 Herein is further disclosed a composition comprising:

- a sartan active compound of formula (I), or one of their pharmaceutically acceptable salts:

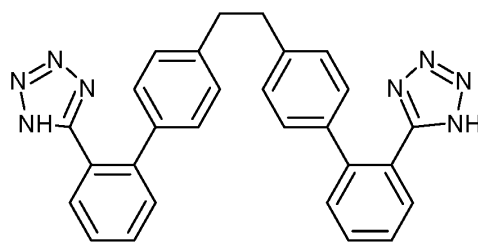


(I), wherein R is as defined above, obtainable by a process as described above, and followed by a tetrazolylolation step as described above, and

- at least one of compounds of formula (V) and (VI):



(V),



(VI).

10

DETAILED DESCRIPTION

Definitions

As used herein, certain terms have the following definitions, unless otherwise mentioned throughout the instant specification:

5 As used herein, the term “base” means a chemical species able to donate electrons, to accept protons, or to release one or more hydroxide (OH⁻) ions.

As used herein, the term “acid” means a chemical species forming a covalent bond with an electron pair by accepting electrons, or able to release one or more protons (H⁺ or H₃O⁺). In particular, an organic acid is able to release one or more protons (H⁺ or H₃O⁺).

10 As used herein, the term “salt” means an inorganic or an organic chemical species. For example, an organic salt is formed by a chemical species containing a nitrogen atom in the form of an ammonium with a chlorine ion as counter ion, also known as chlorohydrate or hydrochloride salt.

As used herein, the terms “starting material” means one or more chemical species taking part in a reaction, being in particular transformed, converted and/or involved in a catalytic cycle.

As used herein, the term “ambient temperature” or “room temperature” (also named RT) refers to a temperature ranging from 15°C to 35°C, more particularly from 25°C to 35°C.

As disclosed herein, 2-n-butyl-1-[(2'-cyanobiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazoline-5-one and 2-n-butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-20 1-ene-4-one are the same product. Said product may be a key intermediate in a synthesis of irbesartan and is herein after called compound of formula (II)(1) as defined above.

In the context of the present disclosure, the terms below have the following definitions unless otherwise mentioned throughout the instant specification:

- an alkyl group: a linear or branched saturated hydrocarbon-based aliphatic group. More particularly a -(C_x-C_y)alkyl group, where x and y are integers, x < y, which is a linear or 25 branched saturated hydrocarbon-based aliphatic group comprising from x to y carbon atoms, for example from 1 to 4 carbon atoms. By way of examples, mention may be made of, but not limited to: methyl, ethyl, propyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl groups, and the like;

30 - an alkylene group: a linear or branched, saturated divalent alkyl group. More particularly, a (C_x-C_y)alkylene group, where x and y are integers, x < y, is a linear or branched, saturated divalent alkyl group comprising from x to y carbon atoms. For example, a (C₁-C₆) alkylene group represents a linear or branched divalent carbon-based chain of 1 to 6 carbon atoms. By way of examples, mention may be made of, but not limited to, a methylene group, an ethylene

group, a 1-methylethylene group, a propylene group, a butylene group, a pentylene group, a hexylene group, and the like;

- an alkoxy group: an -O-alkyl group where the alkyl group is as previously defined. More particularly a $-(C_x-C_y)$ alkoxy group, where x and y are integers, $x < y$, which is an -O- (C_x-C_y) alkyl group where the (C_x-C_y) alkyl group is as previously defined. For example, the alkoxy group is a $-(C_1-C_3)$ alkoxy group or a $-(C_1-C_4)$ alkoxy group. By way of examples, mention may be made of, but not limited to: methoxy, ethoxy, propoxy, isopropoxy, butyloxy, isobutyloxy, tert-butyloxy groups, and the like;

- a cycloalkyl group: a cyclic alkyl group. More particularly, a (C_3-C_z) cycloalkyl group, where z is an integer greater than or equal to 4, which is a cyclic alkyl group comprising, unless otherwise mentioned, from 3 to z carbon atoms and which is saturated or partially unsaturated and unsubstituted or substituted. For example the cycloalkyl group is a (C_3-C_6) cycloalkyl-group. By way of examples, mention may be made of, but not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexyl, and the like;

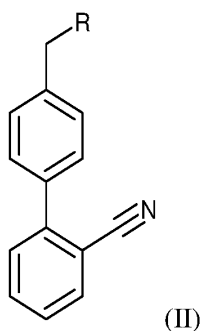
- “optionally substituted” means “unsubstituted or “substituted with”;

- a “aryl group”: a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, and the like. For example, an aryl group is a phenyl.

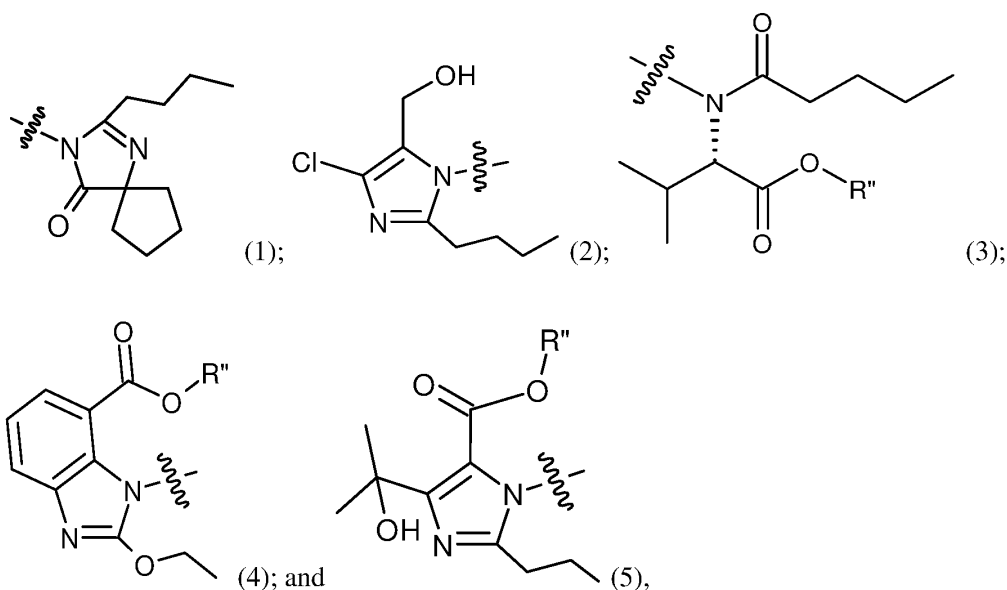
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Metal catalyzed dehydrogenative amidation reaction

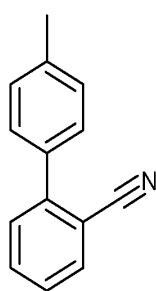
The disclosure relates to a process for preparing a compound of formula (II):



wherein R is selected from formulas (1), (2), (3), (4) and (5):



wherein R" is selected from a hydrogen atom and a (C₁-C₃)alkyl group, comprising reacting a compound of formula (III)



(III) with a compound RH or one of its salts, wherein R is as defined above, under metal catalyzed dehydrogenative amidation conditions.

As used herein, the term "metal catalyzed dehydrogenative amidation" refers to a reaction performed in presence of at least a metal catalyst.

As disclosed herein, compound of formula (III) is also named OTBN which is the abbreviation of o-tolylbenzonitrile.

In an embodiment, herein is further provided a process, wherein R is selected from formulas (1), (2), (3) and (5) as defined above.

Catalyst sources

In an embodiment, herein is further provided a process, wherein the reaction is performed in presence of a metal catalyst selected from copper catalyst, iron catalyst, manganese catalyst,

cobalt catalyst and nickel catalyst and a mixture thereof, in particular in presence of an iron catalyst or a copper catalyst.

As used herein, the term “metal catalyst” means an active metal catalytic species involved in the metal catalyzed dehydrogenative amidation step. A “metal catalyst” may also refer to a “metal complex”.

As used herein, the term “metal complex” means a compound having a metal atom or ion at its center with other molecules or ions surrounding it. Such surrounding molecules or ions being typically attached to the central metal by coordinate bonds and are typically named ligands. A “metal complex” could be a metal catalyst or a metal catalyst source described here above.

In an embodiment, the metal catalyst is generated from a species named a “metal catalyst source”, “metal source” or “pre-catalyst”, said source or pre-catalyst being in particular under different forms, for example a metal salt or a metal complex.

In an embodiment, the metal catalyst can be generated from a commercially metal catalyst source under the form of a salt or complex.

In an embodiment, the metal catalyst is directly generated in the reaction mixture, in other terms is generated *in situ*, from a metal source, as illustrated in examples 1 to 4.

In another embodiment, the metal catalyst is generated from a synthesized metal catalyst source under the form of a salt or a metal complex. For example, synthesized metal catalyst source under the form of a complex is obtained by a premix between a metal under the form of salt or complex and a ligand, before being added in the reaction mixture. For example, a synthesized metal catalyst source may be obtained by a premix between copper(I) iodine or bromine and 1,10-phenanthroline as a ligand.

In a particular embodiment, the reaction is performed in presence of copper catalyst.

In an embodiment, herein is further provided a process, wherein the copper catalyst is generated from copper(I) or copper(II), also respectively called copper(I) source or copper(II) source, each under the form of a salt or a complex, or a mixture thereof, in particular selected from CuCl, CuBr, CuI, copper(I) thiophene-2-carboxylate, CuBr•SMe₂, CuBr(Phen), CuI(Phen), CuCl(Phen), copper(I) acetate, Cu₂S, copper(I) thiophenolate, (4-bromophenyl)-thio-copper(I), mesitylcopper(I), CuCN, CuSCN, (1,10-phenanthroline)(trifluoromethyl)copper(I), CuBr₂, copper(II) acetate anhydrous or hydrate, CuF₂, CuCl₂ anhydrous or hydrate, CuS, CuSO₄ anhydrous or hydrate, CuO, Cu(NO₃)₂ anhydrous or hydrate, copper(II) trifluoromethanesulfonate, copper(II) ethylacetoacetate anhydrous or hydrate, copper(II) 2-ethylhexanoate, copper(II) trifluoroacetate anhydrous or

hydrate, copper(II) trifluoroacetylacetonate, copper(II) tert-butylacetoacetate, copper(II)-butyrate, copper(II) 2-pyrazinecarboxylate, copper(II) hexafluoroacetylacetonate anhydrous or hydrate, copper(II) trifluoromethanesulfonimide anhydrous or hydrate, dichloro(1,10-phenanthroline)copper(II), copper(II) cyclohexanebutyrate, tetrakis(pyridine)copper(II) triflate, copper(II) 3,5-diisopropylsalicylate anhydrous or hydrate, copper(II) tetrafluoroborate anhydrous or hydrate, phthalic acid copper(II), copper(II) di(2-naphthoate), benzoic acid copper(II) anhydrous or hydrate, methyl acetoacetate copper(II), ethyl benzoylacetate copper(II), ethyl 2-fluorobenzoylacetate copper(II), ethyl 2-chlorobenzoylacetate copper(II), 3-(fluorosulfonyl)benzoic acid copper(II), ethyl 3-(fluorosulfonyl)benzoylacetate copper(II), 8-hydroxyquinoline copper(II), dichloro(N-(2-pyridylmethylene)aniline-N,N')copper(II), ethyl 2-(4-(pentyloxy)benzoyl)acetate copper(II), ethyl alpha-acetyl-3-(fluorosulfonyl)benzoylacetate copper(II), ethyl alpha-acetyl-4-(fluorosulfonyl)benzoylacetate copper(II), ethyl alpha-acetyl-3-(methoxycarbonyl)benzoylacetate copper(II), 2,3-diazaspiro[bicyclo[2.2.1]hept[2]ene-7,1'-cyclopropane copper(II), alpha-(3,5-dichloro-2-pyridylimino)-o-cresol copper(II), alpha-(6-methyl-2-pyridylimino)-o-cresol copper(II), alpha-(3-methyl-2-pyridylimino)-o-cresol copper(II), alpha-(5-chloro-2-pyridylimino)-o-cresol copper(II), alpha-(4-methyl-2-pyridylimino)-o-cresol copper(II), copper(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate) and copper(II) bis(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate), more particularly from CuCl, CuBr, CuI, copper(I) thiophene-2-carboxylate, CuBr•SMe₂, CuBr(Phen), CuI(Phen), CuCl(Phen), copper(I) acetate, CuBr₂ and copper(II) acetate anhydrous, even more particularly from CuBr, CuI, CuBr(Phen), CuI(Phen), CuBr•SMe₂ and CuBr₂, for example CuBr•SMe₂.

As used herein, the term “copper(I)” is also named cuprous ion (Cu⁺), in other term “copper(I)” refers to the element copper in +1 oxidation state.

As used herein, the term “copper(II)” is also named cupric ion (Cu²⁺), in other term “copper(II)” refers to the element copper in +2 oxidation state.

In a particular embodiment, copper(I) source is under the form of a salt named “copper(I) salt”, or under the form of a complex named “copper(I) complex”.

In a particular embodiment, copper(II) source is under the form of a salt named “copper(II) salt”, or under the form of a complex named “copper(II) complex”.

In a particular embodiment, the copper catalyst is generated from CuCl, CuBr, CuI, copper(I) thiophene-2-carboxylate, CuBr•SMe₂, CuBr(Phen), CuI(Phen), CuCl(Phen), copper(I) acetate, CuBr₂ and copper(II) acetate anhydrous, or a mixture thereof.

In a particular embodiment, the copper catalyst is generated from the group consisting of CuBr, CuI, CuBr(Phen), CuI(Phen), CuBr•SMe₂ or CuBr₂, or a mixture thereof.

In a particular embodiment, the copper catalyst is generated from CuBr•SMe₂. Such embodiment may be as illustrated in example 1 and 3.

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In another embodiment, herein is further provided a process, wherein the iron catalyst is generated from iron(II) or iron(III), also respectively called iron(II) source or iron (III) source, each under the form of a salt or a complex, or a mixture thereof, in particular selected from FeCl₂, FeCl₃, FePO₄, FeI₃, FeF₃, FeBr₃, Fe₂(SO₄)₃, Fe₂(C₂O₄)₃, Fe(OH)₃, FeCl₃•6H₂O, FeF₃•3H₂O, Fe₄(P₂O₇)₃, Fe₄(Fe(CN)₆)₃ and Fe(H₂PO₂)₃, in particular from FeCl₃, FePO₄, FeI₃, FeF₃, FeBr₃, Fe₂(SO₄)₃, Fe₂(C₂O₄)₃ and Fe(OH)₃, more particularly from FeBr₃, FeCl₂, FeCl₃ and FeCl₃•6H₂O, for example FeBr₃.

In a particular embodiment, the iron catalyst is generated from iron(II) or iron(III) under the form of a salt or a complex, or a mixture thereof.

As used herein, the term “iron(II)” is also named ferrous ion (Fe²⁺), in other term “iron(II)” refers to the element iron in +2 oxidation state.

As used herein, the term “iron(III)” is also named ferric ion (Fe³⁺), in other term “iron(III)” refers to the element iron in +3 oxidation state.

In a particular embodiment, iron(II) source is under the form of a salt named “iron(II) salt”, or under the form of a complex named “iron(II) complex”.

In a particular embodiment, iron(III) source is under the form of a salt named “iron(III) salt”, or under the form of a complex named “iron(III) complex”.

In a particular embodiment, the iron catalyst is generated from the group consisting of FeCl₃, FePO₄, FeI₃, FeF₃, FeBr₃, Fe₂(SO₄)₃, Fe₂(C₂O₄)₃ and Fe(OH)₃.

In a particular embodiment, the iron catalyst is generated from the group consisting of FeBr₃, FeCl₂, FeCl₃ and FeCl₃•6H₂O.

In a particular embodiment, the iron catalyst is generated from FeBr₃. Such embodiment may be as illustrated in examples 2 and 4.

In a particular embodiment, the reaction may be performed in presence of a metal catalyst being a mixture of copper catalyst and iron catalyst, in particular respectively generated from at least one of the previously mentioned copper(I) and/or copper(II) source and at least one of the previously mentioned iron(II) and/or iron(III) source.

In another embodiment, herein is further provided a process, wherein the manganese catalyst, cobalt catalyst and nickel catalyst are generated respectively from:

- (i) a manganese source, also called manganese(II) source, under the form of a salt or a complex, or a mixture thereof, in particular selected from MnBr_2 and MnCl_2 ,
- 5 - (ii) a cobalt source, also called cobalt(II) source, under the form of a salt or a complex, or a mixture thereof, in particular selected from CoCl_2 and CoBr_2 , and
- (iii) a nickel source, also called nickel(II) source, under the form of a salt or a complex, or a mixture thereof, in particular selected from NiBr_2 and NiCl_2 .

10 In a particular embodiment, the manganese catalyst is generated from a manganese source, also called manganese(II) source, under the form of a salt or a complex, or a mixture thereof.

As used herein, the term “manganese(II)” refers to the element manganese in +2 oxidation state.

15 In a particular embodiment, manganese(II) source is under the form of a salt named “manganese (II) salt”, or under the form of a complex named “manganese (II) complex”.

In a particular embodiment, the manganese catalyst is generated from the group consisting of MnBr_2 and MnCl_2 .

20 In a particular embodiment, the cobalt catalyst is generated from a cobalt source, also called cobalt(II) source, under the form of a salt or a complex, or a mixture thereof.

As used herein, the term “cobalt(II)” refers to the element cobalt in +2 oxidation state.

In a particular embodiment, cobalt(II) source is under the form of a salt named “cobalt(II) salt”, or under the form of a complex named “cobalt (II) complex”.

25 In a particular embodiment, the cobalt catalyst is generated from the group consisting of CoCl_2 and CoBr_2 .

In a particular embodiment, the nickel catalyst is generated from a nickel source, also called nickel(II) source, under the form of a salt or a complex, or a mixture thereof.

30 As used herein, the term “nickel(II)” refers to the element nickel in +2 oxidation state.

In a particular embodiment, nickel(II) source is under the form of a salt named “nickel(II) salt”, or under the form of a complex named “nickel (II) complex”.

In a particular embodiment, the nickel catalyst is generated from the group consisting of NiBr_2 and NiCl_2 .

In an embodiment, herein is further provided a process, wherein the metal source, in particular the copper(I) source, the copper(II) source, the iron(II) source and/or the iron (III) source is present at a molar percentage ranging from 0.1% to 20% with respect to the amount
5 of the compound RH as defined above.

In a particular embodiment, the metal source, in particular the copper(I) source, the copper(II) source, the iron(II) source and/or the iron (III) source is present at a molar percentage ranging from 0.5% to 15% with respect to the amount of the compound RH as defined above.

In a particular embodiment, the metal source, in particular the copper(I) source, the
10 copper(II) source, the iron(II) source and/or the iron (III) source is present at a molar percentage ranging from 1% to 10% with respect to the amount of the compound RH as defined above.

Ligand

In an embodiment, herein is further provided a process, wherein the metal catalyst is
15 under the form of a metal complex comprising a ligand, in particular selected from bidentate ligands, monodentate ligands and mixtures thereof, more particularly selected from:

- bidentate or monodentate nitrogen ligands, in particular bidentate nitrogen ligands, more particularly optionally substituted bipyridine ligands, even more particularly phenanthroline ligands, for example 1,10-phenanthroline, 4,4'-di-tert-butyl-2,2'-dipyridyl, dimethylglycine,
20 N,N,N',N'-tetramethylethylenediamine, trans-N,N'-dimethylcyclohexane-1,2-diamine, N-(2-pyridinylmethylene)benzenamine, 1,1'-Binaphthyl-2,2'-diamine or 1-methylimidazole ;

- bidentate or monodentate phosphine ligands, in particular monodentate phosphine ligands, more particularly phosphine ligands optionally substituted by at least one aryl, for example triphenylphosphine; or

25 - bidentate diketone ligands, in particular 1,3-diketone ligands, for example ethyl 2-oxocyclohexanecarboxylate.

As used herein, the term "ligand" refers to a chemical species able to be coordinated to a metal atom or ion.

In a particular embodiment, the ligand is selected from bidentate ligands, monodentate
30 ligands and mixtures thereof.

As used herein, the terms "monodentate ligand" refers to a ligand able to be coordinated to a metal atom or ion with one atom, in particular one heteroatom, for example a nitrogen atom or a phosphine atom, and the like.

As used herein, the terms “bidentate ligand” refers to a ligand able to be coordinated to a metal atom or ion with two atoms, in particular heteroatoms, for example a nitrogen atom(s), a oxygen atom(s) and/or a phosphine atom(s), and the like.

In a particular embodiment, the ligand is selected from bidentate ligands, monodentate
5 nitrogen ligands and mixtures thereof.

As used herein, the terms “monodentate nitrogen ligand” refers to a ligand able to be coordinated to a metal atom or ion with one nitrogen atom, in particular to form a metal complex.

As used herein, the terms “bidentate nitrogen ligand” refers to a ligand able to be
10 coordinated to a metal atom or ion with at least one nitrogen atom and another heteroatom, such as another nitrogen atom or another oxygen atom, in particular to form a metal complex.

In a particular embodiment, the ligand selected from bidentate nitrogen ligands and mixtures thereof.

In a particular embodiment, the ligand selected from an optionally substituted bipyridine
15 ligands and mixtures thereof.

In a particular embodiment, the ligand selected from phenanthroline ligands and mixtures thereof.

In a particular embodiment, the ligand is 1,10-phenanthroline. Such embodiment is illustrated in example 1.

20 In a particular embodiment, the ligand is selected from 1,10-phenanthroline, 4,4'-di-tert-butyl-2,2'-dipyridyl, dimethylglycine, N,N,N',N'-tetramethylethylenediamine, trans-N,N'-dimethylcyclohexane-1,2-diamine, N-(2-pyridinylmethylene)benzenamine, 1,1'-Binaphthyl-2,2'-diamine or 1-methylimidazole and mixtures thereof.

25 In a particular embodiment, the ligand is selected from bidentate ligands, monodentate phosphine ligands and mixtures thereof.

As used herein, the terms “monodentate phosphine ligand” refers to a ligand able to be coordinated to a metal atom or ion with one phosphine atom, in particular to form a metal complex.

30 As used herein, the terms “bidentate phosphine ligand” refers to a ligand able to be coordinated to a metal atom or ion with two phosphine atoms, in particular to form a metal complex.

In a particular embodiment, the ligand is selected from monodentate phosphine ligands optionally substituted by at least one aryl, and mixtures thereof.

In a particular embodiment, the ligand selected from triphenylphosphine, triphenylphosphine derivatives and mixtures thereof.

In a particular embodiment, the ligand is selected from bidentate diketone ligands and mixtures thereof.

As used herein, the terms "bidentate diketone ligand" refers to a ligand able to be coordinated to a metal atom or ion with two oxygen atoms of the diketone, in particular to form a metal complex.

In a particular embodiment, the ligand is selected from 1,3-diketone ligands and mixtures thereof.

In a particular embodiment, the ligand may be ethyl 2-oxocyclohexanecarboxylate.

In a particular embodiment, the reaction is performed in absence of ligand, as illustrated in examples 2 and 4.

15

Oxidant

In an embodiment, herein is further provided a process, wherein the reaction is performed in presence of an oxidant, oxidant being in particular selected from peroxides of formula $R1-O-O-R2$ or of formula $R'1-O-O-R'-O-O-R'2$, oxalates of formula $R3-O-C(O)-C(O)-O-R4$ and mixtures thereof,

$R1$, $R'1$, $R2$ and $R'2$ independently represent a hydrogen atom, an alkyl group optionally substituted by an aryl group, a cycloalkyl group, an aryl group or an oxo group optionally substituted by an alkyl group, an alkoxy or an aryl group,

R' represents a (C_1-C_6) alkylene group, and

$R3$ and $R4$ independently represent a hydrogen atom, an aryl group or an alkyl group optionally substituted by an aryl group.

In a particular embodiment, the oxidant is selected from peroxides of formula $R1-O-O-R2$ and mixtures thereof, $R1$ and $R2$ independently represent a hydrogen atom, an alkyl group optionally substituted by an aryl group, a cycloalkyl group, an aryl group or an oxo group optionally substituted by an alkyl group, an alkoxy or an aryl group.

In a particular embodiment, the oxidant is selected from di-tert-butyl peroxide, tert-butyl hydroperoxide, benzoyl peroxide, dicumyl peroxide, hydrogen peroxide, and mixtures thereof.

In a particular embodiment, the oxidant is selected from di-tert-butyl peroxide, tert-butyl hydroperoxide and dicumyl peroxide.

In a particular embodiment, the oxidant is di-tert-butyl peroxide, as illustrated in examples 1 to 4.

In a particular embodiment, the oxidant is selected from peroxides of formula $R'1-O-O-R'-O-O-R'2$ and mixtures thereof, $R'1$ and $R'2$ independently represent a hydrogen atom, an alkyl group optionally substituted by an aryl group, a cycloalkyl group, an aryl group or an oxo group optionally substituted by an alkyl group, an alkoxy or an aryl group, and R' represents a (C_1-C_6) alkylene group.

In a particular embodiment, the oxidant is selected from 2,5-di(tert-butylperoxy)-2,5-dimethyl-3-hexyne, 2,5-di(tert-butylperoxy)-2,5-dimethyl-3-hexane, 1,1-bis(tert-butylperoxy)cyclohexane and mixtures thereof.

In a particular embodiment, the oxidant is selected from oxalates of formula $R3-O-C(O)-C(O)-O-R4$ and mixtures thereof, $R3$ and $R4$ independently represent a hydrogen atom, an alkyl group optionally substituted by an aryl group, or an aryl group.

In a particular embodiment, the oxidant is ditertbutyloxalate.

In an embodiment, herein is further provided a process, wherein the oxidant is present at an equivalent ranging from 0.1 to 10 with respect to the amount of the compound RH as defined above and corresponding to 1 equivalent, in particular from 0.5 to 8 with respect to the amount of the compound RH as defined above and corresponding to 1 equivalent, and more particularly from 1 to 5 with respect to the amount of the compound RH as defined above and corresponding to 1 equivalent.

In a particular embodiment, the oxidant is present at an equivalent ranging from 0.5 to 8 with respect to the amount of the compound RH as defined above and corresponding to 1 equivalent.

In a particular embodiment, the oxidant is present at an equivalent ranging from 1 to 5 with respect to the amount of the compound RH as defined above and corresponding to 1 equivalent.

Solvent

In an embodiment, herein is further provided a process, wherein the reaction is performed in presence of a solvent, in particular an organic solvent, more particularly selected from:
- aromatic solvents, even more particularly selected from benzonitrile, o-tolylbenzonitrile, chlorobenzene, dichlorobenzene and anisol, such as o-tolylbenzonitrile,

- alcohol solvents, even more particularly selected from hexafluoropropan-2-ol, isobutanol, tert-butanol and n-butanol, such as tert-butanol and n-butanol,
 - ketone solvents, such as methyl isobutyl ketone,
 - ether solvents, such as cyclopentane methyl ether,
 - 5 - hydrocarbon solvents, such as heptane,
 - ester solvents, such as isobutyl acetate,
 - polar solvents, even more particularly selected from acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, diethyl carbonate and n-methyl pyrrolidine (NMP),
 - water,
 - 10 - acid solvents, such as acetic acid,
- and mixtures thereof.

As used herein, the term “solvent” also means a “co-solvent”. The term “co-solvent” may also be used for a mixture of at least two solvents.

- 15 In a particular embodiment, the solvent is selected from aromatic solvents and mixtures thereof.

As used herein, the term “aromatic solvent” means a solvent containing at least an aromatic hydrocarbon derivative, such as benzene or toluene, optionally substituted.

- 20 In a particular embodiment, a metal catalyzed dehydrogenative amidation reaction is performed in presence of a solvent being compound of formula (III) corresponding to o-tolylbenzonitrile. In particular, o-tolylbenzonitrile (OTBN) is a solvent as well as a starting material.

In a particular embodiment, the solvent is selected from benzonitrile, o-tolylbenzonitrile, chlorobenzene, dichlorobenzene, anisol and a mixture thereof.

- 25 In a particular embodiment, the solvent is selected from alcohol solvents and mixtures thereof.

- 30 As used herein, the term “alcohol solvent” means a solvent containing at least an organic optionally substituted alcohol, such as methanol, ethanol, propanol, butanol or pentanol and their isomers.

In a particular embodiment, the solvent is selected from hexafluoropropan-2-ol, isobutanol, tert-butanol, n-butanol and a mixture thereof.

In a particular embodiment, the solvent is tert-butanol alone or in admixture with at least one solvent described above and hereafter.

In a particular embodiment, the solvent is selected from ketone solvents and mixtures thereof.

As used herein, the term “ketone solvent” means a solvent containing at least one ketone
5 function, said function being present in particular on a linear, branched or cyclic hydrocarbon chain, such as aliphatic or aromatic chain, being optionally substituted.

In a particular embodiment, the solvent is methyl isobutyl ketone alone or in admixture with at least one solvent described above and hereafter.

10 In a particular embodiment, the solvent is selected from ether solvents and mixtures thereof.

As used herein, the term “ether solvent” means a solvent containing at least one oxygen atom which interrupts, in particular a linear, branched or cyclic hydrocarbon chain being optionally substituted.

15 In a particular embodiment, the solvent is cyclopentane methyl ether alone or in admixture with at least one solvent described above and hereafter.

In a particular embodiment, the solvent is selected from hydrocarbon solvents and mixtures thereof.

20 As used herein, the term “hydrocarbon solvent” means a solvent containing essentially carbon atoms and hydrogen atoms, in particular (C₁-C₁₀) linear, (C₁-C₁₀) branched or (C₃-C₈) cyclic hydrocarbon chains, such as aliphatic chain or aromatic ring, for example pentane, hexane, heptane or octane.

In a particular embodiment, the solvent is heptane alone or in admixture with at least one
25 solvent described above and hereafter.

In a particular embodiment, the solvent is selected from ester solvents and mixtures thereof.

As used herein, the term “ester solvent” means a solvent containing at least one ester
30 function, said function being present, in particular on a linear, branched or cyclic hydrocarbon chain, such as aliphatic chain or aromatic group, being optionally substituted.

In a particular embodiment, the solvent is isobutyl acetate alone or in admixture with at least one solvent described above and hereafter.

In a particular embodiment, the solvent is selected from polar solvents and mixtures thereof.

As used herein, the term “polar solvent” means a solvent presenting a strong dielectric constant.

5 In a particular embodiment, the solvent is selected from acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, diethyl carbonate, n-methyl pyrrolidine (NMP) and a mixture thereof.

In a particular embodiment, the solvent is water alone or in admixture with at least one solvent described above and hereafter.

10 In a particular embodiment, the solvent is acetic acid alone or in admixture with at least one solvent described above.

RH under salt form and base

In an embodiment, herein is further provided a process, wherein the reaction is performed in presence of a base, in particular when RH as defined above is under the form of a salt, said
15 base being optionally selected from:

- inorganic bases,
- alkoxide bases,
- organic bases comprising at least one nitrogen atom, for example triethylamine or N,N-diisopropylethylamine,
- 20 and mixtures thereof.

In a particular embodiment, the base is selected from inorganic bases and mixtures thereof.

As used herein, the term “inorganic base” or “mineral base” refers to a base under a salt form comprising at least a hydroxide ion, a carbonate ion or a hydrogencarbonate ion also
25 named bicarbonate ion.

In a particular embodiment, the base is selected from Na_2CO_3 , Cs_2CO_3 , K_2CO_3 , NaHCO_3 , NaOH , KOH and mixtures thereof.

In a particular embodiment, the base is K_2CO_3 alone or in admixture with at least one base described above or herein after.

30 In a particular embodiment, the base is selected from alkoxide bases and mixtures thereof.

As used herein, the terms “alkoxide base” refers to a conjugate base of an alcohol. In other terms, an alkoxide comprises an organic group bonded to a negatively charged oxygen atom. As know by one having skills in the art, an alkoxide base comprising a counter ion, such as but not limited to a sodium ion, a lithium ion or a potassium ion.

In a particular embodiment, the base is tBuOK alone or in admixture with at least one base described above or herein after.

In a particular embodiment, the base is selected from organic bases comprising at least one nitrogen atom.

5 In a particular embodiment, the base is selected from triethylamine, N,N-diisopropylethylamine and a mixture thereof.

In an embodiment, herein is further provided a process, wherein the reaction is performed in presence of a base when RH as defined above is under the form of a salt, in particular under the form of a RH hydrochloride salt, for example a RH•HCl salt.

10

Reaction time

In an embodiment, herein is further provided a process, wherein the reaction is performed for 1 hour to 20 hours.

15 In a particular embodiment, the reaction is performed for 8 hours to 18 hours.

In a particular embodiment, the reaction is performed for 10 hours to 16 hours.

In a particular embodiment, the reaction is performed for 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12.5 hours, 14 hours, 15 hours, 16 hours, 18 hours, 20 hours or 24 hours.

In a particular embodiment, the reaction is performed for 8 hours, 15 hours or 20 hours.

20 In a particular embodiment, the reaction is performed for 8 hours or 15 hours.

In a particular embodiment, the reaction is performed for 15 hours.

Temperature and/or photoactivation conditions

25 In an embodiment, herein is further provided a process, wherein the reaction is performed at a temperature ranging from 20°C to 200°C, in particular from 90°C to 180°C, more particularly from 100°C to 150°C and/or under photoactivation conditions with a wavelength ranging from 200 nm to 900 nm, in particular from 200 nm to 800 nm, more particularly from 250 nm to 400 nm, or a combination of wavelengths, and optionally in the presence of a photosensitizer.

30 In a particular embodiment, the reaction is performed at a temperature ranging from 20°C to 200°C.

In a particular embodiment, the reaction is performed at a temperature ranging from 90°C to 180°C.

In a particular embodiment, the reaction is performed at a temperature ranging from 100°C to 150°C.

In a particular embodiment, the reaction is performed under photoactivation conditions.

In a particular embodiment, the reaction is performed under photoactivation conditions
5 with a wavelength ranging from 200 nm to 900 nm or a combination of wavelengths.

In a particular embodiment, the reaction is performed under photoactivation conditions with a wavelength ranging from 200 nm to 800 nm or a combination of wavelengths.

In a particular embodiment, the reaction is performed under photoactivation conditions with a wavelength ranging from 250 nm to 400 nm, or a combination of wavelengths.

10 In a particular embodiment, the reaction is performed at a temperature ranging from 20°C to 80°C under photoactivation conditions.

In a particular embodiment, the reaction is performed at a temperature ranging from 40°C to 60°C under photoactivation conditions.

As used herein, the terms "light induced reaction" refers to a "photochemical reaction"
15 performed under photoactivation conditions, corresponding to an activation of a reaction using incident photons. Said light corresponding to wavelength belonging to UV, visible or IR spectrum.

In a particular embodiment, the reaction is performed at a temperature ranging from 20°C to 80°C under photoactivation conditions with a wavelength ranging from 200 nm to 900 nm,
20 in particular from 200 nm to 800 nm, more particularly from 250 nm to 400 nm, or a combination of wavelengths.

In a particular embodiment, the reaction is performed at a temperature ranging from 40°C to 60°C under photoactivation conditions with a wavelength ranging from 200 nm to 900 nm or a combination of wavelengths.

25 In a particular embodiment, the reaction is performed at a temperature ranging from 40°C to 60°C under photoactivation conditions with a wavelength ranging from 200 nm to 800 nm or a combination of wavelengths.

In a particular embodiment, the reaction is performed at a temperature ranging from 40°C to 60°C under photoactivation conditions with a wavelength ranging from 250 nm to 400 nm
30 or a combination of wavelengths.

In a particular embodiment, when photoactivation conditions are used, the reaction is performed in presence of a photosensitizer.

As used herein, the term "photosensitizer" refers to a chemical species that absorb light of a specific wavelength and transform such into energy useful for the activation of a reaction.

In particular, a photosensitizer is a photocatalyst, more particularly a donor-acceptor photocatalyst, used into photocatalytic conditions.

In a particular embodiment, a photosensitizer is selected from cyanoarene derivatives, diketone derivatives and conjugated ketones or aldehydes, such as aromatic ketones or
5 aldehydes.

In a particular embodiment, a photosensitizer is selected from 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; 2,4,5,6-Tetrakis(9H-carbazol-9-yl) isophthalonitrile also named 4CzIPN; 2,3-butane-dione; fluorenone and mixtures thereof.

In a particular embodiment, the reaction is performed at a temperature ranging from 40°C
10 to 60°C under photoactivation conditions with a combination of wavelengths ranging from 200 nm to 800 nm in presence of a photosensitizer being 2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; 2,4,5,6-Tetrakis(9H-carbazol-9-yl) isophthalonitrile also named 4CzIPN.

Other conditions

15 In an embodiment, herein is further provided a process, wherein a metal catalyzed dehydrogenative amidation reaction is performed in presence of a promoter.

As used herein, the term “promoter” means a chemical species able to improve a reaction rate.

In a particular embodiment, the promoter is a base, more particularly an alkoxide base,
20 for example *t*BuOK.

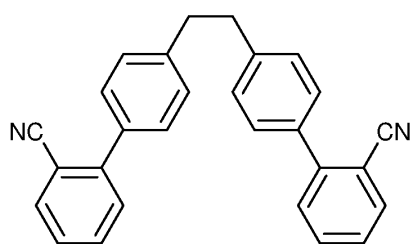
In an embodiment, herein is further provided a process, wherein the reaction is performed under an inert atmosphere.

As used herein “inert atmosphere” means an atmosphere containing an inert gas, for example argon or nitrogen. This means that the atmosphere is free of oxygen. For example, an
25 inert atmosphere may be nitrogen gas or argon gas.

In an embodiment, herein is further provided a process, wherein the reaction is performed under ambient air atmosphere.

Characterization of the process by the presence of a dimer byproduct

30 In an embodiment, herein is further provided a process, wherein a o-tolylbenzonitrile dimer side compound of formula (IV)



(IV) is formed, as illustrated in example 3.

As used herein, compound of formula (IV) is also called OTBN dimer, 4',4''-(ethane-1,2-diyl)di([1,1'-biphenyl]-2-carbonitrile), o-tolylbenzonitrile dimer side product, OTBN dimer side product or OTBN dimer.

5 In a particular embodiment, the process comprises a step of purification further to the catalyzed dehydrogenative amidation reaction, to remove a majority of compound of formula (IV), in particular at least 99% of compound of formula (IV).

10 In an embodiment, herein is further provided a process, wherein a metal catalyzed dehydrogenative amidation reaction is performed, in particular at a temperature ranging from 100°C to 150°C and under inert atmosphere, in presence of:

- a copper catalyst, in particular being generated from $\text{CuBr} \cdot \text{SMe}_2$, the copper catalyst being in particular under the form of a metal complex comprising a ligand, the ligand being in particular 1,10-phenanthroline,
- 15 - an oxidant being in particular di-tert-butyl peroxide, and
- OTBN being a reactant as well as a solvent.

In a particular embodiment, the process described above may provide a compound of formula (II) as defined above wherein R is of formula (1) as defined above, as illustrated in example 1.

20

In an embodiment, herein is further provided a process, wherein a metal catalyzed dehydrogenative amidation reaction is performed, in particular at a temperature ranging from 100°C to 150°C and under inert atmosphere, in presence of:

- an iron catalyst, in particular being generated from FeBr_3 ,
- 25 - an oxidant being in particular di-tert-butyl peroxide, and
- OTBN being a reactant as well as a solvent.

In a particular embodiment, the process described above may provide a compound of formula (II) as defined above wherein R is of formulas (1), (2), (3) and (5) as defined above, as illustrated in examples 2 and 4.

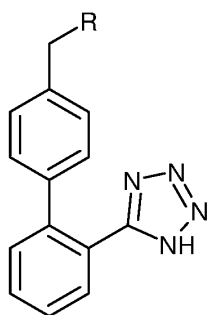
In a particular embodiment, the process comprises a step of purification further to the catalyzed dehydrogenative amidation reaction.

In an embodiment, herein is further provided a process, comprising successively:

- 5
- a catalyzed dehydrogenative amidation reaction, for example as described above,
 - at least a purification step and
 - a tetrazolylolation step.

Tetrazolylolation step

- 10 In an embodiment, herein is further provided a process, for preparing a sartan active compound of formula (I) or one of its pharmaceutically acceptable salts:



(I), wherein R is as defined above,

comprising a tetrazolylolation step reacting the compound of formula (II) as defined above prepared by the process for preparing a compound of formula (II) as defined above.

- 15 Tetrazolylolation means a conversion of nitriles into tetrazoles.

Tetrazolylolation by reaction with azide derivative, for example tributyltin azide or alkali metal azide such as sodium azide, and a base such as triethylamine hydrochloride is described in the literature. Thus, for example, the preparation of 2-n-butyl-3-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (also named irbesartan) from 2-n-butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one (also named Spiro Methyl Biphenyl Nitrile), by heating at reflux in presence of azide of tributyltin is known.

Among sartan active compounds of formula (I) as defined above may be cited irbesartan, losartan, valsartan, candesartan or olmesartan. In particular, among sartan active compounds of formula (I) as defined above may be cited irbesartan, losartan, valsartan or olmesartan.

- 25 In an embodiment, herein is further provided a process, wherein the sartan active compound of formula (I) is irbesartan, also called 2-n-butyl-4-spirocyclopentane-1-[[2'-

(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one or 2-n-butyl-3- [[2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

In an embodiment, a tetrazolylolation step is performed under usual conditions known by one having ordinary skills in the art.

5 In a particular embodiment, a tetrazolylolation step is performed in the presence of an azide derivative selected from the group of hydrazoic acid (HN_3), salt azide for example a metal azide such as sodium azide (NaN_3), potassium azide (KN_3), or calcium azide ($\text{Ca}(\text{N}_3)_2$), SnBu_3N_3 , SnMe_3N_3 , trialkyl ammonium azide, such as triethylammonium azide, in particular a metal or salt azide, such as sodium azide or triethylammonium azide.

10 In an embodiment, a tetrazolylolation step is performed in presence of an azide derivative and one base. In particular, the base is selected from the group of triethylamine (Et_3N), *N,N*-dicyclohexylmethylamine, and a Hunig base such as *N,N*-diisopropylethylamine and the like. Said base may in particular be triethylamine and more particularly triethylamine hydrochloride (also named TEA, HCl).

15 In an embodiment, a tetrazolylolation step is performed with an azide derivative and one base in an inert polar aprotic solvent at a temperature below the reflux temperature and under inert atmosphere.

As used herein, the term “polar aprotic solvent” means a polar solvent unable to release one or more protons. In the contrary, as used herein, the term “polar protic solvent” means a
20 polar solvent able to release one or more protons.

In a particular embodiment, a tetrazolylolation step is performed in the presence of a polar aprotic solvents has reductive properties and is more particularly selected from the group of *N*-methylformamide (MFO), *N,N*-dimethylformamide (DMF), *N*-methyl,*N*-Tert-butylformamide, acetamide (Ac), *N*-methylacetamide (MAc), *N,N*-dimethylacetamide (DMAc), urea,
25 tetramethyl urea (TMU), dimethylpropylene urea (DMPU), dimethylethylene urea (DMEU), triethylamine (TEA), hexamethylphosphoramide (HMPA), hexamethylphosphorotriamide (HMPT), 2-pyrrolidone (2-Py), *N*-methyl-2-pyrrolidone (NMP), *N*-phenyl-2-pyrrolidone (NPP), *N*-vinylpyrrolidone (NVP), and 5-methyl-2-pyrrolidone (MPy). Other polar aprotic solvent having reductive properties may also be used, in particular being selected from
30 *N*-methylformamide (MFO), *N,N*-dimethylformamide (DMF), *N*-methyl,*N*-Tert-butylformamide, acetamide (Ac), *N*-methylacetamide (MAc), *N,N*-dimethylacetamide (DMAc), urea, tetramethyl urea (TMU), dimethylpropylene urea (DMPU), dimethylethylene urea (DMEU), triethylamine (TEA), hexamethylphosphoramide (HMPA), hexamethylphosphorotriamide

(HMPT), 2-pyrrolidone (2-Py), *N*-methyl-2-pyrrolidone (NMP), *N*-phenyl-2-pyrrolidone (NPP), *N*-vinylpyrrolidone (NVP), and 5-methyl-2-pyrrolidone (MPy).

In an embodiment, a tetrazolylolation step is performed with equimolecular amounts of alkali metal azide and of triethylamine hydrochloride in proportions of 1 to 5 moles per mole
5 of compound of formula (II) as defined above, advantageously of about 1.2 to about 2 moles per mole of compound of formula (II) as defined above.

In an embodiment, a tetrazolylolation step is performed at a temperature ranging between room temperature to 150°C, in particular 100°C to 135°C, and for example 150 °C.

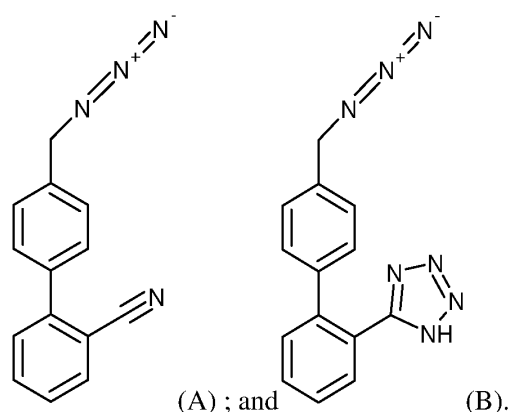
In an embodiment, after 6-20 hours of heating, the tetrazolylolation is complete and the
10 reaction mixture is worked up according to conventional techniques. In particular, the mixture is neutralized by adding a base, for example an alkali metal hydroxide, in aqueous solution, the aqueous phase containing the salts, in particular chlorides and azides, is discarded. The organic phase is then treated with water and various organic solvents (aromatics, halogenated, esters, ketones, ...) such as toluene, ethyl acetate, dichloromethane (DCM), methylethylketone
15 optionally with two different solvents sequentially, making it possible to remove the by-products of the tetrazolylolation reaction. These washing steps are conventional and well known by the skilled person. The final product is then, for example, crystallized *via* a crystallization step also well known by the skilled in the art. Additional conventional filtration and washing steps can then be performed if necessary.

20 In a particular embodiment, a tetrazolylolation step is performed in a reactional medium with at least one azide derivative, wherein benzylic azide impurities formed during said tetrazolylolation are converted into aldehyde derivatives. A tetrazolylolation step may be performed according to the patent application WO 2023/052309, wherein benzylic azide impurities formed during said tetrazolylolation are converted into aldehyde derivatives.

25 As used herein, the terms "benzylic azide impurities" or "azido impurities like" cover all the by-products or impurities likely to be produced by nucleophilic substitution with alkali metal azides of compounds which comprise in their structure at least one activated carbon atom. "Activated carbon atom" means in the context of the present disclosure, a carbon atom which bears a leaving group such as a halogen atom (chlorine, bromine or iodine atom), an alcohol
30 group, a tosylate group, a mesylate group, an alkylphosphate group, an ester group, or an amide group and so on. Such "activated carbon atom" is more particularly a carbon atom linked to a phenyl ring thus forming an activated benzylic structure. Said "benzylic azide impurities" can be thus present during a tetrazolylolation step starting from an intermediate compound having a

cyanophenyl moiety such as compound of formula (II) as defined above, and implementing an alkali metal azide.

In conventional processes to synthesize sartan active compounds involving cyano derivative intermediates for the tetrazolylolation step, two well - known mutagenic benzylic azide impurities are formed, namely azido nitrile of formula (A) also named 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-nitrile or 4'-(azidomethyl)-[1,1'-biphenyl]-2-carbonitrile, and azido
 5 tetrazole of formula (B) also named (5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole or 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-1,2,3,4-tetrazole, as shown below:



10 These two benzylic azide impurities (A) and (B) may be formed during the tetrazolylolation of a compound of formula (II) as defined above from several different potential precursors including the mono-brominated derivative used in the prior art for the synthesis of compound of formula (II) as previously mentioned.

Typically, the conversion of the benzylic azide impurities formed during said
 15 tetrazolylolation into aldehyde derivatives, allows to provide an amount of less than 1 ppm of said benzylic azide impurities with respect to the total amount of irbesartan after the final purification steps, as exemplified in the patent application WO 2023/052309. In particular, benzylic azide impurities are converted into aldehyde derivatives in presence of FeCl₃.

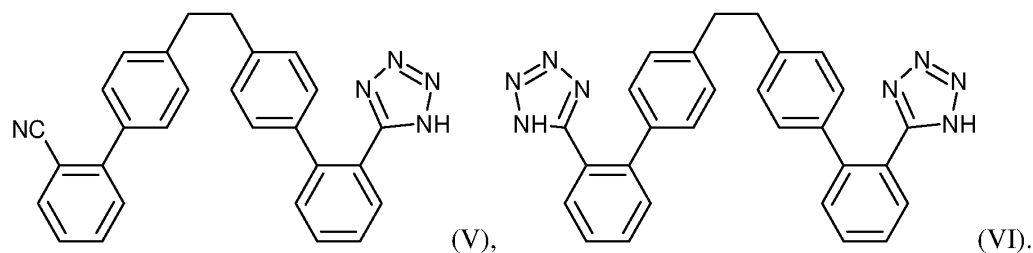
20 Characterization of the process by the presence of a dimer byproduct comprising at least one tetrazole group

In a particular embodiment, the tetrazolylolation step as defined above may lead to the formation of at least one side product of formula (V) and (VI) as defined below. In particular, the tetrazolylolation step may be performed by reacting an admixture comprising the compound
 25 of formula (II) and the o-tolylbenzonitrile dimer side compound of formula (IV) as defined

above, said admixture being prepared by the process for preparing a compound of formula (II) as defined above comprising a metal catalyzed dehydrogenative amidation. A tetrazolylolation step leading to side products of formula (V) and (VI) as defined below may be performed starting from o-tolylbenzonitrile dimer side compound of formula (IV), as illustrated in example

5 5.

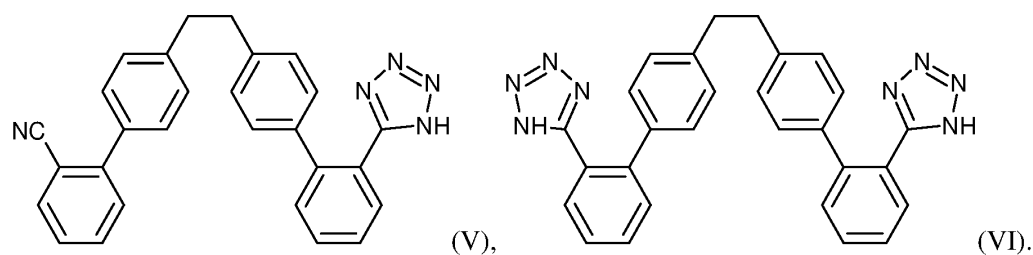
In a particular embodiment, a sartan active compound of formula (I) as described above comprises at least one of compounds of formula (V) and (VI):



In a particular embodiment, herein is further provided a composition comprising:

10 - a sartan active compound of formula (I) as described above, and

- at least one of compounds of formula (V) and (VI):



In a particular embodiment, the sartan active compound is obtained after a purification step following a tetrazolylolation step.

15

In a particular embodiment, the sartan active compound of formula (I) as described above comprise at least one of compounds of formula (V) and (VI) as described above, in particular comprises traces of at least one of compounds of formula (V) and (VI) as described above, and more particularly comprises less than 0.1 % by weight of each compounds of formula (V) and (VI), relative to the total weight of sartan active compound, for example less than 0.05 % by weight of each compounds of formula (V) and (VI), relative to the total weight of sartan active compound.

20

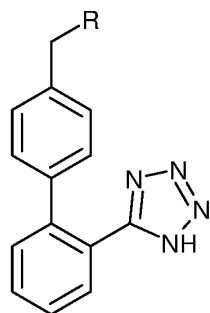
In a particular embodiment, the composition comprising the sartan active compound of formula (I) as described above and at least one of compounds of formula (V) and (VI) as described above, in particular may comprise traces of at least one of compounds of formula (V)

25

and (VI) as described above, and more particularly comprises less than 0.1 % by weight of each compounds of formula (V) and (VI), relative to the total weight of sartan active compound, for example less than 0.05 % by weight of each compounds of formula (V) and (VI), relative to the total weight of sartan active compound.

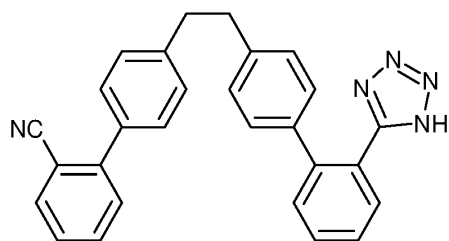
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In an embodiment, herein is further provided a mixture, a sartan active compound of formula (I), or one of their pharmaceutically acceptable salts:

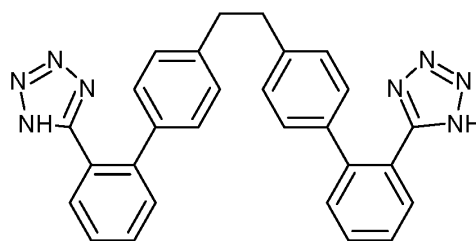


(I), wherein R is as defined above, obtainable by a process for preparing a compound of formula (II) as defined above, and followed by a tetrazolylolation step as defined above, comprising at least one of compounds of formula (V) and (VI):

10



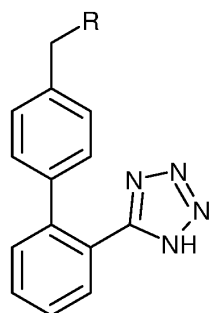
(V),



(VI).

In an embodiment, herein is further provided a composition, in particular a mixture, comprising:

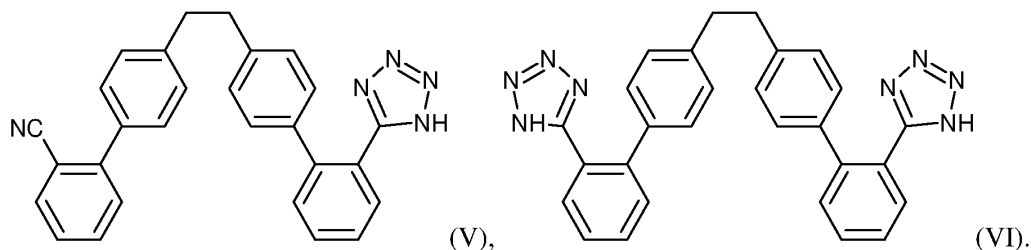
- a sartan active compound of formula (I), or one of their pharmaceutically acceptable salts:



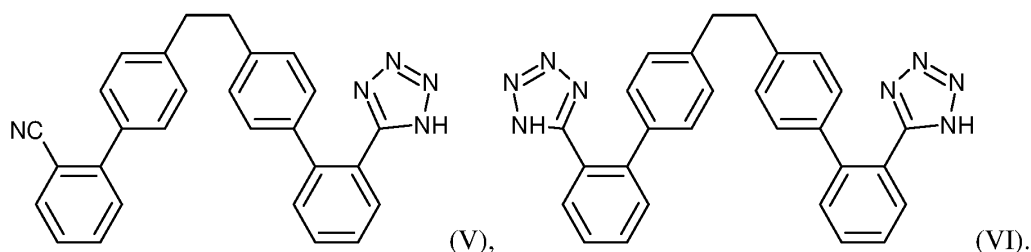
15

(I), wherein R is as defined above, obtainable by a process for preparing a compound of formula (II) as defined above, and followed by a tetrazolylolation step as defined above, and

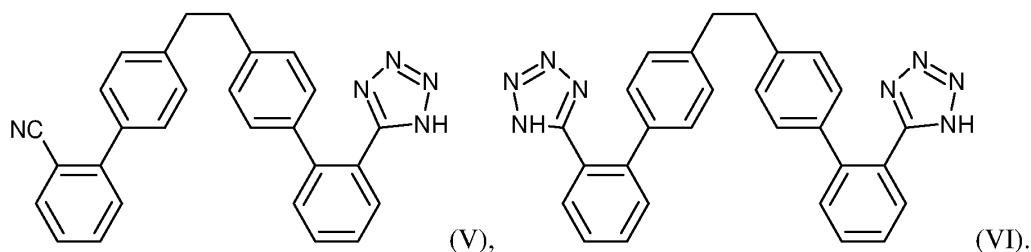
- at least one of compounds of formula (V) and (VI):



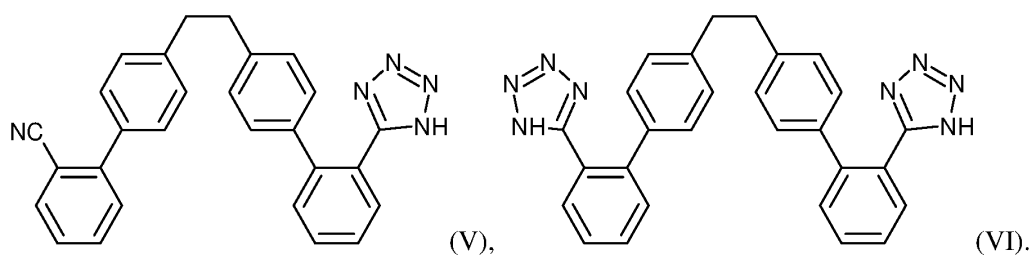
In a particular embodiment, the sartan active compound is irbesartan, also called 2-n-butyl-4-spirocyclopentane-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-2-imidazolin-5-one or
 5 2-n-butyl-3- [[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one, and comprises at least one of compounds of formula (V) and (VI):



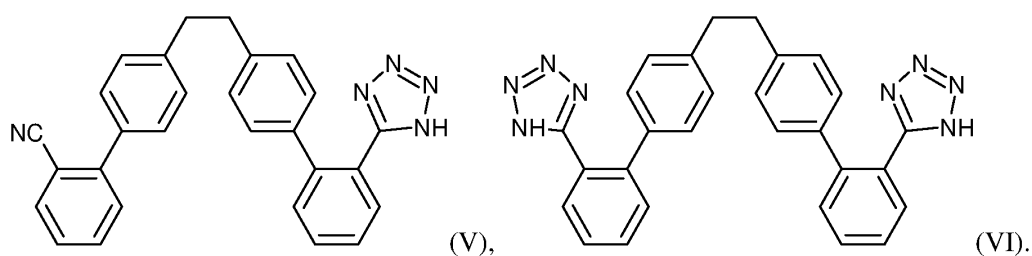
In a particular embodiment, a composition may comprise the sartan active compound being irbesartan, also called 2-n-butyl-4-spirocyclopentane-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-2-imidazolin-5-one or 2-n-butyl-3- [[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-
 10 diazaspiro[4.4]non-1-en-4-one, and at least one of compounds of formula (V) and (VI):



In a particular embodiment, the sartan active compound is selected from losartan, valsartan and its esters, such as methyl ester or ethyl ester, candesartan and its esters, such as
 15 methyl ester or ethyl ester, olmesartan and its esters, such as methyl ester or ethyl ester, and comprises at least one of compounds of formula (V) and (VI):



In a particular embodiment, a composition may comprise the sartan active compound being selected from losartan, valsartan and its esters, such as methyl ester or ethyl ester, candesartan and its esters, such as methyl ester or ethyl ester, olmesartan and its esters, such as methyl ester or ethyl ester, and comprises at least one of compounds of formula (V) and (VI):



EXAMPLES

10

Below are described examples of protocols for the preparation of compound of formula (II) as defined above according to the novel process provided herein. These examples are non-limiting and serve merely to illustrate said novel process. In the examples which follow, the starting compounds and the reactants, when their preparation is not described, are available commercially or are described in the literature, or else may be prepared by methods which are known to a person skilled in the art.

15

In the examples that follow, the following abbreviations and empirical formulae are used:

°C	degrees Celsius
cHex	cyclohexane
cm	centimeter
CuBr•SMe ₂	copper(I) bromide dimethyl sulfide complex
DTBP	di-tert-butyl peroxide
EtOAc	ethyl acetate
eq.	equivalent
FeBr ₃	iron(III) bromide
h	hour
HRMS	high-resolution mass spectrometry

IR	infrared
KMnO ₄	Potassium Permanganate
LC/MS or LC-MS	liquid chromatography/mass spectrometry
MHz	megaHertz
min	minute(s)
mL	milliliter
NMR	nuclear magnetic resonance
qNMR or NMR assay	quantitative NMR
OTBN	o-tolylbenzonitrile
Phen	1,10-phenanthroline
PTFE	polytetrafluoroethylene
R _f	retention factor
TMS	tetramethylsilane
Tr	retention time
UV	ultraviolet

The analytical thin layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized by UV light (254 nm) and/or chemical staining with a KMnO₄ solution.

5

The flash column chromatography for purification was performed using 0.040 – 0.063 mm silica gel.

¹H NMR spectra were recorded on a Bruker DXP 300 MHz spectrometer at 300.1 MHz, ¹³C NMR spectra at 75.5 MHz. Chemical shifts (δ) are quoted in ppm relative to TMS (¹H). Coupling constants (J) are quoted in Hz. The residual solvent signals were used as references (CDCl₃: δH = 7.26 ppm, δC = 77.16 ppm; (CD₃)₂SO: δH = 2.50 ppm, δC = 39.52 ppm.). The following abbreviations were used to show the multiplicities: s: singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, m: multiplet.

15

The high-resolution mass spectrometry (HRMS) was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer.

The infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer Paragon 100 (ATR), the wave numbers (ν) of recorded IR-signals (ATR) are quoted in cm⁻¹.

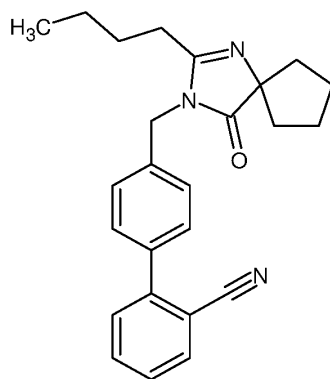
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LC-MS: System: LC system Thermo Vanquish and a MS detector Thermo ISQ EM. Column: Acquity Waters HSS T3 (1.7μm) 2.1mm x 50mm. Phase A: purified water + 0.1% formic acid. Phase B: acetonitrile + 0.1% formic acid.

qNMR: quantification method using 1,3,5-trimethoxybenzene as internal standard and carried out thanks to ^1H NMR spectra recorded as described above, such quantification method being known and commonly used by a person having ordinary skills in the art.

5

In examples 1 to 2, conditions are details for metal catalyzed dehydrogenative amidation for the preparation of compound of formula (II) as defined above with R being of formula (1) as defined above, corresponding to 2-n-butyl-3-[(2'-cyanobiphenyl-4-yl)methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one of following formula (II)(1):



(II)(1)

10

Example 1: Preparation of compound of formula (II) with R being of formula (1) in presence of copper catalyst generated from $\text{CuBr}\cdot\text{SMe}_2$

15 To a flame dried 8 mL microwave vial was placed 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one (48.6 mg, 0.25 mmol), $\text{CuBr}\cdot\text{SMe}_2$ (2.5 mg, 0.0125 mmol) and phenanthroline (4.6 mg, 0.025 mmol) [from glovebox], followed by the addition of OTBN (2.73 g, 14 mmol). The tube was sealed by means of a PTFE septum. The tube was placed under vacuum, then flushed with argon and the procedure was repeated 3 times. Then, placed in an oil bath pre-heated at 135 °C. The
20 reaction mixture was then allowed to reach 135 °C after 30 min, where DTBP (20 μL) was added every hour, for 4 h, reacting a total of DTBP (91 μL , 1 mmol). The reacting mixture was allowed to stir at this temperature for 11 h more. Then, allowed to cool. The crude was purified by silica gel chromatography (10 cm SiO_2 column; 3.5 cm diameter), with cyclohexane and EtOAc as eluent (80/20) for 400 mL, then cyclohexane/EtOAc (70/30) to afford 77.5 mg (81%
25 yield) of the desired product as a yellow sticky oil. R_f = 0.13 (in cHex/EtOAc 7/3).

¹H NMR (300.1 MHz, CDCl₃) δ 7.77 (d, J = 7.7, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.61 – 7.39 (m, 4H), 7.28 (d, J = 8.5 Hz, 2H), 4.75 (s, 2H), 2.40 – 2.30 (m, 2H), 2.01 (dp, J = 15.7, 5.6 Hz, 6H), 1.89 – 1.81 (m, 1H), 1.33 (dt, J = 14.4, 7.2 Hz, 2H), 0.87 (t, J = 7.3 Hz, 4H).

¹³C NMR (75.5 MHz, CDCl₃) δ 186.9, 161.7, 144.9, 137.8, 137.3, 134.0, 133.0, 130.2, 129.5, 127.9, 127.2, 118.7, 111.3, 53.6, 43.4, 37.6, 29.0, 27.9, 26.3, 22.5, 13.9.

HRMS: m/z calculated for C₂₅H₂₈N₃ [M+H]⁺ 365.2232, found 386.2241.

Example 2: Preparation of compound of formula (II) with R being of formula (1) in presence of iron catalyst generated from FeBr₃

To a flame dried 8 mL microwave vial was placed 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one (97.2 mg, 0.5 mmol), FeBr₃ (7.4 mg, 0.03 mmol) followed by the addition of OTBN (2.51 g, 13 mmol). The tube was sealed by means of a PTFE septum. The tube was placed under vacuum, then flushed with argon and the procedure was repeated 3 times. Then, placed in an oil bath pre-heated at 80 °C and stirred for 30 minutes at this temperature. The reaction mixture was heated to 135 °C and DTBP (184 μL, 1 mmol) was added and reaction mixture was stirred for 4 hours at this temperature. Then, allowed to cool to room temperature. The crude was purified by silica gel chromatography with *n*-heptane and EtOAc as eluent (from 90/10 to 70/30) to afford 160.0 mg (83% yield) of the desired product as a yellow sticky oil.

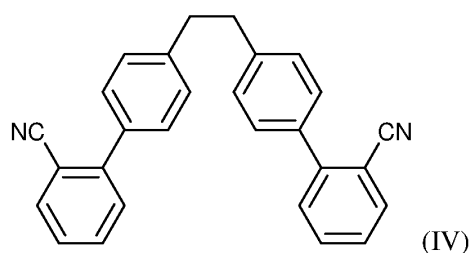
¹H NMR (300.1 MHz, CDCl₃) δ 7.77 (d, J = 7.7, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.61 – 7.39 (m, 4H), 7.28 (d, J = 8.5 Hz, 2H), 4.75 (s, 2H), 2.40 – 2.30 (m, 2H), 2.01 (dp, J = 15.7, 5.6 Hz, 6H), 1.89 – 1.81 (m, 1H), 1.33 (dt, J = 14.4, 7.2 Hz, 2H), 0.87 (t, J = 7.3 Hz, 4H).

¹³C NMR (75.5 MHz, CDCl₃) δ 186.9, 161.7, 144.9, 137.8, 137.3, 134.0, 133.0, 130.2, 129.5, 127.9, 127.2, 118.7, 111.3, 53.6, 43.4, 37.6, 29.0, 27.9, 26.3, 22.5, 13.9.

HRMS: m/z calculated for C₂₅H₂₈N₃ [M+H]⁺ 365.2232, found 386.2241.

Example 3: Formation of a OTBN dimer side product under metal catalyzed dehydrogenation conditions

In some conditions, as described hereafter, metal catalyzed dehydrogenation may lead to the formation of OTBN dimer side product of formula (IV)



To a flame dried 8 mL microwave vial was placed 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one (48.6 mg, 0.25 mmol), CuBr•SMe₂ (2.5 mg, 0.0125 mmol), followed by the addition of OTBN (2.73 g, 14 mmol). The tube was sealed by means of a PTFE septum. The tube was placed under vacuum, then flushed with argon and the procedure was repeated 3 times. The reaction mixture was then allowed to reach 135 °C after 30 min, DTBP (91 µL) was added. The reacting mixture was allowed to stir at this temperature for 15 h. Then, allowed to cool. The crude was purified by silica gel chromatography (h= 10 cm, d= 3 cm) using cyclohexane/EtOAc (7/3) as eluent. The first fraction was isolated (R_f=0.7, cHex/EtOAc 7/3). The fraction was concentrated and was found to contain a mixture of OTBN dimer side product of formula (IV) and 2-butyl-1,3-diazaspiro[4.4]non-1-ene-4-one dimer. The fraction was then subjected to preparative thin layer chromatography with eluent cyclohexane/EtOAc (9/1) to 28.5 mg of the OTBN dimer side product of formula (IV) (R_f= 0.52; in cyclohexane/EtOAc).

The chemical analysis of OTBN dimer side product of formula (IV) was described hereafter:
¹H NMR (300.1 MHz, CDCl₃) δ 7.78 – 7.73 (m, 2H), 7.70 – 7.58 (m, 2H), 7.58 – 7.47 (m, 8H), 7.43 (m, 2H), 7.39 – 7.28 (d, J = 8.3 Hz, 4H), 3.04 (s, 4H).
¹³C NMR (75.5 MHz, CDCl₃) δ 145.6, 133.9, 132.9, 130.2, 130.2, 129.0, 128.9, 127.5, 111.4, 37.6.
IR: ν (cm⁻¹) 2923, 2223, 1704, 1478, 762.
HRMS: m/z calculated for C₂₈H₂₀N₂H [M+H]⁺ 385.1705, found 385.1709.

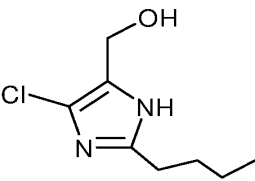
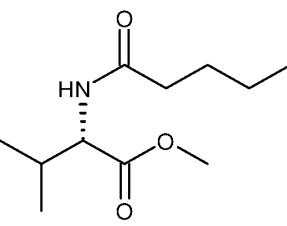
Example 4: preparation of compounds of formula (II) with R being of formulas (2), (3) and (5) in presence of iron catalyst generated from FeBr₃

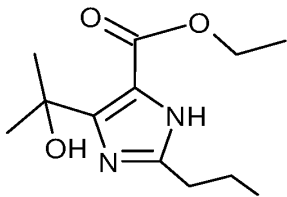
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To a flame dried 8 mL microwave vial was placed one of the compound RH, with R being of formulas (2), (3) or (5) as defined above (see table 1 herein after for the quantity of RH starting material used), FeBr₃ (7.4 mg, 0.03 mmol) followed by the addition of OTBN (2.51 g, 13 mmol). The tube was sealed by means of a PTFE septum. The tube was placed under vacuum,

then flushed with argon and the procedure was repeated 3 times. Then, placed in an oil bath pre-heated at 80 °C. The reaction mixture was then allowed to reach 135 °C after 30 min, where DTBP (184 µL, 1 mmol) was added. The reacting mixture was allowed to stir at this temperature for 4 h. Then, reacting mixture was cooled and analyzed by LC-MS and qNMR (¹H NMR quantification) as described above. In particular, ¹H NMR quantification was used to determine yields of compounds of formula (II) with R being of formulas (2), (3) and (5), as described in table 1. Typically, ¹H NMR quantification was performed by using 1,3,5-trimethoxybenzene as internal standard, in other terms a known amount of 1,3,5-trimethoxybenzene as internal standard was added to a mixture where a metal catalyzed dehydrogenative amidation was performed.

Table 1

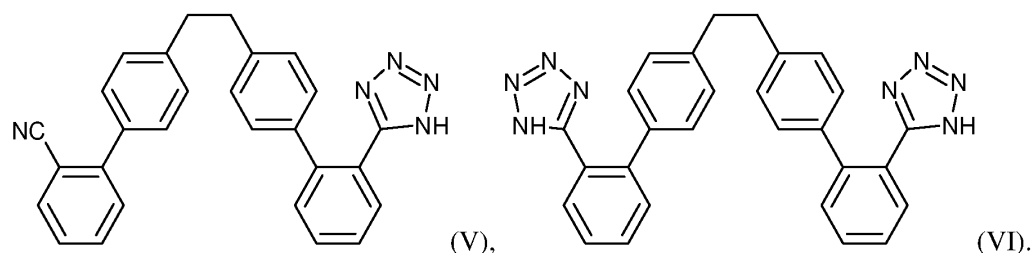
Formula R	Structure of RH	Amount of RH (mg)	Yield of compound of formula (II) (%)	Mass analysis of compound of formula (II) (LC-MS analysis)
(2)		94.3 mg	3% (Compound of formula (II)(2))	m/z calculated for C ₂₂ H ₂₂ ClN ₃ OH [M+H] ⁺ 380.9, found 380.9. (Compound of formula (II)(2))
(3) with R" = methyl		107.6 mg	44% (Compound of formula (II)(3) with R" = methyl)	m/z calculated for C ₂₅ H ₃₀ N ₂ O ₃ H [M+H] ⁺ 407.5, found 407.5. (Compound of formula (II)(3) with R" = methyl)
(5) with R" = ethyl		120.2 mg	16% (Compound of formula (II)(5) with R" = ethyl)	m/z calculated for C ₂₆ H ₂₉ N ₃ O ₃ H [M+H] ⁺ 431.5, found 431.5.

				(Compound of formula (II)(5) with R" = ethyl)
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As illustrated in the examples above, the process for preparing compound of formula (II) as described above implements metal catalyzed dehydrogenative amidation conditions and allows to prepare various sartan intermediates, with only one reaction step compared to the classical synthetic route, in particular using a cheap metal catalyst such as copper catalyst or iron catalyst being generated more particularly from copper(II) source or iron(III) source.

Example 5: Tetrazoylation of OTBN dimer side product

In some conditions, as described hereafter, tetrazoylation step leads to the formation of OTBN dimer mono- and/or di-tetrazole side products respectively of formula (V) and (VI):



To a flame dried 8 mL microwave vial was placed OTBN dimer (358.2 mg, 1 mmol) of formula (IV) as a starting material, NaN₃ (143.0 mg, 2.2 mmol), triethylamine hydrochloride (344.3 mg, 2.5 mmol) followed by the addition of NMP (2 mL) and reaction mixture was heated at 130 °C for 18 h. After this time, reaction mixture was cooled to room temperature and a precipitate appeared which was filtered. Solid was washed with water (3*5 mL) and EtOAc (3*5 mL) to obtain a the OTBN dimer di-tetrazole side product of formula (VI).

Filtrate was purified by silica gel chromatography using DCM/MeOH (9/1) as eluent. The fraction containing neither the starting material nor the OTBN dimer di-tetrazole side product of formula (VI) were concentrated to obtain the OTBN dimer mono-tetrazole side product of formula (V).

The chemical analysis of OTBN dimer mono-tetrazole side product of formula (V) was described hereafter:

¹H NMR (300.1 MHz, *d*-DMSO) δ 7.96-7.92 (m, 1H), 7.81 – 7.76 (m, 1H), 7.74-7.61 (m, 4H), 7.59-7.53 (m, 2H) 7.51 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 2.21-2.14 (m, 4H).

LC/MS : m/z calculated for C₂₈H₂₁N₅H [M+H]⁺ 428.2, found 428.4.

The chemical analysis of OTBN dimer di-tetrazole side product of formula (VI) was described hereafter:

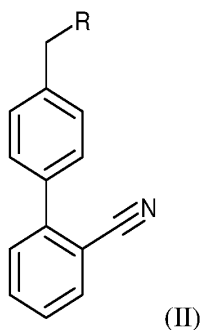
¹H NMR (300.1 MHz, *d*-DMSO) δ 7.69 – 7.61 (m, 4H), 7.58 – 7.51 (m, 4H), 7.18 (d, J = 8.2 Hz, 4H) 7.01 (d, J = 8.2 Hz, 4H), 2.85 (s, 4H).

LC/MS : m/z calculated for C₂₈H₂₂N₈H [M+H]⁺ 471.2, found 471.4.

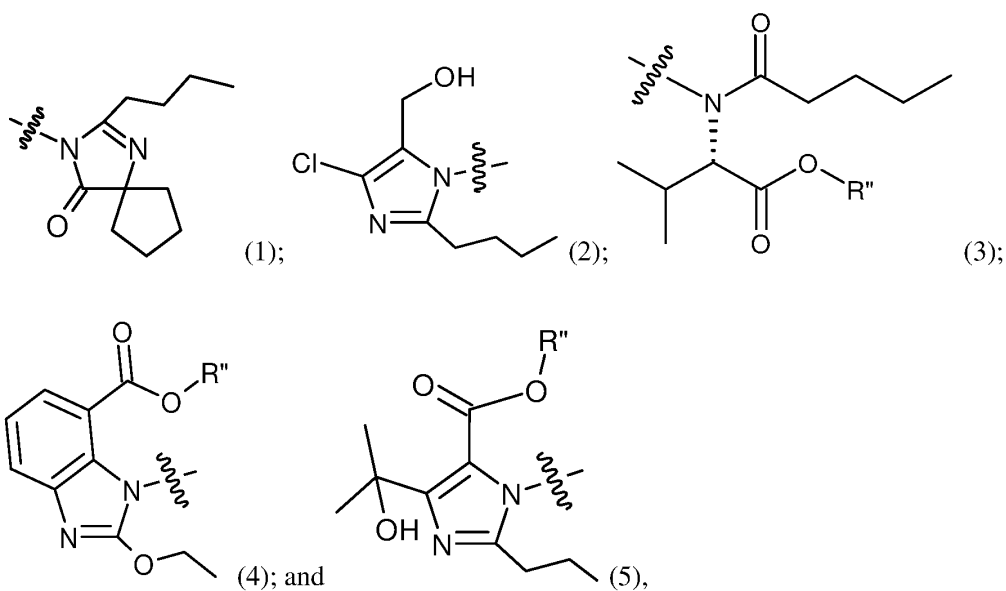
While preferred embodiments of the present disclosure have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the disclosure. It should be understood that various alternatives to the embodiments of the disclosure described herein may be employed in practicing the disclosure. It is intended that the following claims define the scope of the disclosure and that methods and structures within the scope of these claims and their equivalents be covered thereby. The disclosures of all patent and scientific literature cited herein are expressly incorporated herein in their entirety by reference. To the extent that any incorporated material is inconsistent with the express content of this disclosure, the express content controls.

CLAIMS

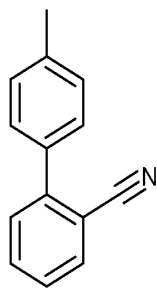
1. A process for preparing a compound of formula (II):



- 5 wherein R is selected from formulas (1), (2), (3), (4) and (5):



wherein R'' is selected from a hydrogen atom and a (C₁-C₃)alkyl group,
comprising reacting a compound of formula (III)



10

(III) with a compound RH or one of its salts, wherein R is as defined above, under metal catalyzed dehydrogenative amidation conditions.

2. The process according to claim 1, wherein the reaction is performed in presence of a metal catalyst selected from copper catalyst, iron catalyst, manganese catalyst, cobalt catalyst and nickel catalyst and a mixture thereof, in particular in presence of an iron catalyst or a copper catalyst.

3. The process according to the preceding claim, wherein the copper catalyst is generated from copper(I) or copper(II), also respectively called copper(I) source or copper(II) source, each under the form of a salt or a complex, or a mixture thereof, in particular selected from CuCl, CuBr, CuI, copper(I) thiophene-2-carboxylate, CuBr•SMe₂, CuBr(Phen), CuI(Phen), CuCl(Phen), copper(I) acetate, Cu₂S, copper(I) thiophenolate, (4-bromophenyl)-thio-copper(I), mesitylcopper(I), CuCN, CuSCN, (1,10-phenanthroline)(trifluoromethyl)copper(I), CuBr₂, copper(II) acetate anhydrous or hydrate, CuF₂, CuCl₂ anhydrous or hydrate, CuS, CuSO₄ anhydrous or hydrate, CuO, Cu(NO₃)₂ anhydrous or hydrate, copper(II) trifluoromethanesulfonate, copper(II) ethylacetoacetate anhydrous or hydrate, copper(II) 2-ethylhexanoate, copper(II) trifluoroacetate anhydrous or hydrate, copper(II) trifluoroacetylacetonate, copper(II) tert-butylacetoacetate, copper(II)i-butyrate, copper(II) 2-pyrazinecarboxylate, copper(II) hexafluoroacetylacetonate anhydrous or hydrate, copper(II) trifluoromethanesulfonimide anhydrous or hydrate, dichloro(1,10-phenanthroline)copper(II), copper(II) cyclohexanebutyrate, tetrakis(pyridine)copper(II) triflate, copper(II) 3,5-diisopropylsalicylate anhydrous or hydrate, copper(II) tetrafluoroborate anhydrous or hydrate, phthalic acid copper(II), copper(II) di(2-naphthoate), benzoic acid copper(II) anhydrous or hydrate, methyl acetoacetate copper(II), ethyl benzoylacetate copper(II), ethyl 2-fluorobenzoylacetate copper(II), ethyl 2-chlorobenzoylacetate copper(II), 3-(fluorosulfonyl)benzoic acid copper(II), ethyl 3-(fluorosulfonyl)benzoylacetate copper(II), 8-hydroxyquinoline copper(II), dichloro(N-(2-pyridylmethylene)aniline-N,N')copper(II), ethyl 2-(4-(pentyloxy)benzoyl)acetate copper(II), ethyl alpha-acetyl-3-(fluorosulfonyl)benzoylacetate copper(II), ethyl alpha-acetyl-4-(fluorosulfonyl)benzoylacetate copper(II), ethyl alpha-acetyl-3-(methoxycarbonyl)benzoylacetate copper(II), 2,3-diazaspiro[bicyclo[2.2.1]hept[2]ene-7,1'-cyclopropane copper(II), alpha-(3,5-dichloro-2-pyridylimino)-o-cresol copper(II), alpha-(6-methyl-2-pyridylimino)-o-cresol copper(II), alpha-(3-methyl-2-pyridylimino)-o-cresol copper(II), alpha-(5-chloro-2-pyridylimino)-o-cresol copper(II), alpha-(4-methyl-2-pyridylimino)-o-cresol copper(II), copper(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate) and copper(II) bis(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-

octanedionate), more particularly from CuCl, CuBr, CuI, copper(I) thiophene-2-carboxylate, CuBr•SMe₂, CuBr(Phen), CuI(Phen), CuCl(Phen), copper(I) acetate, CuBr₂ and copper(II) acetate anhydrous, even more particularly from CuBr, CuI, CuBr(Phen), CuI(Phen), CuBr•SMe₂ and CuBr₂, for example CuBr•SMe₂.

5

4. The process according to claim 2, wherein the iron catalyst is generated from iron(II) or iron(III), also respectively called iron(II) source or iron (III) source, each under the form of a salt or a complex, or a mixture thereof, in particular selected from FeCl₂, FeCl₃, FePO₄, FeI₃, FeF₃, FeBr₃, Fe₂(SO₄)₃, Fe₂(C₂O₄)₃, Fe(OH)₃, FeCl₃•6H₂O, FeF₃•3H₂O, Fe₄(P₂O₇)₃,
10 Fe₄(Fe(CN)₆)₃ and Fe(H₂PO₂)₃, in particular from FeCl₃, FePO₄, FeI₃, FeF₃, FeBr₃, Fe₂(SO₄)₃, Fe₂(C₂O₄)₃ and Fe(OH)₃, more particularly from FeBr₃, FeCl₂, FeCl₃ and FeCl₃•6H₂O, for example FeBr₃.

5. The process according to claim 2, wherein the manganese catalyst, cobalt catalyst and
15 nickel catalyst are generated respectively from:

- (i) a manganese source, also called manganese(II) source, under the form of a salt or a complex, or a mixture thereof, in particular selected from MnBr₂ and MnCl₂,
- (ii) a cobalt source, also called cobalt(II) source, under the form of a salt or a complex, or a mixture thereof, in particular selected from CoCl₂ and CoBr₂, and
- 20 - (iii) a nickel source, also called nickel(II) source, under the form of a salt or a complex, or a mixture thereof, in particular selected from NiBr₂ and NiCl₂.

6. The process according to any of claims 1 to 5, wherein the metal catalyst is under the form of a metal complex comprising a ligand, in particular selected from bidentate ligands,
25 monodentate ligands and mixtures thereof, more particularly selected from:

- bidentate or monodentate nitrogen ligands, in particular bidentate nitrogen ligands, more particularly optionally substituted bipyridine ligands, even more particularly phenanthroline ligands, for example 1,10-phenanthroline, 4,4'-di-tert-butyl-2,2'-dipyridyl, dimethylglycine, N,N,N',N'-tetramethylethylenediamine, trans-N,N'-dimethylcyclohexane-1,2-diamine, N-(2-pyridinylmethylene)benzenamine, 1,1'-Binaphthyl-2,2'-diamine or 1-methylimidazole ;
- 30 - bidentate or monodentate phosphine ligands, in particular monodentate phosphine ligands, more particularly phosphine ligands optionally substituted by at least one aryl, for example triphenylphosphine; or

- bidentate diketone ligands, in particular 1,3-diketone ligands, for example ethyl 2-oxocyclohexanecarboxylate.

7. The process according to any of claims 2 to 5, wherein the metal source, in particular the copper(I) source, the copper(II) source, the iron(II) source and/or the iron (III) source is present at a molar percentage ranging from 0.1% to 20%, in particular from 0.5% to 15%, and more particularly from 1% to 10% with respect to the amount of the compound RH as defined in claim 1.

8. The process according to any of claims 1 to 7, wherein the reaction is performed in presence of an oxidant, in particular selected from peroxides of formula $R1-O-O-R2$ or of formula $R'1-O-O-R'-O-O-R'2$, and oxalates of formula $R3-O-C(O)-C(O)-O-R4$ and mixtures thereof,

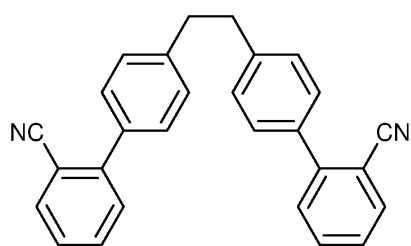
$R1$, $R'1$, $R2$ and $R'2$ independently represent a hydrogen atom, an alkyl group optionally substituted by an aryl group, a cycloalkyl group, an aryl group or an oxo group optionally substituted by an alkyl group, an alkoxy or an aryl group, in particular said peroxide of formula $R1-O-O-R2$ is selected from di-tert-butyl peroxide, tert-butyl hydroperoxide, benzoyl peroxide, dicumyl peroxide and hydrogen peroxide, even more particularly selected from di-tert-butyl peroxide, tert-butyl hydroperoxide and dicumyl peroxide, for example di-tert-butyl peroxide;

R' represents a (C_1-C_6) alkylene group, in particular said peroxide of formula $R'1-O-O-R'-O-O-R'2$ is selected from 2,5-di(tert-butylperoxy)-2,5-dimethyl-3-hexyne, 2,5-di(tert-butylperoxy)-2,5-dimethyl-3-hexane and 1,1-bis(tert-butylperoxy)cyclohexane; and $R3$ and $R4$ independently represent a hydrogen atom, an aryl group or an alkyl group optionally substituted by an aryl group, for example ditertbutyloxalate.

9. The process according to the preceding claim, wherein the oxidant is present at an equivalent ranging from 0.1 to 10 with respect to the amount of the compound RH as defined in claim 1 and corresponding to 1 equivalent, in particular from 0.5 to 8 with respect to the amount of the compound RH as defined in claim 1 and corresponding to 1 equivalent, and more particularly from 1 to 5 with respect to the amount of the compound RH as defined in claim 1 and corresponding to 1 equivalent.

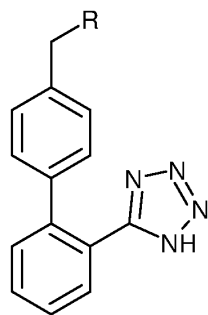
10. The process according to any of claims 1 to 9, wherein the reaction is performed in presence of a solvent, in particular an organic solvent, more particularly selected from:

- aromatic solvents, even more particularly selected from benzonitrile, o-tolylbenzonitrile, chlorobenzene, dichlorobenzene and anisol, such as o-tolylbenzonitrile,
 - alcohol solvents, even more particularly selected from hexafluoropropan-2-ol, isobutanol, tert-butanol and n-butanol, such as tert-butanol and n-butanol,
 - 5 - ketone solvents, such as methyl isobutyl ketone,
 - ether solvents, such as cyclopentane methyl ether,
 - hydrocarbon solvents, such as heptane,
 - ester solvents, such as isobutyl acetate,
 - polar solvents, even more particularly selected from acetonitrile, N,N-dimethylformamide,
 - 10 dimethyl sulfoxide, diethyl carbonate and n-methyl pyrrolidine (NMP),
 - water,
 - acid solvents, such as acetic acid,
 - and mixtures thereof.
- 15 11. The process according to any of claims 1 to 10, wherein the reaction is performed in presence of a base, in particular when RH as defined in claim 1 is under the form of a salt, said base being optionally selected from:
- inorganic bases, for example Na_2CO_3 , Cs_2CO_3 , K_2CO_3 , NaHCO_3 , NaOH , or KOH ,
 - alkoxide bases, for example tBuOK,
 - 20 - organic bases comprising at least one nitrogen atom, for example triethylamine or N,N-diisopropylethylamine,
 - and mixtures thereof.
12. The process according to any of claims 1 to 11, wherein the reaction is performed at a
- 25 temperature ranging from 20°C to 200°C, in particular from 90°C to 180°C, more particularly from 100°C to 150°C and/or under photoactivation conditions with a wavelength ranging from 200 nm to 900 nm, in particular from 200 nm to 800 nm, more particularly from 250 nm to 400 nm, or a combination of wavelengths, and optionally in the presence of a photosensitizer.
- 30 13. The process according to any of claims 1 to 12, wherein a o-tolylbenzonitrile dimer side compound of formula (IV)



(IV) is formed.

14. A process for preparing a sartan active compound of formula (I) or one of its pharmaceutically acceptable salts:



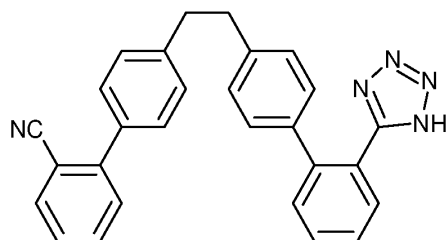
5 (I), wherein R is as defined in claim 1,

comprising a tetrazolylolation step reacting the compound of formula (II) as defined in claim 1 prepared by the process according to any of claims 1 to 13, in particular a tetrazolylolation step wherein it is performed in a reactional medium with at least one azide derivative, wherein benzylic azide impurities formed during said tetrazolylolation are converted into aldehyde derivatives.

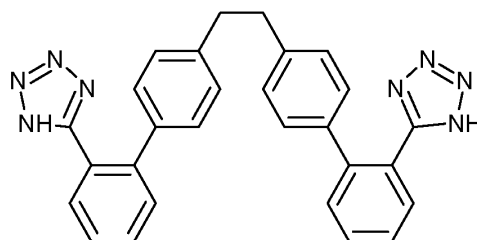
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15. The process according to the preceding claim, wherein the sartan active compound of formula (I) is irbesartan, also called 2-n-butyl-4-spirocyclopentane-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-2-imidazolin-5-one or 2-n-butyl-3-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

16. The process according to any of claims 14 or 15, wherein the sartan active compound of formula (I) comprises at least one of compounds of formula (V) and (VI):



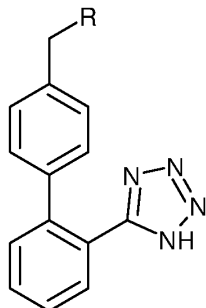
(V),



(VI).

17. A composition comprising:

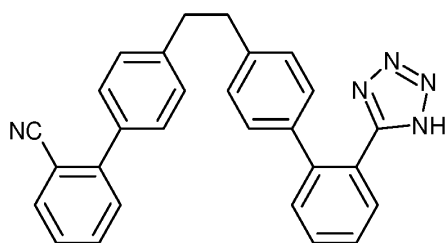
- a sartan active compound of formula (I), or one of their pharmaceutically acceptable salts:



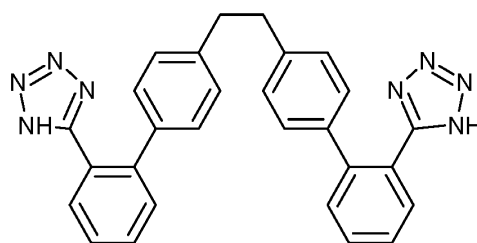
(I), wherein R is as defined in claim 1, obtainable by a process according to

5 any of claims 1 to 13 and followed by a tetrazolylolation step as defined in claim 14, and

- at least one of compounds of formula (V) and (VI):

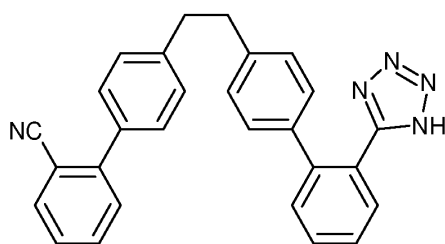


(V),

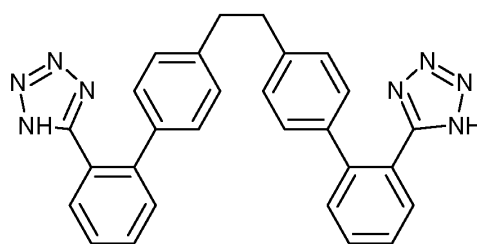


(VI).

18. The composition according to the preceding claim, wherein the sartan active compound of
10 formula (I) is irbesartan, also called 2-n-butyl-4-spirocyclopentane-1-[[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-2-imidazolin-5-one or 2-n-butyl-3- [[2'-(tetrazol-5-yl)biphenyl-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one, and comprises at least one of compounds of formula (V) and (VI):



(V),



(VI).

15

19. The composition according to claim 17, wherein the sartan active compound of formula (I) is selected from losartan, valsartan and its esters, candesartan and its esters, olmesartan and its esters, and comprises at least one of compounds of formula (V) and (VI):

