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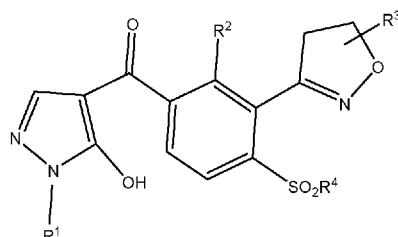
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(54) Title: PROCESS FOR PREPARATION OF HETEROARYLKETONES



(I)

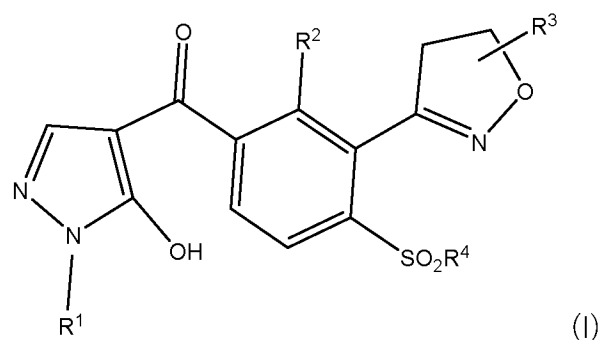
(57) Abstract: The present invention relates to a process for preparation of heteroarylketones of formula (I). The invention relates to an efficient process for the preparation of heteroarylketones for formula (I) which find use as herbicides. (I)



PROCESS FOR THE PREPARATION OF HETEROARYLKETONES

FIELD OF THE INVENTION

- 5 The present invention relates to a process for the preparation of heteroarylketones of the formula (I). The invention relates to an efficient process for the preparation of heteroarylketones of the formula (I) which are used as herbicides.



10

BACKGROUND OF THE INVENTION

Heteroarylketones of formula (I) are described in WO96/26206 and WO98/31681. The heteroarylketones of formula (I) are directed to an herbicidal compound 4-[3-(4,5-dihydro-1,2-oxazol-3-yl)-2-methyl-4-methylsulfonylbenzoyl]-2-methyl-1H-pyrazol-3-one or [3-(4,5-dihydroisoxazol-3-yl)-2-methyl-4-methylsulfonyl-phenyl]-(5-hydroxy-1-methyl-pyrazol-4-yl)methanone.

WO 96/26206 discloses a process for preparing 4-(3-(4,5-dihydroisoxazol-3-yl) benzoyl)-5-hydroxypyrazoles where, in the last step, a 5-hydroxypyrazole is reacted with a 3-(4,5-dihydroisoxazol-3-yl) benzoic acid derivative. The 3-(4,5-dihydroisoxazol-3-yl) benzoic acid derivative required for this process can only be obtained with difficulty, via several steps. Accordingly, the process is relatively expensive and not optimal economically.

DE 197 09 118 describes a process for preparing 3-(4,5-dihydroisoxazol-3-yl) benzoic acids starting from 3-bromo-(4,5-dihydroisoxazol-3-yl) benzene, Grignard reagents and carbon dioxide.

WO 99/58509 describes a process for preparing 3-heterocyclyl-substituted benzoyl derivatives with reduced steps. However, the yields obtained by the process are not satisfactory.

The known prior art describe processes to synthesize 4-[3-(4,5-dihydro-1,2-oxazol-3-yl)-2-methyl-4-methylsulfonylbenzoyl]-2-methyl-1H-pyrazol-3-one from a compound of formula (III). However, there are several disadvantages in terms of reaction conditions, the yields and/or work-up requirements rendering them unsuitable for industrial scale production.

Another disadvantage of the processes described in the prior art is the formation of impurities which lead to further reduction of the yield.

An object of the presently claimed invention is to provide an improved process for the synthesis of heteroaryl ketones that have herbicidal activity. Furthermore, the object underlying the presently claimed invention is to optimize the synthesis of heteroarylketones of formula (I). The present invention includes several advantages, for example, a more efficient process having minimal waste throughput and waste treatment. The presently claimed process is shown to avoid the need for carefully controlled reaction conditions, tedious multiple purification techniques, and the use of stoichiometric amounts of organometallic reagents.

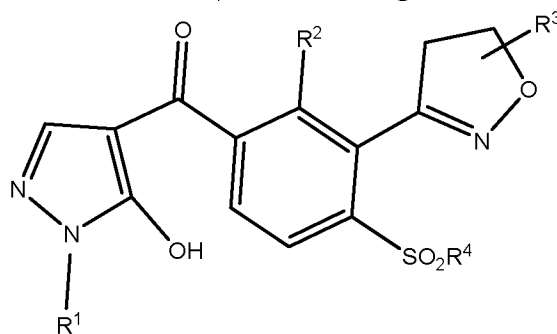
Description

This object is achieved by the processes described in detail hereafter.

A first aspect of the present invention relates to a process for the preparation of a compound of the general formula (I) or its salts as describes in step (A).

Step (A):

The process for the preparation of a compound of the general formula (I) or its salts

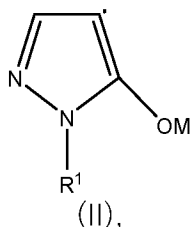


(I)

wherein

R¹ is C₁-C₄ alkyl, R² is Cl or C₁-C₄ alkyl, R³ is hydrogen or C₁-C₄ alkyl and R⁴ is C₁-C₄ alkyl,

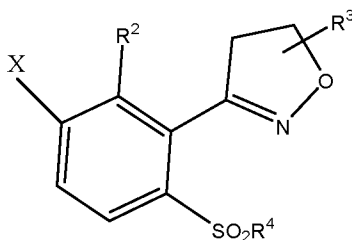
comprising at least the step of reacting a compound of formula (II),



wherein

R^1 is C_1 - C_4 alkyl and M is H or an alkali metal atom

5 with a compound of formula (III),



(III),

wherein

10 X is Cl, Br, I, $S(=O)_2-CH_3$ or $S(=O)_2-CF_3$, R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, and R^4 is C_1 - C_4 alkyl,

in the presence of carbon monoxide, at least one alkali metal iodide, at least one base, at least one metal catalyst and at least one phosphine compound.

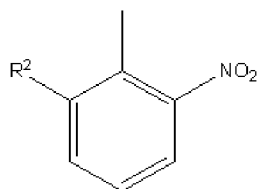
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Step B:

Further, the compound of general formula (III) is obtained by one or more of the following steps:

20

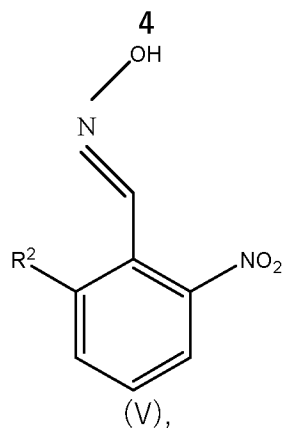
a) reacting a nitro-methylphenyl compound of formula IV,



(IV),

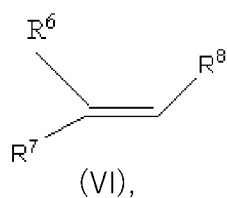
25 wherein R^2 is Cl or C_1 - C_4 alkyl,

with an organic nitrile of the formula R^5-ONO , wherein R^5 is n-butyl, in the presence of at least one base to give an oxime of the formula (V),

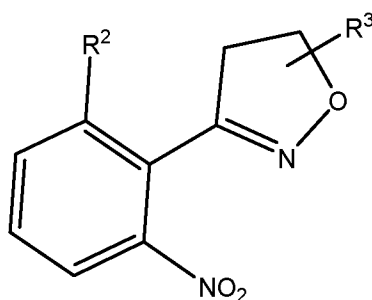


wherein R^2 is Cl or C_1 - C_4 alkyl,

- 5 a) cyclization of the oxime of the formula (V) with an alkene of the formula (VI),

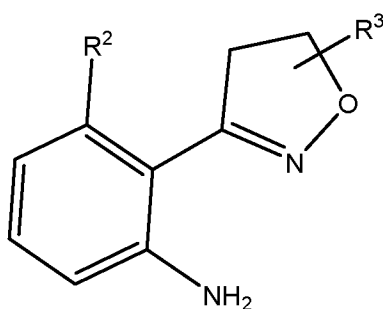


- 10 wherein R^6 , R^7 , R^8 are, identical or different, hydrogen or C_1 - C_4 alkyl, in the presence of at least one base to give a compound of formula (VII),



- 15 wherein R^2 is Cl or C_1 - C_4 alkyl and R^3 is hydrogen or C_1 - C_4 alkyl,

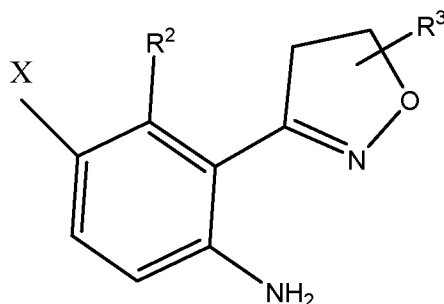
- b) reducing the compound of formula (VII) in the presence of at least one catalyst to give the compound of formula (VIII),



(VIII),

wherein R^2 is Cl or C_1 - C_4 alkyl, and R^3 is hydrogen or C_1 - C_4 alkyl,

- 5 c) substituting the para amino position in the compound of formula (VIII) to give the compound of formula (IX),



(IX),

- 10 wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl and X is Cl, Br, I, $S(=O)_2-CH_3$ or $S(=O)_2-CF_3$;

- d) reacting the compound of formula (IX) with a dialkyl disulfide of formula (X)

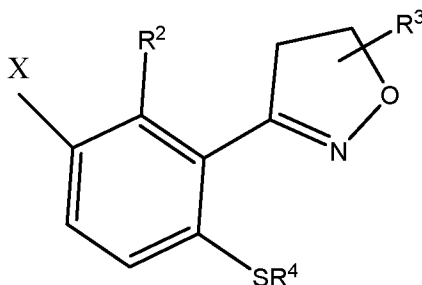
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(X)

wherein R^4 is C_1 - C_4 alkyl,

- 20 in the presence of an organic nitrile of the formula R^5-ONO , wherein R^5 is n-butyl, and at least one catalyst to give the compound of formula (XI),

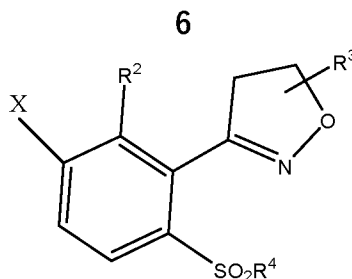


25

(XI),

wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, R^4 is C_1 - C_4 alkyl, and X is Cl, Br, I, $S(=O)_2-CH_3$ or $S(=O)_2-CF_3$

- 30 e) oxidizing the compound of formula (XI) with at least one oxidizing agent to obtain the compound of formula (III),



(III),

- 5 wherein X is Cl, Br, I, S(=O)₂-CH₃ or S(=O)₂-CF₃, R² is Cl or C₁-C₄ alkyl, R³ is hydrogen or C₁-C₄ alkyl, and R⁴ is C₁-C₄ alkyl,

10 Salts of the compounds according to the invention can be formed in a customary manner, for example, by reacting the compound with an acid of the anion in question, if the compounds according to the invention have a basic functionality or by reacting acidic compounds according to the invention with a suitable base. Salts of the compounds prepared according to the invention are preferably agriculturally acceptable salts.

15 The organic moieties or groups mentioned in the above definitions of the variables are - like the term halogen - collective terms for individual listings of the individual group members. The term "C_v-C_w" indicates the number of carbon atom possible in each case.

The term "halogen" refers to fluoro, chloro, bromo and iodo.

20 The term "C₁-C₄-alkyl" refers to a straight-chained or branched saturated hydrocarbon group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl.

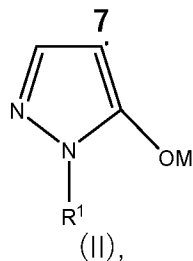
25 The term "substituted" if not specified otherwise refers to substituted with 1, 2 or maximum possible number of substituents. If substituents are more than one, then they are independently from each other are same or different, if not mentioned otherwise.

Meanings of the terms that are not defined herein are generally known to a person skilled in the art or in the literature.

30 Preferred embodiments of the present invention are described below.

Step (A) of the present invention for the preparation of a compound of the general formula (I) or its salts is as follows:

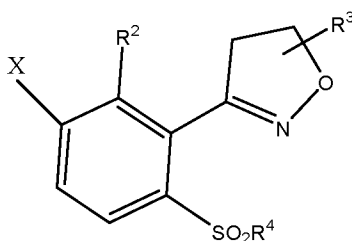
35 Reacting a compound of formula (II),



wherein

R¹ is C₁-C₄ alkyl and M is H or an alkali metal atom

with a compound of formula (III),



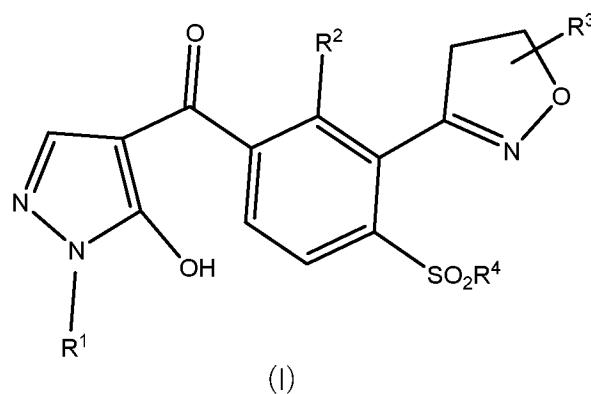
(III),

wherein

X is Cl, Br, I, S(=O)₂-CH₃ or S(=O)₂-CF₃, R² is Cl or C₁-C₄ alkyl, R³ is hydrogen or C₁-C₄ alkyl, and R⁴ is C₁-C₄ alkyl,

in the presence of carbon monoxide, at least one alkali metal iodide, at least one base, at least one metal catalyst and at least one phosphine compound

to obtain a compound of formula (I)



wherein

R¹ is C₁-C₄ alkyl, R² is Cl or C₁-C₄ alkyl, R³ is hydrogen or C₁-C₄ alkyl and R⁴ is C₁-C₄ alkyl.

In an embodiment, of the present invention R^1 is C_1 - C_2 alkyl, R^2 is C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, R^4 is C_1 - C_4 alkyl.

5 In another embodiment, of the present invention R^1 is methyl, R^2 is C_1 - C_2 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl and R^4 is C_1 - C_4 alkyl.

In another embodiment, of the present invention R^1 is methyl, R^2 is methyl, R^3 is hydrogen or C_1 - C_4 alkyl and R^4 is C_1 - C_4 alkyl.

In another embodiment, of the present invention R^1 is methyl, R^2 is methyl, R^3 is hydrogen and R^4 is C_1 - C_4 alkyl.

10 In yet another embodiment, of the present invention R^1 is methyl, R^2 is methyl, R^3 is hydrogen and R^4 is C_1 - C_2 alkyl.

In another embodiment, of the present invention R^1 is methyl, R^2 is methyl, R^3 is methyl and R^4 is methyl.

15 In a preferred embodiment, of the present invention R^1 is methyl, R^2 is methyl, R^3 is hydrogen and R^4 is methyl.

The temperatures and the duration times of the reactions may be varied in broad ranges, which the person skilled in the art knows from analogous reactions. The temperatures often depend on the reflux temperature of the solvents or at higher temperature under pressure.

20 The end of the reaction can be monitored by methods known to a person skilled in the art, for example, thin layer chromatography or HPLC or GC.

In an embodiment, the mass ratio of reactant to solvent is in the range of 1: 5 to 1: 20,

25 In another embodiment, the mass ratio of reactant to solvent is in the range of 1:6 to 1:10.

If not otherwise indicated, the reactants can in principle be contacted with one another in any desired sequence.

30 The person skilled in the art also knows the best work-up of the reaction mixture after the end of the reaction.

In the present invention, step (A) takes place in the presence of at least one alkali metal iodide, at least one base, at least one metal catalyst and at least one phosphine compound and at least one solvent, wherein the at least one metal is preferably in a form of a free state
35 of formula M or in a form of a metal complex of formula $M(L)_n$.

In the following, preferred embodiments regarding step (A) of the invention are provided. It is to be understood that the preferred embodiments mentioned above and those still to be illustrated below of step (A) of the invention are to be understood as preferred alone or in
40 combination with each other.

In one embodiment, the at least one alkali metal iodide is selected from the group consisting of sodium iodide, potassium iodide, lithium iodide.

In a preferred embodiment, the at least one alkali metal iodide is sodium iodide.

In one embodiment, the at least one metal (M) is selected from the group consisting of nickel (Ni), cobalt (Co), iron (Fe), ruthenium (Ru), rhodium (Rh), palladium (Pd), iridium (Ir),
 5 platinum (Pt), silver (Ag), copper (Cu), zinc (Zn), molybdenum (Mo) and tungsten (W).

In preferred embodiment, the at least one metal (M) is selected from the group consisting of palladium (Pd), nickel (Ni), copper (Cu) and iron (Fe).

- 10 In one embodiment, L, identical or different, is Cl, Br, I, $P(C_5-C_{14}\text{-aryl})_m$, $P(C_5-C_{12}\text{-heteroaryl})_m$, $P(C_5-C_{12}\text{-heteroaryl})_m(C_5-C_{14}\text{-aryl})_{3-m}$, CN, $C_1-C_6\text{-alkyl}$, $C_1-C_6\text{-alkyl-O-C}_1-C_6\text{-alkyl}$, $-O-CO-C_1-C_6\text{-alkyl}$, OH, nitro, $-O-C_1-C_6\text{-alkyl}$, $C_1-C_4\text{-haloalkoxy}$, $C_3-C_8\text{-cycloalkyl}$, $C_3-C_8\text{-halocycloalkyl}$, $C_3-C_8\text{-cycloalkenyl}$, $C_5-C_{14}\text{-aryl}$, $C_5-C_{14}\text{-aryl}-(CH_2)_o-(Q)_p-(CH_2)_o-C_5-C_{14}\text{-aryl}$ and 1,1'-*bis*(diphenyl phosphino)ferrocene; whereby Q represents a bridging group selected from the
 15 group consisting of $-CR^8R^9$, $-O-$, $-S-$, $-NR^{10}R^{11}$, $-SiR^{12}R^{13}$ and $-CO-$, wherein R^8 and R^9 , identical or different, are hydrogen, $C_1-C_{12}\text{ alkyl}$, $C_5-C_{14}\text{-aryl}$ or $C_5-C_{12}\text{-heteroaryl}$; wherein R^{10} , R^{11} , R^{12} and R^{13} , identical or different, are hydrogen or $C_1-C_4\text{ alkyl}$ or R^{10} together with R^{11} forms $C_5-C_{12}\text{-membered heterocycloalkyl}$, $C_5-C_{12}\text{-membered heterocycloalkenyl}$ or $C_5-C_{12}\text{-membered heteroaryl}$ and L is unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different
 20 groups selected from the group consisting of Cl; F; Br; I; CN; $-NO_2$; $-NR^{10}R^{11}$, $-P(phenyl)_2$, $-OH$, unsubstituted or substituted $C_1-C_{12}\text{-alkyl}$, $C_2-C_6\text{-alkenyl}$, $C_2-C_6\text{-alkynyl}$, unsubstituted or substituted $C_5-C_{14}\text{-aryl}$, unsubstituted or substituted $C_5-C_{12}\text{-heteroaryl}$, $C_5-C_{12}\text{-membered heterocycloalkyl}$, $C_5-C_{12}\text{-membered heterocycloalkenyl}$, $-O-(CH_2)_r-O-$, $-C(=O)R^{14}$, $-C(=O)-O-R^{15}$, $-C=N-R^{16}$, $-SO_3H$, $-O-C_1-C_6\text{-alkyl}$ and $-O-Si-C_1-C_4\text{-alkyl}$; wherein
 25 R^{14} is hydrogen or $C_1-C_4\text{-alkyl}$;
 R^{15} is hydrogen or $C_1-C_4\text{-alkyl}$;
 R^{16} is hydrogen, $C_1-C_{12}\text{-alkyl}$, $C_2-C_6\text{-alkenyl}$, $C_2-C_6\text{-alkynyl}$, $C_5-C_{14}\text{-aryl}$, $C_5-C_{12}\text{-heteroaryl}$ or $C_3-C_{12}\text{-cycloalkyl}$;
 n is 0,1,2,3,4,5 or 6
 30 m is 1,2 or 3;
 o is 0,1 or 2
 p is 0,1 or 2 and
 r is 1,2,3,4 or 5.
- 35 In yet another embodiment, L is, identical or different, Cl, Br, I, $P(C_5-C_{14}\text{-aryl})_m$, CN, unsubstituted or substituted $C_1-C_{12}\text{-alkyl}$, $C_1-C_4\text{-alkoxy}$, $C_3-C_8\text{-cycloalkenyl}$, $-O-CO-C_1-C_6\text{-alkyl}$, $C_5-C_{14}\text{-aryl}$, 1,1'-*bis*(diphenyl phosphino)ferrocene and $C_5-C_{14}\text{-aryl}-(CH_2)_o-(Q)_p-(CH_2)_o-C_5-C_{14}\text{-aryl}$;
 wherein
 40 m is 1,2 or 3;
 o is 0,1 or 2
 p is 0,1 or 2.

In more preferred embodiment, L is, identical or different, Cl, $-\text{OCOCH}_3$, $\text{P}(\text{phenyl})_3$, $\text{P}(\text{o-tolyl})_3$, CN, dibenzylidene acetone, $-\text{CH}_3\text{CN}$, 1,5-cyclooctadiene or 1,1'-bis(diphenyl phosphino) ferrocene.

- 5 In another embodiment, Ln is supported on silica gel, dendrimers, polystyrenes or mesoporous siliceous foam, for example as described in Vivek et. al., *Tetrahedron*, **63**, 2007, 6949-6976.

In another embodiment, R^8 is hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_5\text{-C}_{14}$ -aryl or $\text{C}_5\text{-C}_{12}$ -heteroaryl.

- 10 In another embodiment, R^8 is hydrogen, methyl or ethyl.

In another embodiment, R^9 is hydrogen, $\text{C}_1\text{-C}_{12}$ alkyl, $\text{C}_5\text{-C}_{14}$ -aryl or $\text{C}_5\text{-C}_{12}$ -heteroaryl.

In more preferred embodiment, R^9 is hydrogen.

In another embodiment, R^{10} is hydrogen, methyl, ethyl, propyl or n-butyl.

In another embodiment, R^{11} is hydrogen, methyl, ethyl, propyl or butyl.

- 15 In another embodiment, R^{12} is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment, R^{13} is hydrogen, methyl, ethyl, propyl or butyl.

In another preferred embodiment, R^{13} is hydrogen, methyl or ethyl.

In yet another embodiment, R^{10} together with R^{11} forms $\text{C}_5\text{-C}_{12}$ -membered heterocycloalkyl, $\text{C}_5\text{-C}_{12}$ -membered heterocycloalkenyl or $\text{C}_5\text{-C}_{12}$ -membered heteroaryl.

- 20 In another embodiment, R^{14} is hydrogen or $\text{C}_1\text{-C}_4$ -alkyl.

In yet another embodiment, R^{14} is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment, R^{15} is hydrogen, methyl, ethyl, propyl or butyl.

In another embodiment, R^{16} is hydrogen, $\text{C}_1\text{-C}_{12}$ -alkyl, $\text{C}_2\text{-C}_6$ -alkenyl, $\text{C}_2\text{-C}_6$ -alkynyl, $\text{C}_5\text{-C}_{14}$ -aryl, $\text{C}_5\text{-C}_{12}$ -heteroaryl or $\text{C}_3\text{-C}_{12}$ -cycloalkyl.

- 25 In another embodiment, n is 0,1,2,3,4,5 or 6.

In yet another preferred embodiment, n is 0,1 or 2.

In yet another preferred embodiment, n is 3,4,5 or 6.

In more preferred embodiment, n is 2, 3 or 4.

In another embodiment, m is 1, 2 or 3.

- 30 In another embodiment, o is 0,1 or 2

In another embodiment, p is 0,1 or 2 and

In another embodiment, r is 1,2,3,4 or 5.

In more preferred embodiment, M, L and n are as follows in Table 1:

- 35 Table 1

Metal (M)	L	n	MLn
Pd	OCOCH_3	2	$\text{Pd}(\text{OCOCH}_3)_2$
Pd	Cl	2	$\text{Pd}(\text{Cl})_2$
Pd	Cl; CH_3CN	4	$\text{PdCl}_2(\text{CH}_3\text{CN})_2$
Pd	Cl; 1,1'-bis(diphenyl phosphino)ferrocene	3	$\text{Pd}(1,1'\text{-bis(diphenyl phosphino)ferrocene})\text{Cl}_2$
Pd	dibenzylideneacetone	3	$\text{Pd}_2(\text{dibenzylideneacetone})_3$
Pd	dibenzylideneacetone	2	$\text{Pd}(\text{dibenzylideneacetone})_2$
Ni	Cl; $\text{P}(\text{phenyl})_3$	4	$\text{Ni}(\text{Cl})_2(\text{P}(\text{phenyl})_3)_2$

Ni	1,5-cyclooctadiene	2	Ni(1,5-cyclooctadiene) ₂
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The amount of at least one M and/or ML_n is in the ratio of 1: 100 mole to 1:500 mole of the compound of formula (III).

- 5 In a preferred embodiment the amount of at least one M and/or ML_n is in the ratio of 1: 150 mole to 1:400 mole of the compound of formula (III)

In a preferred embodiment, the at least one metal catalyst is in a free state of palladium such as Pd/C.

- 10 In a preferred embodiment, the at least one metal catalyst is in a form of a metal complex selected from the group consisting of Pd(OCOCH₃)₂ and Pd(Cl)₂.

- In one embodiment, the phosphine compound is PX₁X₂X₃ or (PX₁X₂)₂(B)_q, whereby X₁, X₂ and X₃, identical or different, are F, Cl, Br, I, -NR¹⁷R¹⁸, hydrogen, -O-C₁-C₆-alkyl, -O-CO-C₁-C₆-alkyl, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₅-C₁₄-aryl, C₅-C₁₂-heteroaryl, C₃-C₁₂-cycloalkyl, C₃-C₁₂-cycloalkenyl, C₃-C₁₂-heterocycloalkyl, C₃-C₁₂-heterocycloalkenyl or -Si-(C₁-C₁₂-alkyl)₃, whereby B is CR¹⁹R²⁰, -O-, -phenyl-O-phenyl-, -S-, -NR¹⁷R¹⁸, -SiR²¹R²² or -C(=O)-, wherein R¹⁹ and R²⁰, identical or different, are hydrogen, C₁-C₁₂-alkyl, C₅-C₁₄-aryl or C₅-C₁₂-heteroaryl, wherein R¹⁷, R¹⁸, R²¹ and R²², identical or different, are hydrogen or C₁-C₄-alkyl or R¹⁷ together with R¹⁸ forms heterocycloalkyl, heterocycloalkenyl or C₅-C₁₂-heteroaryl; whereby X₁, X₂ and X₃, identical or different, are unsubstituted or substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; -NO₂; -NR¹⁷R¹⁸, -P(phenyl)₂, -OH, unsubstituted or substituted C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, unsubstituted or substituted C₅-C₁₄-aryl, unsubstituted or substituted C₅-C₁₂-heteroaryl, -O-(CH₂)_r-O-, -C(=O)R²³, -C(=O)-O-R²⁴, -C=N-R²⁵, -SO₃H, -O-C₁-C₆-alkyl and -O-Si-C₁-C₄-alkyl, C₅-C₁₂-membered heterocycloalkyl, C₅-C₁₂-membered heterocycloalkenyl and C₅-C₁₂-heteroaryl; wherein q is 1,2,3,4,5 or 6; r is 1,2,3,4 or 5; R²³ is hydrogen or C₁-C₄-alkyl; R²⁴ is hydrogen or C₁-C₄-alkyl; and R²⁵ is hydrogen, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₅-C₁₄-aryl, C₅-C₁₂-heteroaryl or C₃-C₁₂-cycloalkyl; or their acceptable salts thereof.

- 35 In another embodiment, X₁, X₂ and X₃, identical or different, are C₁-C₁₂-alkyl, C₅-C₁₄-aryl or C₅-C₁₂-heteroaryl.

- In more preferred embodiment, X₁, X₂ and X₃, identical or different, are methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-

trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl, n-octyl, 1-methylpropyl, 2-methylheptyl or 1,1-dimethylethyl.

5 In yet another preferred embodiment, X_1 , X_2 and X_3 , identical or different, are phenyl or naphthyl.

10 In yet another preferred embodiment, X_1 , X_2 and X_3 , identical or different, are pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, and tetrazolyl rings, and the fused bicyclic moieties formed by fusing one of these monocyclic groups with a phenyl ring or with any of the heteroaromatic monocyclic groups to form a C_8 - C_{10} bicyclic group such as indolyl, benzimidazolyl, indazolyl, benzotriazolyl, isoquinolinyl, quinolinyl, benzothiazolyl, benzofuranyl, benzothienyl, benzisoxazolyl, pyrazolopyridyl, quinazolinyl, quinoxalinyl or cinnolinyl.

15 In another embodiment, R^{17} is hydrogen or C_1 - C_4 alkyl.
 In another embodiment, R^{17} is hydrogen, methyl, ethyl, propyl or butyl.
 In another embodiment, R^{18} is hydrogen, methyl, ethyl, propyl or butyl.
 In another preferred embodiment, R^{18} is hydrogen.
 20 In yet another embodiment, R^{17} together with R^{18} forms C_5 - C_{12} -membered heterocycloalkyl, C_5 - C_{14} -membered heterocycloalkenyl or C_5 - C_{12} -heteroaryl.
 In another embodiment, R^{19} is hydrogen, C_1 - C_{12} -alkyl, C_5 - C_{14} -aryl or C_5 - C_{12} -heteroaryl.
 In yet another embodiment, R^{19} is hydrogen, methyl ethyl, propyl, phenyl or naphthyl.
 In another embodiment, R^{20} is hydrogen, C_1 - C_{12} -alkyl, C_5 - C_{14} -aryl or C_5 - C_{12} -heteroaryl.
 25 In yet another embodiment, R^{20} is hydrogen, methyl ethyl, propyl or butyl.
 In another embodiment, R^{21} is hydrogen or C_1 - C_4 alkyl.
 In another preferred embodiment, R^{21} is hydrogen.
 In another embodiment, R^{22} is hydrogen, methyl, ethyl, propyl or butyl.
 In yet another embodiment, R^{22} is hydrogen, methyl or ethyl.
 30 In another embodiment, R^{23} is hydrogen or C_1 - C_4 -alkyl.
 In another preferred embodiment, R^{23} is hydrogen, methyl, ethyl, propyl or butyl.
 In another embodiment, R^{24} is hydrogen methyl, ethyl, propyl or butyl.

35 In another embodiment, the at least one phosphine compound is selected from the group consisting of allyldiphenylphosphine; 1,3-*bis*(diphenylphosphino)propane; 1,3-*bis*(dicyclohexylphosphino)propane, 1,4-*bis*(diphenylphosphino)butane, di-*tert*-butyl(phenyl)phosphine, tri-*tert*-butylphosphine, di-*tert*-butyl(phenyl)phosphine tetrafluoroborate; (2-ammonioethyl) di-*tert*-butylphosphonium *bis*(tetrafluoroborate); (2-ammonioethyl) diisopropylphosphonium *bis*(tetrafluoroborate); (3-ammoniopropyl) di-*tert*-butylphosphonium
 40 *bis*(tetrafluoroborate); (3-ammoniopropyl) diisopropylphosphonium *bis*(tetrafluoroborate); *bis*(3,5-*bis*(trifluoromethyl)phenyl)(2',6'-*bis*(isopropoxy)-3,6-dimethoxybiphenyl-2-yl)phosphine; benzyldiphenylphosphine; (2-biphenyl)di-1-adamantylphosphine; 1-[2-[*bis*(*tert*-butyl)phosphino]phenyl]-3,5-diphenyl-1H-pyrazole; *bis*[2-(diadamantylphosphino)ethyl]amine; 2-[*bis*(3,5-di-*tert*-butyl-4-

methoxyphenyl)phosphino]benzaldehyde; 2,6-*bis*(di-*tert*-butylphosphinomethyl)pyridine; *bis*(dicyclohexylphosphinophenyl)ether; *bis*(diethylamino)phenylphosphine; *bis*(dimethylamino)chlorophosphine; 2-[*bis*(3,5-dimethylphenyl)phosphino]benzaldehyde; *bis*[4-(3,3,4,4,5,5,5-heptafluor-*o*-2,2-*bis*(trifluoromethyl)pentyl)phenyl]phenylphosphine;

5 *bis*(2-methoxyphenyl)phosphine; *bis*[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phenylphosphine; 1,1'-*bis*(phenylphosphinidene)ferrocene; (2-bromophenyl)dicyclohexylphosphine; (2-bromophenyl)diphenylphosphine; *tert*-butyldicyclohexylphosphine; *tert*-butyldicyclohexylphosphonium tetrafluoroborate; *tert*-butyldiisopropylphosphine; *tert*-butyldiphenylphosphine; 1-(dicyclohexylphosphino)-2,2-

10 Diphenyl-1-methylcyclopropane; cyclohexyldiphenylphosphine; di(1-adamantyl)-2-dimethylaminophenylphosphine; di-1-adamantylphosphine; di(1-adamantyl)-(2-triisopropylsiloxyphenyl)phosphine; (5H-dibenzo[*a,d*]cyclohepten-5-yl)diphenylphosphine; di-*tert*-butylcyclohexylphosphine; di-*tert*-butyl N,N-diisopropylphosphoramidite; di-*tert*-butylmethylphosphine; di-*tert*-butyl(methyl)phosphonium tetrafluoroborate; di-*tert*-

15 butyl(methyl)phosphonium tetrafluoroborate; di-*tert*-butylneopentylphosphine; di-*tert*-butylneopentylphosphonium tetrafluoroborate; di-*tert*-butylphenylphosphine; di-*tert*-butylphosphate potassium salt; 2'-(di-*tert*-butylphosphino)acetophenone ethylene ketal; 2-(di-*tert*-butylphosphino)dimethylaminobenzene; 2-(di-*tert*-butylphosphino)ethylamine; 2-((di-*tert*-butylphosphinomethyl)-6-diethylaminomethyl)pyridine; 5-(di-*tert*-butylphosphino)-

20 1-(naphthalen-1-yl)-1H-pyrazole; 5-(di-*tert*-butylphosphino)-1', 3', 5'-triphenyl-1' H-[1,4']bipyrazole; 3-(di-*tert*-butylphosphonium)propane sulfonate; P,P-dichloroferrocenylphosphine; dicyclohexyl-(2,6-diisopropylphenyl)phosphine; dicyclohexyl(4-(N,N-dimethylamino)phenyl)phosphine; dicyclohexyl(ethyl)phosphine; dicyclohexyl(4-isopropylphenyl)phosphine; dicyclohexyl(2-methylphenyl)phosphine;

25 dicyclohexylphenylphosphine; 2'-(dicyclohexylphosphino)acetophenone ethylene ketal; 2-(dicyclohexylphosphino)benzophenone; 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-indole-1-carboxamide; N-(dicyclohexyl phosphino)-2-(2'-methoxyphenyl)indole; 2-[(dicyclohexylphosphino)methyl]-1,3-*bis*(2,6-diisopropylphenyl)-4,5-dimethylimidazolium iodide; 2-(2-dicyclohexylphosphinophenyl)-1,3-dioxolane; 2-[2-

30 (dicyclohexylphosphino)phenyl]-N-methylindole; dicyclohexyl(2,4,6-trimethylphenyl)phosphine; diethylphenylphosphine; diethylphosphine; 4-(diethylphosphino)-N,N-dimethylaniline; 9-[2-(diisopropylphosphino)phenyl]-9H-carbazole; 2-[di(2-methoxyphenyl)phosphino]benzenesulfonic acid; dimethylaminophenylchlorophosphine; 4-(dimethylamino)phenyldiphenylphosphine; 2-(1,1-

35 dimethylpropyl)-6-(diphenylphosphino)pyridine; diphenyl(2-methoxyphenyl)phosphine; 4-diphenylphosphanylbenzoic acid; 2-(diphenylphosphino)benzaldehyde; 2-(diphenylphosphino)benzaldehyde oxime; 3-(diphenylphosphino)benzenesulfonic acid sodium salt; 2-(diphenylphosphino)benzoic acid; 4-(diphenylphosphino)benzoic acid; N-[2-(diphenylphosphino)benzylidene] cyclohexylamine; 2-(diphenylphosphino)-N,N-

40 dimethylbenzylamine; 2-(diphenylphosphino)ethanaminium tetrafluoroborate; 2-(diphenylphosphino)ethylamine; 2-(2-(diphenylphosphino)ethyl)pyridine; 3-(diphenylphosphino)propan-1-aminium tetrafluoroborate; 3-(diphenylphosphino)-1-propylamine; 4-(diphenylphosphino) styrene; 2-(diphenylphosphino)-N,N,N-trimethylbenzylammonium triflate; diphenyl-2-pyridylphosphine; diphenyl(*o*-tolyl)phosphine;

- diphenyl(p-tolyl)phosphine; diphenylvinylphosphine; 2-(di-p-tolylphosphino)benzaldehyde; ethyldiphenylphosphine; [4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)phenyl] diphenylphosphine; (4-hydroxyphenyl)diphenylphosphine; isopropyldiphenylphosphine; 1-methyl-2-(2-dicyclohexylphosphinophenyl)-1H-
5 benzoimidazole; 1-methyl-2-(2-diisopropylphosphinophenyl)-1H-benzoimidazole; methyldiphenylphosphine; 1-methyl-2-(2-diphenylphosphinophenyl)-1H-benzoimidazole; 1,2,3,4,5-pentaphenyl-1' -(di-*tert*-butylphosphino)ferrocene; phenyl*bis*[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphine; phenyldi(*o*-tolyl)phosphine; phenylphosphine; 4,4' -(phenylphosphinidene)*bis*(benzenesulfonic acid) dipotassium salt
10 hydrate; tetrapropylphosphonium bromide; triallylphosphine; tribenzylphosphine; tributylphosphine; tri-*n*-butylphosphine; tri-*tert*-butylphosphine; tri-*tert*-butylphosphine; tri-*tert*-butylphosphine; tributylphosphine tetrafluoroborate; tri-*tert*-butylphosphonium tetrafluoroborate; tricyclohexylphosphine; tricyclohexylphosphine; tricyclohexylphosphine; tricyclohexylphosphine tetrafluoroborate; tricyclopentylphosphine; tricyclopentylphosphine
15 tetrafluoroborate; triethylphosphine; triethylphosphine; ((4-trifluoromethyl)phenyl)di-*tert*-butylphosphine, tri(2-furyl)phosphine; ((2,4,6-tri-isopropyl)phenyl)di-cyclohexylphosphine; triisopropylphosphine; triisopropylphosphonium tetrafluoroborate; trimethylphosphine; trimethylphosphonium tetrafluoroborate; tri-1-naphthylphosphine; trioctylphosphine; triphenylphosphine; triphenylphosphine hydrobromide; 4-(triphenylphosphonio)butane-1-
20 sulfonate; tripropylphosphine; tris[3,5-*bis*(trifluoromethyl)phenyl]phosphine; tris(4-chlorophenyl)phosphine; tris(diethylamino)phosphine; tris(2,6-dimethoxyphenyl)phosphine; tris(dimethylamino)phosphine; tris(3,5-dimethylphenyl)phosphine; tris(2,4-dimethyl-5-sulfanatophenyl)phosphine trisodium salt; tris[2-(diphenylphosphino)ethyl]phosphine; tris(4-fluorophenyl)phosphine; tris[4-(heptadecafluorooctyl)phenyl]phosphine;
25 tris(hydroxymethyl)phosphine; tris(4-methoxy-3,5-dimethylphenyl)phosphine; tris(*o*-methoxyphenyl)phosphine; tris(4-methoxyphenyl)phosphine; tris(4-methyl-1-piperazinyl)phosphine; tris(pentafluorophenyl)phosphine; tris(1-pyrrolidinyl)phosphine; tris[4-(tridecafluorohexyl)phenyl]phosphine; tris[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphine; tris(4-trifluoromethylphenyl)phosphine; tris(2,4,6-
30 trimethoxyphenyl)phosphine; tris(2,4,6-trimethylphenyl)phosphine; tris(trimethylsilyl)phosphine; tri(*o*-tolyl)phosphine; tri(*p*-tolyl)phosphine; tri-*o*-tolylphosphine tetrafluoroborate; and 2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl or acceptable salts thereof.
- 35 In another preferred embodiment, the at least one phosphine compound is selected from the group consisting of triphenylphosphine, 1,3-bis(dicyclohexylphosphino)propane, 1,4-bis(diphenylphosphino)butane, di-*tert*-butyl(phenyl)phosphine and tri-*tert*-butylphosphine.
- In an embodiment, the mole ratio of at least one phosphine compound to the at least one
40 metal catalyst is in the range of 1:0.010 to 1:0.20
- In another embodiment, the mole ratio of at least one phosphine compound to the at least one metal catalyst is in the range of 1:0.025 to 1:0.175.
- In a most preferred embodiment, the mole ratio of the at least phosphine compound to the at least one metal catalyst is in the range of 1:0.05 to 1:0.160

In a most preferred embodiment, the mole ratio of the at least phosphine compound to the at least one metal catalyst is in the range of 1:0.075 to 1:0.15.

In an embodiment, reaction temperature of the step (A) is kept within a range of from 50°C to 150° C, preferably in the range of from 50° C to 130° C, more preferably in the range of from 55° C to 120° C.

In an embodiment, the reaction of the step (A) is carried out at of pressure of 5 bar to 20 bar, preferably in the range of from 7 bar to 15 bar, more preferably in the range of 9 bar to 15 bar.

In an embodiment, the at least one solvent of step (A) is selected from the group consisting of esters, ethers, aromatic hydrocarbons and acetals.

In one embodiment, the solvent of step (A) is triethylorthoformate, trimethylorthoformate, tripropylorthoformate, tributylorthoformate, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, di-n-propyl ether, di-n-butyl ether, methyl-tert-butyl ether, diisobutyl ether, tetrahydropyran, dimethoxymethane, dimethoxypropane, dimethoxybutane, toluene, xylene, cyclohexane and monochlorobenzene.

In an embodiment, the at least one base in step (A) is selected from organic bases or inorganic bases.

In an embodiment, the organic bases are selected from the group consisting of $N(R^{27})_3$, N-methyl piperidine, N-methyl pyrrolidine, N-methyl morpholine, piperidine, dimethyl amino pyridine, pyridine, lithium hexamethyldisilazide, sodium hexamethyldisilazide and tetra- C_1 - C_6 -alkyl ammonium hydroxide, wherein R^{27} is, identical or different, hydrogen, C_1 - C_6 -alkyl, C_5 - C_{14} -aryl, or C_3 - C_6 -cycloalkyl.

In an embodiment, the inorganic bases are selected from the group consisting of alkali metal hydroxide, alkaline earth hydroxide, alkali metal bicarbonate, alkaline earth bicarbonate, alkali metal carbonate, alkaline earth carbonate, alkali metal phosphate, alkali metal alkoxide and alkaline earth alkoxide.

In another embodiment, the alkali metal hydroxide is selected from group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide and cesium hydroxide; the alkaline earth hydroxide is selected from the group consisting of magnesium hydroxide, calcium hydroxide, strontium hydroxide and barium hydroxide; the alkali metal bicarbonate is selected from the group consisting of lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, rubidium bicarbonate and cesium bicarbonate; the alkaline earth bicarbonate is selected from the group consisting of magnesium bicarbonate, calcium bicarbonate, strontium bicarbonate and barium bicarbonate; the alkali metal carbonate is selected from the group consisting of lithium carbonate, sodium carbonate, potassium carbonate, rubidium carbonate and cesium carbonate; the alkaline earth carbonate is selected from group the consisting of magnesium carbonate, calcium carbonate, strontium carbonate and barium carbonate; the alkali metal phosphate is selected from the group consisting of monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate; the alkali metal alkoxide is selected

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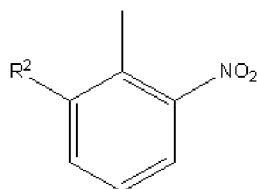
from the group consisting of NaOR^{28} , KOR^{28} , RbOR^{28} and CsOR^{28} ; the alkaline earth alkoxide is selected from the group consisting of $\text{Mg}(\text{OR}^{28})_2$, $\text{Ca}(\text{OR}^{28})_2$ and $\text{Ba}(\text{OR}^{28})_2$; wherein R^{28} is, identical or different, C_1 - C_4 -alkyl.

- 5 In a preferred embodiment, the at least one inorganic base is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate.
- 10 In a most preferred embodiment, the at least one base is selected from the group consisting of potassium carbonate, 4-dimethylaminopyridine and triethylamine.

Step (B) of the present invention for the preparation of a compound of the general formula (III) is as follows and involves the steps from a) to f)

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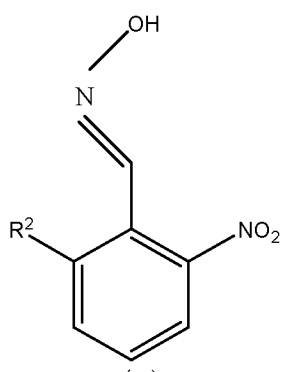
- a) reacting a nitro-methylphenyl compound of formula IV,



(IV),

- 20 wherein R^2 is Cl or C_1 - C_4 alkyl,

with an organic nitrile of the formula R^5 -ONO, wherein R^5 is n-butyl, in the presence of at least one base to give an oxime of the formula (V),



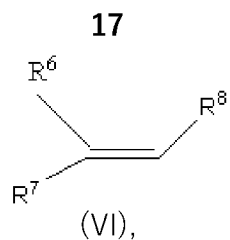
(V),

25

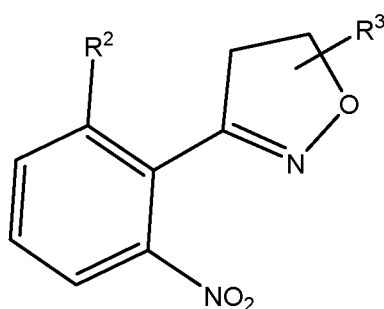
wherein R^2 is Cl or C_1 - C_4 alkyl,

- b) cyclization of the oxime of the formula (V) with an alkene of the formula (VI),

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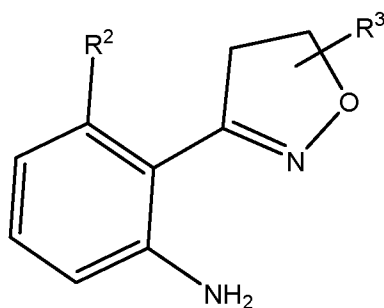


wherein R^6 , R^7 , R^8 are, identical or different, hydrogen or C_1 - C_4 alkyl, in the presence of at least one base to give a compound of formula (VII),



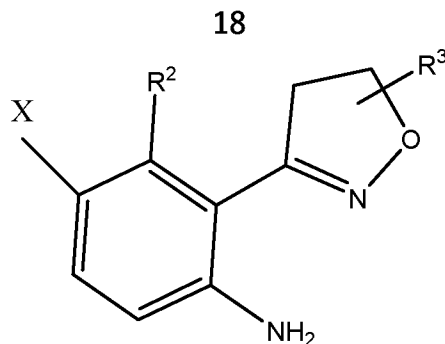
(VII),
wherein R^2 is Cl or C_1 - C_4 alkyl and R^3 is hydrogen or C_1 - C_4 alkyl,

c) reducing the compound of formula (VII) in the presence of at least one catalyst to give the compound of formula (VIII),



(VIII),
wherein R^2 is Cl or C_1 - C_4 alkyl, and R^3 is hydrogen or C_1 - C_4 alkyl,

d) substituting the para amino position in the compound of formula (VIII) to give the compound of formula (IX),



(IX),

wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl and X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3 ;

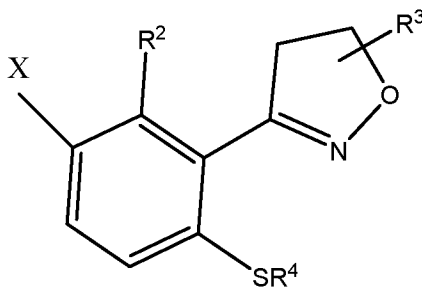
e) reacting the compound of formula (IX) with a dialkyl disulfide of formula (X)



(X)

wherein R^4 is C_1 - C_4 alkyl,

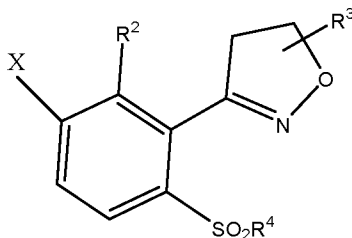
in the presence of an organic nitrile of the formula R^5 -ONO, wherein R^5 is n-butyl, and at least one catalyst to give the compound of formula (XI),



(XI),

wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, R^4 is C_1 - C_4 alkyl, and X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3

f) oxidizing the compound of formula (XI) with at least one oxidizing agent to obtain the compound of formula (III),



wherein X is Cl, Br, I, $S(=O)_2-CH_3$ or $S(=O)_2-CF_3$, R^2 is Cl or C_1-C_4 alkyl, R^3 is hydrogen or C_1-C_4 alkyl, and R^4 is C_1-C_4 alkyl,

- 5 In an embodiment, R^1 is C_1-C_2 alkyl, R^2 is C_1-C_4 alkyl, R^3 is hydrogen or C_1-C_4 alkyl, R^4 is C_1-C_4 alkyl.
In another embodiment, R^1 is methyl, R^2 is C_1-C_2 alkyl, R^3 is hydrogen or C_1-C_4 alkyl, R^4 is C_1-C_4 alkyl.
In another embodiment, R^1 is methyl, R^2 is methyl, R^3 is hydrogen or C_1-C_4 alkyl, R^4 is C_1-C_4 alkyl.
10 In another embodiment, R^1 is methyl, R^2 is methyl, R^3 is hydrogen, R^4 is C_1-C_4 alkyl.
In yet another embodiment, R^1 is methyl, R^2 is methyl, R^3 is hydrogen, R^4 is C_1-C_2 alkyl.
In another embodiment, R^1 is methyl, R^2 is methyl, R^3 is methyl, R^4 is methyl.
In a preferred embodiment, R^1 is methyl, R^2 is methyl, R^3 is hydrogen, R^4 is methyl.
15 In an embodiment, R^6 , R^7 , R^8 are, identical or different, hydrogen or C_1-C_4 alkyl
In another embodiment, R^6 , R^7 , R^8 are, identical or different, hydrogen or C_1-C_2 alkyl
In an embodiment, X is Cl, Br, I, $S(=O)_2-CH_3$ or $S(=O)_2-CF_3$.
In yet another embodiment, X is Cl, Br, I, $-CF_3$.
In a preferred embodiment, X is Cl, Br.
20 In a most preferred embodiment, X is Br.

In an embodiment, step (B) takes place in the presence of at least one base, at least one metal catalyst and at least one solvent.

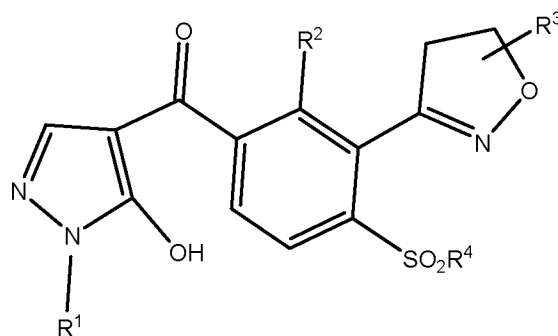
- 25 In an embodiment, the at least one base used in step (B) is selected from the group of tertiary amines, for example triethylamine, cyclic amines, such as N-methylpiperidine or N,N'-dimethylpiperazine, pyridine, alkali metal carbonates, for example sodium carbonate or potassium carbonate, alkali metal bicarbonates, for example sodium bicarbonate or potassium bicarbonate, alkaline earth metal carbonates, for example calcium carbonate, and
30 alkali metal hydroxides, for example sodium hydroxide or potassium hydroxide.

- In an embodiment, the at least one metal catalyst in step (B) is Ni, Pt/C, Pd/C, copper powder, elemental copper in a different form, such as, for example, turnings, wire, granules, pellets, rods; copper(I) salts, for example copper(I) chloride, copper(I) bromide or copper(I) iodide,
35 copper(II) salts, or elemental iodine.

- In an embodiment, the at least one solvent in step (B) is a haloalkane, such as 1,2-dichloroethane or methylene chloride; aromatic compounds, such as benzene, toluene, chlorobenzene, nitrobenzene or xylene; polar aprotic solvents, for example N,N-dialkylformamides, N,N-dialkylacetamides, N-methylpyrrolidone, dimethylpropyleneurea;
40 tetramethylurea, acetonitrile, propionitrile; alcohols, such as methanol, ethanol, n-propanol or isopropanol; carboxylic acids, such as acetic acid or propionic acid; carboxylic esters, such as ethyl acetate.

In the following, there is provided a list of embodiments to further illustrate the present disclosure without intending to limit the disclosure to the specific embodiments listed below.

1. A process for the preparation of a compound of the general formula (I) or its salts,

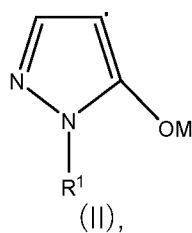


(I),

wherein

R¹ is C₁-C₄ alkyl, R² is Cl or C₁-C₄ alkyl, R³ is hydrogen or C₁-C₄ alkyl and R⁴ is C₁-C₄ alkyl,

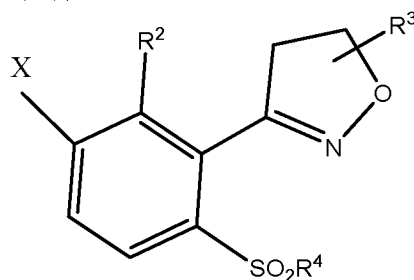
comprising at least the step of reacting a compound of formula (II),



wherein

R¹ is C₁-C₄ alkyl and M is H or an alkali metal atom

with a compound of formula (III),



(III),

wherein

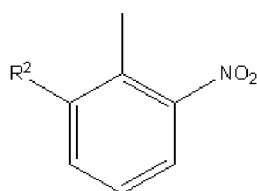
21

X is Cl, Br, I, $S(=O)_2-CH_3$ or $S(=O)_2-CF_3$, R^2 is Cl or C_1-C_4 alkyl, R^3 is hydrogen or C_1-C_4 alkyl, and R^4 is C_1-C_4 alkyl,

in the presence of carbon monoxide, at least one alkali metal iodide, at least one base,
at least one metal catalyst and at least one phosphine compound.

2. The process according to embodiment 1, wherein the compound of general formula (III) is obtained by one or more of the following steps:

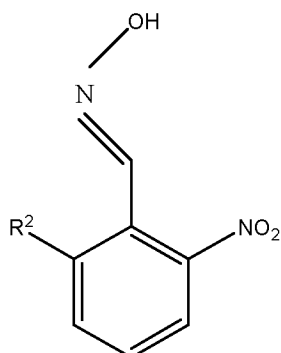
- a) reacting a nitro-methylphenyl compound of formula IV,



(IV),

wherein R^2 is Cl or C_1-C_4 alkyl,

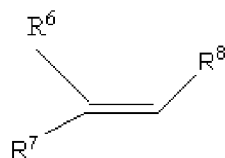
with an organic nitrile of the formula R^5-ONO , wherein R^5 is n-butyl, in the presence of at least one base to give an oxime of the formula (V),



(V),

wherein R^2 is Cl or C_1-C_4 alkyl,

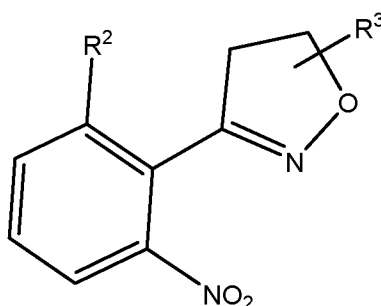
- b) cyclization of the oxime of the formula (V) with an alkene of the formula (VI),



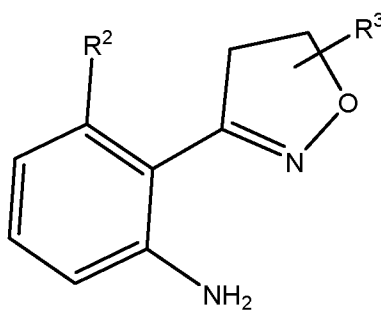
(VI),

wherein R^6 , R^7 , R^8 are, identical or different, hydrogen or C_1-C_4 alkyl, in the presence of at least one base to give a compound of formula (VII),

22



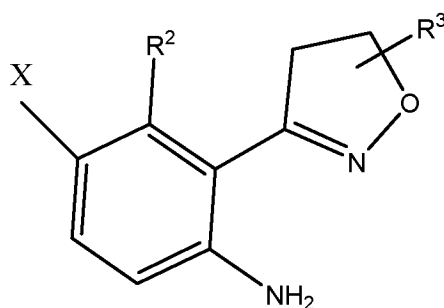
- 5 (VII),
 wherein R^2 is Cl or C_1 - C_4 alkyl and R^3 is hydrogen or C_1 - C_4 alkyl,
- c) reducing the compound of formula (VII) in the presence of at least one catalyst to give the compound of formula (VIII),



10

- (VIII),
 15 wherein R^2 is Cl or C_1 - C_4 alkyl, and R^3 is hydrogen or C_1 - C_4 alkyl,

- d) substituting the para amino position in the compound of formula (VIII) to give the compound of formula (IX),



20

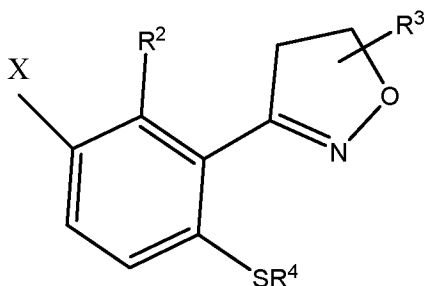
- (IX),
 wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl and X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3 ;

- 25 e) reacting the compound of formula (IX) with a dialkyl disulfide of formula (X)



(X)

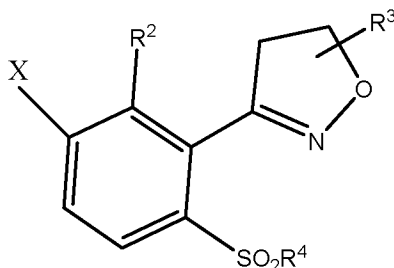
- 5 wherein R^4 is C_1 - C_4 alkyl,
in the presence of an organic nitrile of the formula R^5 -ONO, wherein R^5 is n-butyl, and at least one catalyst to give the compound of formula (XI),



(XI),

wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, R^4 is C_1 - C_4 alkyl, and X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3

- 15 f) oxidizing the compound of formula (XI) with at least one oxidizing agent to obtain the compound of formula (III),



(III),

wherein X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3 , R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, and R^4 is C_1 - C_4 alkyl,

- 25 3. The process according to embodiments 1 or 2, wherein R^1 , R^2 and R^4 are each methyl and R^3 is hydrogen.
- 30 4. The process according to embodiment 1, wherein the alkali metal iodide is selected from the group consisting of sodium iodide, potassium iodide and lithium iodide.

5. The process according to embodiment 1, wherein the at least one metal catalyst is in a form of a free state of formula M or in a form of a metal complex of formula M(L)_n, wherein

M is selected from the group consisting of nickel (Ni), cobalt (Co), iron (Fe), ruthenium (Ru), rhodium (Rh), palladium (Pd), iridium (Ir), platinum (Pt), silver (Ag), copper (Cu), zinc (Zn), molybdenum (Mo) and tungsten (W);

L is, identical or different, selected from the group consisting of Cl, Br, I, P(C₅-C₁₄-aryl)_m, P(C₅-C₁₂-heteroaryl)_m, P(C₅-C₁₂-heteroaryl)_m(C₅-C₁₄-aryl)_{3-m}, CN, C₁-C₆-alkyl, C₁-C₆-alkyl-O-C₁-C₆-alkyl, -O-CO-C₁-C₆-alkyl, OH, nitro, -O-C₁-C₆-alkyl, C₁-C₄-haloalkoxy, C₃-C₈-cycloalkyl, C₃-C₈-halocycloalkyl, C₃-C₈-cycloalkenyl, C₅-C₁₄-aryl, C₅-C₁₄-aryl-(CH₂)_o-(Q)_p-(CH₂)_o-C₅-C₁₄-aryl and 1,1'-bis(diphenyl phosphino)ferrocene; whereby Q represents a bridging group selected from the group consisting of -CR⁹R¹⁰, -O-, -S-, -NR¹¹R¹², -SiR¹³R¹⁴ and -CO-, wherein R⁹ and R¹⁰, identical or different, are hydrogen, C₁-C₁₂ alkyl, C₅-C₁₄-aryl or C₅-C₁₂-heteroaryl; wherein R¹¹, R¹², R¹³ and R¹⁴, identical or different, are hydrogen or C₁-C₄ alkyl or R¹¹ together with R¹² forms C₅-C₁₂-membered heterocycloalkyl, C₅-C₁₄-membered heterocycloalkenyl or C₅-C₁₂-membered heteroaryl; and L is unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; -NO₂; -NR¹⁰R¹¹, -P(phenyl)₂, -OH, unsubstituted or substituted C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, unsubstituted or substituted C₅-C₁₄-aryl, unsubstituted or substituted C₅-C₁₂-heteroaryl, C₅-C₁₂-membered heterocycloalkyl, C₅-C₁₄-membered heterocycloalkenyl, -O-(CH₂)_r-O-, -C(=O)R¹⁵, -C(=O)-O-R¹⁶, -C=N-R¹⁷, -SO₃H, -O-C₁-C₆-alkyl and -O-Si-C₁-C₄-alkyl; or L is supported on silica gel, dendrimers, polystyrenes or mesoporous siliceous foam,

wherein

R¹⁵ is hydrogen or C₁-C₄-alkyl;

R¹⁶ is hydrogen or C₁-C₄-alkyl;

R¹⁷ is hydrogen, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₅-C₁₄-aryl, C₅-C₁₂-heteroaryl or C₃-C₁₂-cycloalkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

m is 1, 2 or 3;

o is 0, 1 or 2

p is 0, 1 or 2 and

r is 1, 2, 3, 4 or 5,

or their acceptable salts thereof.

6. The process according to embodiment 5, wherein M is selected from the group consisting of nickel (Ni), iron (Fe), palladium (Pd) and copper (Cu).

7. The process according to embodiment 5, wherein L is, identical or different, selected from the group consisting of Cl, Br, I, P(C₅-C₁₄-aryl)_m, CN, unsubstituted or substituted C₁-C₁₂-alkyl, C₁-C₄-alkoxy, C₃-C₈-cycloalkenyl, -O-CO-C₁-C₆-alkyl, C₅-C₁₄-aryl, 1,1'-bis(diphenyl phosphino)ferrocene and C₅-C₁₄-aryl-(CH₂)_o-(Q)_p-(CH₂)_o-C₅-C₁₄-aryl, whereby m, o, Q and p are as defined as in claim 7.

8. The process according to embodiment 5, wherein the metal complex of formula $M(L)_n$ is selected from the group consisting of $Pd(OCOCH_3)_2$, $PdCl_2$, $PdCl_2(CH_3CN)_2$, $Pd(1,1'$ -bis(diphenyl phosphino)ferrocene) Cl_2 , $Pd_2(dibenzylideneacetone)_3$ and $Pd(dibenzylideneacetone)_2$.

9. The process according to embodiments 5 to 8, wherein the at least one metal catalyst is in a form of a free state of palladium such as Pd/C or in a form of a metal complex selected from the group consisting of $Pd(OCOCH_3)_2$ and $PdCl_2$.

10. The process according to embodiment 1, wherein the at least one phosphine compound is of the formula $PX_1X_2X_3$ or $(PX_1X_2)_2(B)_q$, whereby X_1 , X_2 and X_3 , identical or different, are F, Cl, Br, I, $-NR^{18}R^{19}$, hydrogen, $-O-C_1-C_6$ -alkyl, $-O-CO-C_1-C_6$ -alkyl, C_1-C_{12} -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, C_5-C_{14} -aryl, C_5-C_{12} -heteroaryl, C_3-C_{12} -cycloalkyl, C_3-C_{12} -cycloalkenyl, C_3-C_{12} -heterocycloalkyl, C_3-C_{14} -heterocycloalkenyl or $-Si-(C_1-C_{12}-alkyl)_3$, whereby B is $CR^{20}R^{21}$, $-O-$, $-phenyl-O-phenyl-$, $-S-$, $-NR^{18}R^{19}$, $-SiR^{22}R^{23}$ or $-C(=O)-$, wherein R^{20} and R^{21} , identical or different, are hydrogen, C_1-C_{12} -alkyl, C_5-C_{14} -aryl or C_5-C_{12} -heteroaryl, wherein R^{18} , R^{19} , R^{20} and R^{21} , identical or different, are hydrogen or C_1-C_4 -alkyl or R^{18} together with R^{19} forms C_5-C_{12} -membered heterocycloalkyl, C_5-C_{14} -membered heterocycloalkenyl or C_5-C_{12} -heteroaryl; whereby X_1 , X_2 and X_3 , identical or different, are unsubstituted or substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; $-NO_2$; $-NR^{18}R^{19}$, $-P(phenyl)_2$, $-OH$, unsubstituted or substituted C_1-C_{12} -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, unsubstituted or substituted C_5-C_{14} -aryl, unsubstituted or substituted C_5-C_{12} -heteroaryl, $-O-(CH_2)_r-O-$, $-C(=O)R^{24}$, $-C(=O)-O-R^{25}$, $-C=N-R^{26}$, $-SO_3H$, $-O-C_1-C_6$ -alkyl and $-O-Si-C_1-C_4$ -alkyl, C_5-C_{12} -membered heterocycloalkyl, C_5-C_{14} -membered heterocycloalkenyl and C_5-C_{12} -heteroaryl;

wherein q is 1, 2, 3, 4, 5 or 6;

r is 1, 2, 3, 4 or 5;

R^{24} is hydrogen or C_1-C_4 -alkyl;

R^{25} is hydrogen or C_1-C_4 -alkyl; and

R^{26} is hydrogen, C_1-C_{12} -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, C_5-C_{14} -aryl, C_5-C_{12} heteroaryl or C_3-C_{12} -cycloalkyl;

or their acceptable salts thereof.

11. The process according to embodiment 10, wherein the at least one phosphine compound is selected from the group consisting of allyldiphenylphosphine; 1,3-bis(diphenylphosphino)propane; 1,3-bis(dicyclohexylphosphino)propane, 1,4-bis(diphenylphosphino)butane, di-*tert*-butyl(phenyl)phosphine, tri-*tert*-butylphosphine, di-*tert*-butyl(phenyl)phosphine tetrafluoroborate; (2-ammonioethyl) di-*tert*-butylphosphonium bis(tetrafluoroborate); (2-ammonioethyl) diisopropylphosphonium bis(tetrafluoroborate); (3-ammoniopropyl) di-*tert*-butylphosphonium bis(tetrafluoroborate); (3-ammoniopropyl) diisopropylphosphonium

bis(tetrafluoroborate); *bis*(3,5-*bis*(trifluoromethyl)phenyl)(2',6' -*bis*(isopropoxy)-3,6-dimethoxybiphenyl-2-yl)phosphine; benzyldiphenylphosphine; (2-biphenyl)di-1-adamantylphosphine; 1-[2-[*bis*(*tert*-butyl)phosphino]phenyl]-3,5-diphenyl-1H-pyrazole; *bis*[2-(diadamantylphosphino)ethyl]amine; 2-[*bis*(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]benzaldehyde; 2,6-*bis*(di-*tert*-butylphosphinomethyl)pyridine; *bis*(dicyclohexylphosphinophenyl)ether; *bis*(diethylamino)phenylphosphine; *bis*(dimethylamino)chlorophosphine; 2-[*bis*(3,5-dimethylphenyl)phosphino]benzaldehyde; *bis*[4-(3,3,4,4,5,5,5-heptafluor-*o*-2,2-*bis*(trifluoromethyl)pentyl)phenyl]phenylphosphine; *bis*(2-methoxyphenyl)phosphine; *bis*[4-(1H,1H,2H,2H-perfluorodecyl)phenyl]phenylphosphine; 1,1' -*bis*(phenylphosphinidene)ferrocene; (2-bromophenyl)dicyclohexylphosphine; (2-bromophenyl)diphenylphosphine; *tert*-butyldicyclohexylphosphine; *tert*-butyldicyclohexylphosphonium tetrafluoroborate; *tert*-butyldiisopropylphosphine; *tert*-butyldiphenylphosphine; 1-(dicyclohexylphosphino)-2,2-Diphenyl-1-methylcyclopropane; cyclohexyldiphenylphosphine; di(1-adamantyl)-2-dimethylaminophenylphosphine; di-1-adamantylphosphine; di(1-adamantyl)-(2-triisopropylsiloxyphenyl)phosphine; (5H-dibenzo[a,d]cyclohepten-5-yl)diphenylphosphine; di-*tert*-butylcyclohexylphosphine; di-*tert*-butyl N,N-diisopropylphosphoramidite; di-*tert*-butylmethylphosphine; di-*tert*-butyl(methyl)phosphonium tetrafluoroborate; di-*tert*-butyl(methyl)phosphonium tetrafluoroborate; di-*tert*-butylneopentylphosphine; di-*tert*-butylneopentylphosphonium tetrafluoroborate; di-*tert*-butylphenylphosphine; di-*tert*-butylphosphate potassium salt; 2' -(di-*tert*-butylphosphino)acetophenone ethylene ketal; 2-(di-*tert*-butylphosphino)dimethylaminobenzene; 2-(di-*tert*-butylphosphino)ethylamine; 2-((di-*tert*-butylphosphinomethyl)-6-diethylaminomethyl)pyridine; 5-(di-*tert*-butylphosphino)-1-(naphthalen-1-yl)-1H-pyrazole; 5-(di-*tert*-butylphosphino)-1',3',5'-triphenyl-1'H-[1,4']bipyrazole; 3-(di-*tert*-butylphosphonium)propane sulfonate; P,P-dichloroferrocenylphosphine; dicyclohexyl-(2,6-diisopropylphenyl)phosphine; dicyclohexyl(4-(N,N-dimethylamino)phenyl)phosphine; dicyclohexyl(ethyl)phosphine; dicyclohexyl(4-isopropylphenyl)phosphine; dicyclohexyl(2-methylphenyl)phosphine; dicyclohexylphenylphosphine; 2' -(dicyclohexylphosphino)acetophenone ethylene ketal; 2-(dicyclohexylphosphino)benzophenone; 2-(dicyclohexylphosphino)-N,N-diisopropyl-1H-indole-1-carboxamide; N -(dicyclohexyl phosphino)-2-(2' -methoxyphenyl)indole; 2-[(dicyclohexylphosphino)methyl]-1,3-*bis*(2,6-diisopropylphenyl)-4,5-dimethylimidazolium iodide; 2-(2-dicyclohexylphosphinophenyl)-1,3-dioxolane; 2-[2-(dicyclohexylphosphino)phenyl]-N-methylindole; dicyclohexyl(2,4,6-trimethylphenyl)phosphine; diethylphenylphosphine; diethylphosphine; 4-(diethylphosphino)-N,N-dimethylaniline; 9-[2-(diisopropylphosphino)phenyl]-9H-carbazole; 2-[di(2-methoxyphenyl)phosphino]benzenesulfonic acid; dimethylaminophenylchlorophosphine; 4-(dimethylamino)phenyldiphenylphosphine; 2-(1,1-dimethylpropyl)-6-(diphenylphosphino)pyridine; diphenyl(2-methoxyphenyl)phosphine; 4-diphenylphosphanylbenzoic acid; 2-

(diphenylphosphino)benzaldehyde; 2-(diphenylphosphino)benzaldehyde oxime; 3-(diphenylphosphino)benzenesulfonic acid sodium salt; 2-(diphenylphosphino)benzoic acid; 4-(diphenylphosphino)benzoic acid; N-[2-(diphenylphosphino)benzylidene]cyclohexylamine; 2-(diphenylphosphino)-N,N-dimethylbenzylamine; 2-

5 (diphenylphosphino)ethanaminium tetrafluoroborate; 2-(diphenylphosphino)ethylamine; 2-(2-(diphenylphosphino)ethyl)pyridine; 3-(diphenylphosphino)propan-1-aminium tetrafluoroborate; 3-(diphenylphosphino)-1-propylamine; 4-(diphenylphosphino) styrene; 2-(diphenylphosphino)-N,N,N-trimethylbenzylammonium triflate; diphenyl-2-pyridylphosphine; diphenyl(*o*-tolyl)phosphine; diphenyl(*p*-tolyl)phosphine; diphenylvinylphosphine; 2-(di-*p*-tolylphosphino)benzaldehyde; ethyldiphenylphosphine; [4-

10 (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl)phenyl] diphenylphosphine; (4-hydroxyphenyl)diphenylphosphine; isopropyldiphenylphosphine; 1-methyl-2-(2-dicyclohexylphosphinophenyl)-1H-benzimidazole; 1-methyl-2-(2-diisopropylphosphinophenyl)-1H-benzimidazole; methyl-diphenylphosphine; 1-methyl-2-(2-diphenylphosphinophenyl)-1H-benzimidazole; 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene; phenyl *bis*[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphine; phenyldi(*o*-tolyl)phosphine; phenylphosphine; 4,4'-(phenylphosphinidene) *bis*(benzenesulfonic acid) dipotassium salt hydrate;

20 tetrapropylphosphonium bromide; triallylphosphine; tribenzylphosphine; tributylphosphine; tri-*n*-butylphosphine; tri-*tert*-butylphosphine; tri-*tert*-butylphosphine; tri-*tert*-butylphosphine tetrafluoroborate; tri-*tert*-butylphosphonium tetrafluoroborate; tricyclohexylphosphine; tricyclohexylphosphine; tricyclohexylphosphine tetrafluoroborate;

25 tricyclopentylphosphine; tricyclopentylphosphine tetrafluoroborate; triethylphosphine; triethylphosphine; ((4-trifluoromethyl)phenyl)di-*tert*-butylphosphine, tri(2-furyl)phosphine; ((2,4,6-tri-isopropyl)phenyl)di-cyclohexylphosphine; triisopropylphosphine; triisopropylphosphonium tetrafluoroborate; trimethylphosphine; trimethylphosphonium tetrafluoroborate; tri-1-naphthylphosphine; trioctylphosphine;

30 triphenylphosphine; triphenylphosphine hydrobromide; 4-(triphenylphosphonio)butane-1-sulfonate; tripropylphosphine; tris[3,5-*bis*(trifluoromethyl)phenyl]phosphine; tris(4-chlorophenyl)phosphine; tris(diethylamino)phosphine; tris(2,6-dimethoxyphenyl)phosphine; tris(dimethylamino)phosphine; tris(3,5-dimethylphenyl)phosphine; tris(2,4-dimethyl-5-sulfanatophenyl)phosphine trisodium salt; tris[2-(diphenylphosphino)ethyl]phosphine;

35 tris(4-fluorophenyl)phosphine; tris[4-(heptafluorooctyl)phenyl]phosphine; tris(hydroxymethyl)phosphine; tris(4-methoxy-3,5-dimethylphenyl)phosphine; tris(*o*-methoxyphenyl)phosphine; tris(4-methoxyphenyl)phosphine; tris(4-methyl-1-piperazinyl)phosphine; tris(pentafluorophenyl)phosphine; tris(1-pyrrolidinyl)phosphine; tris[4-(tridecafluorohexyl)phenyl]phosphine; tris[4-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphine; tris(4-trifluoromethylphenyl)phosphine; tris(2,4,6-trimethoxyphenyl)phosphine; tris(2,4,6-trimethylphenyl)phosphine; tris(trimethylsilyl)phosphine; tri(*o*-tolyl)phosphine; tri(*p*-tolyl)phosphine; tri-*o*-tolylphosphine tetrafluoroborate; and 2-

40

(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl or acceptable salts thereof.

12. The process according to claim 11, wherein the at least one phosphine compound is selected from the group consisting of triphenylphosphine, 1,3-

5 bis(dicyclohexylphosphino)propane, 1,4-bis(diphenylphosphino)butane, di-tert-butyl(phenyl)phosphine and tri-tert-butylphosphine.

13. The process according to embodiment 1, wherein the at least one base is selected from the group consisting of organic bases and inorganic bases.

10

14. The process according to embodiment 13, wherein the organic bases are selected from the group consisting of $N(R^{27})_3$, N-methyl piperidine, N-methyl pyrrolidine, N-methyl morpholine, piperidine, dimethyl amino pyridine, pyridine, lithium hexamethyldisilazide, sodium hexamethyldisilazide and tetra- C_1 - C_6 -alkyl ammonium hydroxide, wherein R^{27}

15

is, identical or different, hydrogen, C_1 - C_6 -alkyl, C_5 - C_{14} -aryl, or C_3 - C_6 -cycloalkyl.

15. The process according to embodiment 13, wherein the inorganic bases are selected from the group consisting of alkali metal hydroxide, alkaline earth hydroxide, alkali metal bicarbonate, alkaline earth bicarbonate, alkali metal carbonate, alkaline earth carbonate, alkali metal phosphate, alkali metal alkoxide and alkaline earth alkoxide.

20

16. The process according to embodiment 15, wherein the alkali metal hydroxide is selected from group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide and cesium hydroxide;

25

wherein the alkaline earth hydroxide is selected from the group consisting of magnesium hydroxide, calcium hydroxide, strontium hydroxide and barium hydroxide; wherein the alkali metal bicarbonate is selected from the group consisting of lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, rubidium bicarbonate and cesium bicarbonate;

30

wherein the alkaline earth bicarbonate is selected from the group consisting of magnesium bicarbonate, calcium bicarbonate, strontium bicarbonate and barium bicarbonate;

35

wherein the alkali metal carbonate is selected from the group consisting of lithium carbonate, sodium carbonate, potassium carbonate, rubidium carbonate and cesium carbonate;

40

wherein the alkaline earth carbonate is selected from group the consisting of magnesium carbonate, calcium carbonate, strontium carbonate and barium carbonate; wherein the alkali metal phosphate is selected from the group consisting of monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate;

40

wherein the alkali metal alkoxide is selected from the group consisting of $NaOR^{28}$, KOR^{28} , $RbOR^{28}$ and $CsOR^{28}$;

wherein the alkaline earth alkoxide is selected from the group consisting of $\text{Mg}(\text{OR}^{28})_2$, $\text{Ca}(\text{OR}^{28})_2$ and $\text{Ba}(\text{OR}^{28})_2$; wherein R^{28} is, identical or different, C_1 - C_4 -alkyl.

- 5 17. The process according to embodiment 16, wherein the at least one inorganic base is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, monosodium phosphate, disodium phosphate, trisodium phosphate, monopotassium phosphate, dipotassium phosphate and tripotassium phosphate.
- 10 18. The process according to embodiments 13 to 17, wherein the at least one base is selected from the group consisting of potassium carbonate, 4-dimethylaminopyridine and triethylamine.
- 15 19. The process according to embodiment 1, wherein the process is performed in the presence of at least one solvent which is selected from the group consisting of esters, ethers, aromatic hydrocarbons and acetals.
- 20 20. The process according to embodiment 19, wherein the esters are selected from the group consisting of triethylorthoformate, trimethylorthoformate, tripropylorthoformate and tributylorthoformate.
- 25 21. The process according to embodiment 19, wherein the ethers are selected from the group consisting of tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, diethyl ether, diisopropyl ether, di-n-propyl ether, di-n-butyl ether, methyl-tert-butyl ether, diisobutyl ether and tetrahydropyran.
22. The process according to embodiment 19, wherein the acetals are selected from the group consisting of dimethoxymethane, dimethoxypropane and dimethoxybutane.
- 30 23. The process according to embodiment 19, wherein the aromatic hydrocarbons are selected from the group consisting of toluene, xylene, cyclohexane and monochlorobenzene.
- 35 24. The process according to embodiment 1, wherein the ratio of the at least one metal catalyst to the at least one compound of formula (III) is in the range of 1:100 moles to 1:500 moles.
25. The process according to embodiment 1, wherein the mole ratio of the at least phosphine compound to the at least one metal catalyst is in the range of 1:0.075

to 1:0.015.

26. The process according to embodiment 1, wherein the process is performed at a temperature in the range of 50 ° C to 150 ° C.

27. The process according to embodiment 1, wherein the process is performed at a pressure in the range of 5 bar to 20 bar.

28. The process according to embodiment 1, wherein the compound of the general formula (I) or its salts are isolated by at least one of the following steps:

a) filtering the reaction mixture through celite bed to remove the catalyst and washing the bed with water,

b) concentrating the filtrate to remove the solvent and water,

c) diluting the concentrated mass with alcohol,

d) heating the reaction mixture of step c) to 60°C and adjusting the pH to 1.5 using 35% hydrochloric acid,

e) cooling the reaction mixture to 20°C and separating the product by filtration,

f) drying the product at 70 °C -75 °C under vacuum for 12 hours to isolate the compound of formula (I).

EXAMPLES

The characterization can be done by High Performance Liquid chromatography

General Procedure:

With due modification of the starting compounds, the compound of formula (I) can be prepared by procedures as given in below schemes.

Example 1: Preparation of [3-(4,5-dihydroisoxazol-3-yl)-2-methyl-4-methylsulfonyl-phenyl]-(5-hydroxy-1-methyl-pyrazol-4-yl)methanone.

A round bottom flask (RBF) was charged with 22 gm (0.069 moles) of 3-(3-bromo-2-methyl-6-methylsulfonyl-phenyl)-4,5-dihydroisoxazole followed by 100 gm of 1,4-dioxane and stirred it for 15 min. 17.6 gm (0.127 moles) of potassium carbonate was then charged in the round bottom flask. The reaction mixture was refluxed, and 50 gm of solvent was distilled off atmospherically. The slurry formed was then cooled to 25° C and transferred to clean pressure reactor, followed by addition of 6.8 gm (0.069 moles) of 2-methylpyrazol-3-ol, 2.07 gm (0.013 moles) of Sodium iodide, 0.72 gm (0.0027 moles) of Triphenylphosphine and 130 gm 1,4-dioxane. This reaction mixture was flushed with carbon monoxide gas, heated and stirred at 60° C for 30 min under carbon monoxide atmosphere. The reaction mixture was later cooled to 30° C. 0.88 gm (0.0003 moles) of Pd/C (RD-383) was added to the reaction mixture and the reaction mass was flushed with carbon monoxide gas and the reaction

mixture was heated to 120° C under pressure of 15 bar of carbon monoxide gas for 20 hours. The reaction mass is then cooled to 60° C and the reactor was depressurized. 200 gm of water was added to the reaction mixture and was filtered through celite bed to remove catalyst and further the bed was washed with water. The filtrate was concentrated to remove 1,4-dioxane and water and the concentrated reaction mass was then diluted with 125 gm methanol. This reaction mixture was heated to 60° C and pH of reaction mixture was adjusted to 1.5 using 35% hydrochloric acid. The reaction mixture was then cooled to 20° C within 3-4 hours and the product was separated by filtration. The filtered product was then dried at 70-75° C under vacuum for 12 hours. The isolated product (i.e. [3-(4,5-dihydroisoxazol-3-yl)-2-methyl-4-methylsulfonyl-phenyl]-(5-hydroxy-1-methyl-pyrazol-4-yl)methanone) had a yield of 84.4% with purity of 99.37%.

Example 2: Preparation of [3-(4,5-dihydroisoxazol-3-yl)-2-methyl-4-methylsulfonyl-phenyl]-(5-hydroxy-1-methyl-pyrazol-4-yl)methanone

A pressure reactor was charged with 22 gm (0.069 moles) of 3-(3-bromo-2-methyl-6-methylsulfonyl-phenyl)-4,5-dihydroisoxazole followed by 180 gm 1,4-dioxane, 17.6 gm (0.12 moles) of Potassium Carbonate, 0.72 gm (0.0027 moles) of triphenylphosphine and 6.8 gm (0.069 moles) of 2-methylpyrazol-3-ol. This reaction mixture was flushed with carbon monoxide gas then heated and stirred at 60° C for 30 min under carbon monoxide atmosphere. The reaction mixture was cooled to 30° C and 0.071 gm (0.0004 moles) Palladium Chloride catalyst was added to the reaction mixture and the reaction mass was flushed with carbon monoxide gas. The reaction mixture was heated to 120° C under pressure of 15 bar of carbon monoxide gas for 20 hours. The reaction mass was then cooled to 60° C followed by depressurizing the reactor. Further 200 gm of DM water was added to reaction mixture followed by 0.7 gm activated carbon and the reaction mixture was filtered through the celite bed to remove catalyst and the bed was washed with 100 gm water. The main filtrate and the washings were combined and were concentrated to remove 1,4-dioxane and water. The concentrated reaction mass was then diluted with 125 gm methanol and further the reaction mixture was heated to 60° C and the pH of reaction mixture was adjusted to 1.5 using 35% hydrochloric acid. The reaction mixture was then cooled to 20° C over a period of 3-4 hours and the product was separated by filtration. The filtered product was then dried at 70-75° C under vacuum for 12 hours. The isolated product (i.e. [3-(4,5-dihydroisoxazol-3-yl)-2-methyl-4-methylsulfonyl-phenyl]-(5-hydroxy-1-methyl-pyrazol-4-yl)methanone) had a yield of 76% with a purity of 99.81%.

Example 3 to 10 were performed as per examples 1, however the reaction conditions for the same are illustrated in table 2.

The above examples do not restrict the invention in any manner.

Ex.		Base (K ₂ CO ₃)	Ligand	Catalyst	Additive (NaI)	Temp °C	Yi
	KSM						

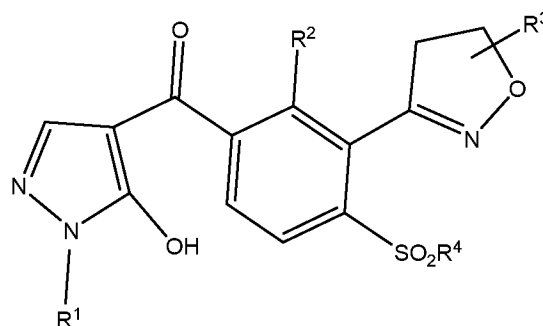
3	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	Pd/C: 0.0002 Moles, 0.003 M/R	0.0138 Moles, 0.2 M/R	120	83
4	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	Pd/C: 0.0002 Moles, 0.003 M/R	0.0138 Moles, 0.2 M/R	120	82
5	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	Pd/C: 0.0004 Moles, 0.006 M/R	0.0138 Moles, 0.2 M/R	120	82
6	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	Pd/C: 0.0002 Moles, 0.003 M/R	0.0069 Moles, 0.1 M/R	120	82
7	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	PdCl ₂ : 0.0004 Moles, 0.006 M/R	0.0138 Moles, 0.2 M/R	120	79
8	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	Pd/C: 0.0002 Moles, 0.003 M/R	0.003 Moles, 0.05 M/R	120	78
9	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	PdCl ₂ : 0.0004 Moles, 0.006 M/R	0.0138 Moles, 0.2 M/R	130	78
10	0.069 Moles	0.127 Moles, 1.84 M/R	bisdiphenyl phosphinobutane: 0.0027 Moles, 0.04 M/R	PdCl ₂ : 0.0004 Moles, 0.006 M/R	0.0138 Moles, 0.2 M/R	120	76
11	0.069 Moles	0.127 Moles, 1.84 M/R	TPP: 0.0027 Moles, 0.04. M/R	PdCl ₂ : 0.0004 Moles, 0.006 M/R	Nil	130	72

M/R= Mole ratio (Equivalentants)

Purity of the isolated product: at least 99%

Claims:

1. A process for the preparation of a compound of the general formula (I) or its salts,

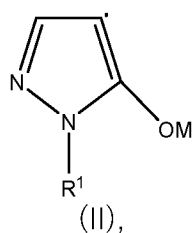


(I),

wherein

R^1 is $\text{C}_1\text{-C}_4$ alkyl, R^2 is Cl or $\text{C}_1\text{-C}_4$ alkyl, R^3 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl and R^4 is $\text{C}_1\text{-C}_4$ alkyl,

comprising at least the step of reacting a compound of formula (II),

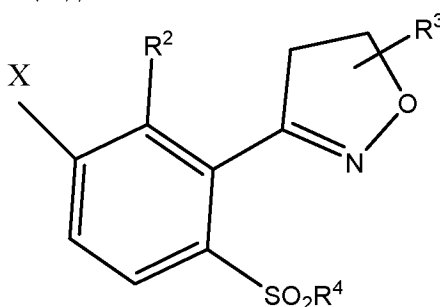


(II),

wherein

R^1 is $\text{C}_1\text{-C}_4$ alkyl and M is H or an alkali metal atom

with a compound of formula (III),



(III),

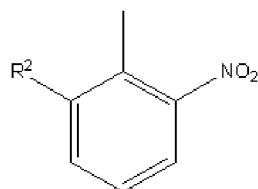
wherein

X is Cl, Br, I, $\text{S}(=\text{O})_2\text{-CH}_3$ or $\text{S}(=\text{O})_2\text{-CF}_3$, R^2 is Cl or $\text{C}_1\text{-C}_4$ alkyl, R^3 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl, and R^4 is $\text{C}_1\text{-C}_4$ alkyl,

in the presence of carbon monoxide, at least one alkali metal iodide, at least one base, at least one metal catalyst and at least one phosphine compound.

- 5 2. The process according to claim 1, wherein the compound of general formula (III) is obtained by one or more of the following steps:

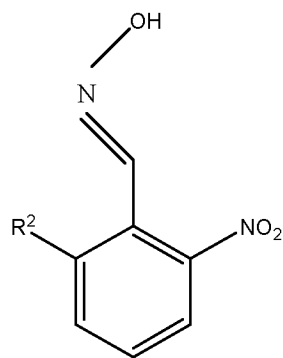
10 a) reacting a nitro-methylphenyl compound of formula IV,



(IV),

wherein R^2 is Cl or C_1 - C_4 alkyl,

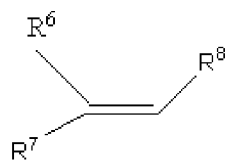
- 15 with an organic nitrile of the formula R^5 -ONO, wherein R^5 is n-butyl, in the presence of at least one base to give an oxime of the formula (V),



(V),

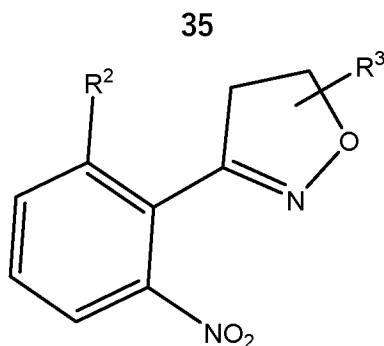
- 20 wherein R^2 is Cl or C_1 - C_4 alkyl,

b) cyclization of the oxime of the formula (V) with an alkene of the formula (VI),



(VI),

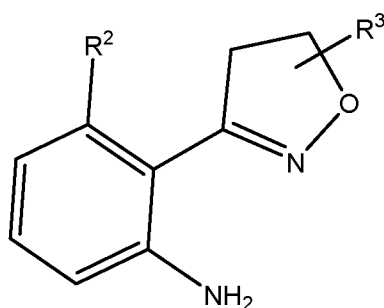
25 wherein R^6 , R^7 , R^8 are, identical or different, hydrogen or C_1 - C_4 alkyl, in the presence of at least one base to give a compound of formula (VII),



(VII),

5 wherein R^2 is Cl or C_1 - C_4 alkyl and R^3 is hydrogen or C_1 - C_4 alkyl,

c) reducing the compound of formula (VII) in the presence of at least one catalyst to give the compound of formula (VIII),



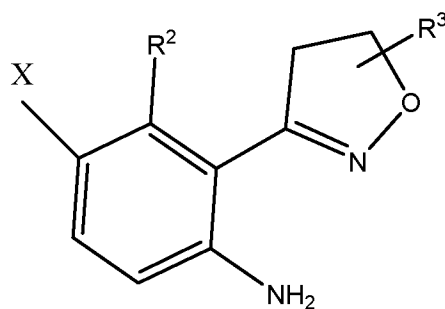
10

(VIII),

wherein R^2 is Cl or C_1 - C_4 alkyl, and R^3 is hydrogen or C_1 - C_4 alkyl,

15

d) substituting the para amino position in the compound of formula (VIII) to give the compound of formula (IX),



20

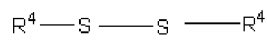
(IX),

wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl and X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3 ;

e) reacting the compound of formula (IX) with a dialkyl disulfide of formula (X)

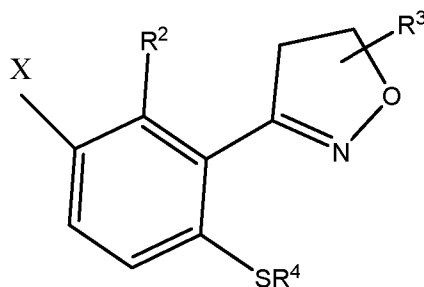
25

36



(X)

- 5 wherein R^4 is C_1 - C_4 alkyl,
in the presence of an organic nitrile of the formula R^5 -ONO, wherein R^5 is n-butyl, and at least one catalyst to give the compound of formula (XI),

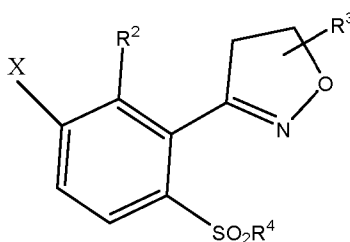


10

(XI),

wherein R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, R^4 is C_1 - C_4 alkyl, and X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3

- 15 f) oxidizing the compound of formula (XI) with at least one oxidizing agent to obtain the compound of formula (III),



20

(III),

wherein X is Cl, Br, I, $S(=O)_2$ - CH_3 or $S(=O)_2$ - CF_3 , R^2 is Cl or C_1 - C_4 alkyl, R^3 is hydrogen or C_1 - C_4 alkyl, and R^4 is C_1 - C_4 alkyl.

25

3. The process according to claim 1 or 2, wherein R^1 , R^2 and R^4 are each methyl and R^3 is hydrogen.
4. The process according to claim 1, wherein the alkali metal iodide is selected from the group consisting of sodium iodide, potassium iodide and lithium iodide.
5. The process according to claim 1, wherein the at least one metal catalyst is in a form of a free state of formula M or in a form of a metal complex of formula $M(L)_n$, wherein

M is selected from the group consisting of nickel (Ni), cobalt (Co), iron (Fe), ruthenium (Ru), rhodium (Rh), palladium (Pd), iridium (Ir), platinum (Pt), silver (Ag), copper (Cu), zinc (Zn), molybdenum (Mo) and tungsten (W);

L is, identical or different, selected from the group consisting of Cl, Br, I, P(C₅-C₁₄-aryl)_m, P(C₅-C₁₂-heteroaryl)_m, P(C₅-C₁₂-heteroaryl)_m(C₅-C₁₄-aryl)_{3-m}, CN, C₁-C₆-alkyl, C₁-C₆-alkyl-O-C₁-C₆-alkyl, -O-CO-C₁-C₆-alkyl, OH, nitro, -O-C₁-C₆-alkyl, C₁-C₄-haloalkoxy, C₃-C₈-cycloalkyl, C₃-C₈-halocycloalkyl, C₃-C₈-cycloalkenyl, C₅-C₁₄-aryl, C₅-C₁₄-aryl-(CH₂)_o-(Q)_p-(CH₂)_o-C₅-C₁₄-aryl and 1,1'-bis(diphenyl phosphino)ferrocene; whereby Q represents a bridging group selected from the group consisting of -CR⁹R¹⁰, -O-, -S-, -NR¹¹R¹², -SiR¹³R¹⁴ and -CO-, wherein R⁹ and R¹⁰, identical or different, are hydrogen, C₁-C₁₂ alkyl, C₅-C₁₄-aryl or C₅-C₁₂-heteroaryl; wherein R¹¹, R¹², R¹³ and R¹⁴, identical or different, are hydrogen or C₁-C₄ alkyl or R¹¹ together with R¹² forms C₅-C₁₂-membered heterocycloalkyl, C₅-C₁₄-membered heterocycloalkenyl or C₅-C₁₂-membered heteroaryl; and L is unsubstituted or further substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; -NO₂; -NR¹⁰R¹¹, -P(phenyl)₂, -OH, unsubstituted or substituted C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, unsubstituted or substituted C₅-C₁₄-aryl, unsubstituted or substituted C₅-C₁₂-heteroaryl, C₅-C₁₂-membered heterocycloalkyl, C₅-C₁₄-membered heterocycloalkenyl, -O-(CH₂)_r-O-, -C(=O)R¹⁵, -C(=O)-O-R¹⁶, -C=N-R¹⁷, -SO₃H, -O-C₁-C₆-alkyl and -O-Si-C₁-C₄-alkyl; or

L is supported on silica gel, dendrimers, polystyrenes or mesoporous siliceous foam, wherein

R¹⁵ is hydrogen or C₁-C₄-alkyl;

R¹⁶ is hydrogen or C₁-C₄-alkyl;

R¹⁷ is hydrogen, C₁-C₁₂-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₅-C₁₄-aryl, C₅-C₁₂-heteroaryl or C₃-C₁₂-cycloalkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

m is 1, 2 or 3;

o is 0, 1 or 2

p is 0, 1 or 2 and

r is 1, 2, 3, 4 or 5,

or their acceptable salts thereof.

6. The process according to claim 5, wherein M is selected from the group consisting of nickel (Ni), iron (Fe), palladium (Pd) and copper (Cu).

7. The process according to claim 5, wherein L is, identical or different, selected from the group consisting of Cl, Br, I, P(C₅-C₁₄-aryl)_m, CN, unsubstituted or substituted C₁-C₁₂-alkyl, C₁-C₄-alkoxy, C₃-C₈-cycloalkenyl, -O-CO-C₁-C₆-alkyl, C₅-C₁₄-aryl, 1,1'-bis(diphenyl phosphino)ferrocene and C₅-C₁₄-aryl-(CH₂)_o-(Q)_p-(CH₂)_o-C₅-C₁₄-aryl, whereby m, o, Q and p are as defined as in claim 7.

8. The process according to claim 1, wherein the at least one phosphine compound is of the formula $PX_1X_2X_3$ or $(PX_1X_2)_2(B)_q$, whereby X_1 , X_2 and X_3 , identical or different, are F, Cl, Br, I, $-NR^{18}R^{19}$, hydrogen, $-O-C_1-C_6$ -alkyl, $-O-CO-C_1-C_6$ -alkyl, C_1-C_{12} -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, C_5-C_{14} -aryl, C_5-C_{12} -heteroaryl, C_3-C_{12} -cycloalkyl, C_3-C_{12} -cycloalkenyl, C_3-C_{12} -heterocycloalkyl, C_3-C_{14} -heterocycloalkenyl or $-Si-(C_1-C_{12}-alkyl)_3$, whereby B is $CR^{20}R^{21}$, $-O-$, $-phenyl-O-phenyl-$, $-S-$, $-NR^{18}R^{19}$, $-SiR^{22}R^{23}$ or $-C(=O)-$, wherein R^{20} and R^{21} , identical or different, are hydrogen, C_1-C_{12} -alkyl, C_5-C_{14} -aryl or C_5-C_{12} -heteroaryl, wherein R^{18} , R^{19} , R^{20} and R^{21} , identical or different, are hydrogen or C_1-C_4 -alkyl or R^{18} together with R^{19} forms C_5-C_{12} -membered heterocycloalkyl, C_5-C_{14} -membered heterocycloalkenyl or C_5-C_{12} -heteroaryl; whereby X_1 , X_2 and X_3 , identical or different, are unsubstituted or substituted by 1, 2, 3, 4 or 5 identical or different groups selected from the group consisting of Cl; F; Br; I; CN; $-NO_2$; $-NR^{18}R^{19}$, $-P(phenyl)_2$, $-OH$, unsubstituted or substituted C_1-C_{12} -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, unsubstituted or substituted C_5-C_{14} -aryl, unsubstituted or substituted C_5-C_{12} -heteroaryl, $-O-(CH_2)_r-O-$, $-C(=O)R^{24}$, $-C(=O)-O-R^{25}$, $-C=N-R^{26}$, $-SO_3H$, $-O-C_1-C_6$ -alkyl and $-O-Si-C_1-C_4$ -alkyl, C_5-C_{12} -membered heterocycloalkyl, C_5-C_{14} -membered heterocycloalkenyl and C_5-C_{12} -heteroaryl;
- wherein q is 1, 2, 3, 4, 5 or 6;
r is 1, 2, 3, 4 or 5;
 R^{24} is hydrogen or C_1-C_4 -alkyl;
 R^{25} is hydrogen or C_1-C_4 -alkyl; and
 R^{26} is hydrogen, C_1-C_{12} -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, C_5-C_{14} -aryl, C_5-C_{12} heteroaryl or C_3-C_{12} -cycloalkyl;
or their acceptable salts thereof.
9. The process according to claim 1, wherein the at least one base is selected from the group consisting of organic bases and inorganic bases.
10. The process according to claim 9, wherein the organic bases are selected from the group consisting of $N(R^{27})_3$, N-methyl piperidine, N-methyl pyrrolidine, N-methyl morpholine, piperidine, dimethyl amino pyridine, pyridine, lithium hexamethyldisilazide, sodium hexamethyldisilazide and tetra- C_1-C_6 -alkyl ammonium hydroxide, wherein R^{27} is, identical or different, hydrogen, C_1-C_6 -alkyl, C_5-C_{14} -aryl, or C_3-C_6 -cycloalkyl.
11. The process according to claim 9, wherein the inorganic bases are selected from the group consisting of alkali metal hydroxide, alkaline earth hydroxide, alkali metal bicarbonate, alkaline earth bicarbonate, alkali metal carbonate, alkaline earth carbonate, alkali metal phosphate, alkali metal alkoxide and alkaline earth alkoxide.
12. The process according to claim 1, wherein the process is performed in the presence of at least one solvent which is selected from the group consisting of esters, ethers, aromatic hydrocarbons and acetals.

13. The process according to claim 1, wherein the ratio of the at least one metal catalyst to the at least one compound of formula (III) is in the range of 1:100 to 1:500 moles.
- 5 14. The process according to claim 1, wherein the ratio of the at least phosphine compound to the at least one metal catalyst is in the range of 1:0.010 to 1:0.2.
15. The process according to claim 1, wherein the process is performed at a temperature in the range of 50 ° C to 150 ° C.
- 10 16. The process according to claim 1, wherein the process is performed at a pressure in the range of 5 bar to 20 bar.
- 15 17. The process according to claim 1, wherein the compound of the general formula (I) or its salts are isolated by at least one of the following steps:
- a) filtering the reaction mixture through celite bed to remove the catalyst and washing the bed with water,
 - b) concentrating the filtrate to remove the solvent and water,
 - 20 c) diluting the concentrated mass with alcohol,
 - d) heating the reaction mixture of step c) to 60°C and adjusting the pH to 1.5 using 35% hydrochloric acid,
 - e) cooling the reaction mixture to 20°C and separating the product by filtration,
 - 25 f) drying the product at 70 °C -75 °C under vacuum for 12 hours to isolate the compound of formula (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/051465

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/10
ADD.

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/58509 A1 (BASF AG [DE]; RHEINHEIMER JOACHIM [DE]; DEYN WOLFGANG VON [DE]; GEBHAR) 18 November 1999 (1999-11-18) examples 8,9 step g; claim 1 claim 11	1-17
Y	WO 2009/007329 A1 (BASF SE [DE]; GEBHARDT JOACHIM [DE]; ERK PETER [DE]; SAXELL HEIDI EMIL) 15 January 2009 (2009-01-15) example 12	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

20 March 2020

Date of mailing of the international search report

08/04/2020

Name and mailing address of the ISA/

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Stix-Malaun, Elke

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/051465

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