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(71) Applicant *(for all designated States except US)*: **SOLVAY SA** [BE/BE]; Rue du Prince Albert, 33, B-1050 Bruxelles (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRAUN, Max Josef** [DE/DE]; Varloh 8, 30900 Wedemark (DE). **JAUNZEMS, Janis** [DE/DE]; Brabeckstr. 21, 30559 Hannover (DE). **KASUBKE, Michael** [DE/DE]; Freundallee 5, 30173 Hannover (DE).

(74) Agents: **MROSS, Stefan** et al.; Solvay Sa, Intellectual Property Department, Rue de Ransbeek, 310, B-1120 Bruxelles (BE).

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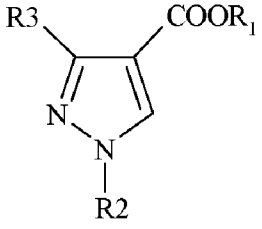
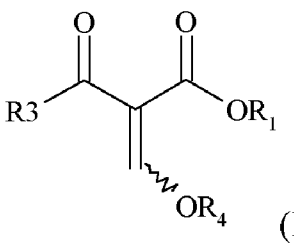
(54) **Title**: IMPROVED PROCESS FOR THE PREPARATION OF ESTERS OF 1-H-PYRAZOLE-4-CARBOXYLIC ACIDS



(I)



(II)

(57) **Abstract**: Process for the manufacture of an ester of a 1-H-pyrazole-4-carboxylic acid of formula (I) wherein - R1 is H or an organic residue - R2 is H or an organic residue - R3 is H, an alkyl group having from 1 to 12 carbon atoms, an halogenated alkyl group having from 1 to 12 carbon atoms, an aralkyl group, an aryl group, a halogen. which comprises reacting a compound of formula (II): wherein R4 is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkenyl, benzyl or phenyl,R1 and R3, are as defined above with a hydrazine of formula (III): $R2NHNH_2$ (III) wherein R2 is as defined above, in the presence of an organic solvent comprising at least one halogen.

Improved process for the preparation of esters of 1-H-pyrazole-4-carboxylic acids

The present application claims the benefit of the European application no. 10173899.5 filed on August 24, 2010, herein incorporated by reference.

The invention concerns an improved process for the manufacture of esters of 1H-pyrazole-4-carboxylic acid, in particular esters of 3-difluoromethyl-1-methyl- 1H-pyrazole-4-carboxylic acid, which are useful e.g. as intermediates for pharmaceuticals and agrochemicals.

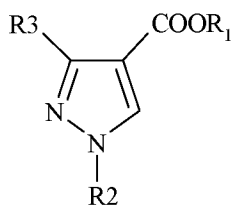
US patent 5,223,526 describes the preparation of 1H-pyrazole-4-carboxylic acid derivatives which are intermediates for the manufacture of pyrazole carboxanilide fungicides. US patent 5,498,624 describes in particular the preparation of 3-difluoromethyl-1-methyl- 1H-pyrazole-4-carboxylic acid derivatives.

WO 2008/053043 discloses a process for the synthesis of difluoromethyl -substituted-pyrazole-4-carboxylic acid esters. The synthesis is carried out by reacting 4,4,4-trihalogen-substituted acetoacetic ester derivatives with chlorosilanes in the presence of magnesium or other metals of the 1st, 2nd, 3rd, 4th or 12th group of the Periodic Table of the Elements and subsequent reaction of the reaction product with a hydrazine or hydrazine derivative.

US patent application 2008/0154045-A1 discloses a process for producing 1-substituted-3-fluoroalkyl-pyrazole-4-carboxylate by reaction of 2-alkoxymetylenefluoroacylacetate and hydrazine. Said reaction is carried out in the presence of water and a base.

It is an object of the present invention to provide a process for the synthesis of esters of 1H-pyrazole-4-carboxylic acid which allows, in particular, for high selectivity, high yield, high purity, and high efficiency for the manufacture of the target product. The process can have environmental benefits.

The invention consequently relates to a process for the manufacture of an ester of a 1-H-pyrazole-4-carboxylic acid of formula (I)

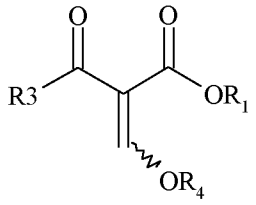


(I)

wherein

- R1 is H or an organic residue
- R2 is H or an organic residue
- R3 is H, an alkyl group, an halogenated alkyl group, an aralkyl group, an aryl group, a halogen.

which comprises reacting a compound of formula (II):



(II)

wherein R4 is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkenyl, benzyl or phenyl, R1 and R3, are as defined above with a hydrazine of formula (III): $R2NHNH_2$ (III) wherein R2 is as defined above, in the presence of an organic solvent which comprises at least one halogen.

The term "organic residue" is intended to denote in particular linear or branched alkyl or alkylene groups which may contain hetero atoms, such as in particular boron, silicon, nitrogen, oxygen or sulphur atoms and halogen atoms, cycloalkyl groups, heterocycles and aromatic systems. The organic residue may contain double or triple bonds and functional groups.

The organic residue comprises at least 1 carbon atom. It often comprises at least 2 carbon atoms. It preferably comprises at least 3 carbon atoms. More particularly preferably, it comprises at least 5 carbon atoms.

The organic residue generally comprises at most 100 carbon atoms. It often comprises at most 50 carbon atoms. It preferably comprises at most 40 carbon atoms. More particularly preferably, it comprises at most 30 carbon atoms.

R1 is typically selected from the group consisting of H, linear or branched alkyl or alkylene groups, cycloalkyl or cycloalkylene groups, heterocycles and aromatic systems, optionally containing heteroatoms, double bonds, triple bonds, functional groups and mixtures thereof.

R2 is usually selected from the group consisting of H, linear or branched alkyl or alkylene groups, cycloalkyl or cycloalkylene groups, heterocycles and aromatic systems, optionally containing heteroatoms, double bonds, triple bonds, functional groups and mixtures thereof.

The term "alkyl group" is intended to denote in particular a linear or branched alkyl substituent comprising from 1 to 20 carbon atoms, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. Specific examples of such substituents are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, 2-hexyl, n-heptyl, n-octyl and benzyl.

The term "cycloalkyl group" is intended to denote in particular a substituent comprising at least one saturated carbocycle containing 3 to 10 carbon atoms, preferably 5, 6 or 7 carbon atoms. Specific examples of such substituents are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "alkylene group" or "cycloalkylene group" is intended to denote in particular the divalent radicals derived from the alkyl or cycloalkyl groups as defined above.

When the organic residue contains one or optionally more double bonds, it is often chosen from an alkenyl or cycloalkenyl group comprising from 2 to 20 carbon atoms, preferably 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. Specific examples of such groups are vinyl, 1-allyl, 2-allyl, n-but-2-enyl, isobutenyl, 1,3-butadienyl, cyclopentenyl, cyclohexenyl and styryl.

When the organic residue contains one or optionally more triple bonds, it is often chosen from an alkinyl group comprising from 2 to 20 carbon atoms, preferably 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. Specific examples of such groups are ethinyl, 1-propinyl, 2-propinyl, n-but-2-inyl and 2-phenylethinyl.

When the organic residue contains one or optionally more aromatic systems, it is often an aryl group comprising from 6 to 24 carbon atoms, preferably from 6 to 12 carbon atoms. Specific examples of such groups are phenyl, 1-tolyl, 2-tolyl, 3-tolyl, xylyl, 1-naphthyl and 2-naphthyl.

The term "heterocycle" is intended to denote in particular a cyclic system comprising at least one saturated or unsaturated ring made up of 3, 4, 5, 6, 7 or 8 atoms, at least one of which is a hetero atom. The hetero atom is often chosen from B, N, O, Si, P and S. It is more often chosen from N, O and S.

Specific examples of such heterocycles are aziridine, azetidine, pyrrolidine, piperidine, morpholine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, perhydroquinoline, perhydroisoquinoline, isoxazolidine, pyrazoline, imidazoline, thiazoline, tetrahydrofuran, tetrahydrothiophene, pyran, tetrahydropyran and dioxane.

The organic residues as defined above may be unsubstituted or substituted

with functional groups. The term "functional group" is intended to denote in particular a substituent comprising or consisting of a hetero atom. The hetero atom is often chosen from B, N, O, Al, Si, P, S, Sn, As and Se and the halogens. It is more often chosen from N, O, S and P, in particular N, O and S.

The functional group generally comprises 1, 2, 3, 4, 5 or 6 atoms.

By way of functional groups, mention may, for example, be made of halogens, a hydroxyl group, an alkoxy group, a mercapto group, an amino group, a nitro group, a carbonyl group, an acyl group, an optionally esterified carboxyl group, a carboxamide group, a urea group, a urethane group and the thiol derivatives of the abovementioned groups containing a carbonyl group, phosphine, phosphonate or phosphate groups, a sulphoxide group, a sulphone group and a sulphonate group.

The term "halogenated alkyl group" is intended to denote in particular an alkyl group comprising from 1 to 20 carbon atoms and at least one halogen, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and at least one halogen. Suitable halogenated alkyl groups are selected for example from chlorinated alkyl groups such as chloromethyl, dichloromethyl, trichloromethyl, 1 – chloroethyl or 2,2,2-trichloroethyl fluorinated alkyl groups such as fluoromethyl, difluoromethyl, trifluoromethyl, 1 -fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or pentafluoroethyl, chlorofluorinated alkyl groups such as chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl or 2,2- dichloro-2-fluoroethyl, brominated alkyl groups such as bromomethyl and 1 –bromoethyl.

In a preferred embodiment of the process according to the invention, R1 is H, C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, C_3-C_8-cycloalkoxy-C_1-C_4-alkyl, C_2-C_8-alkenyl or is benzyl which is optionally substituted by 1,2 or 3 substituents R^{Y1} independently of one another selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-alkoxy and nitro; and

R2 is hydrogen, C_1-C_4-alkyl, benzyl or phenyl, where the two last-mentioned substituents may be unsubstituted or optionally substituted by 1,2 or 3 substituents R^{Y2} independently of one another selected from the group consisting of halogen, nitrile, nitro, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy; and

R3 is a halogenated alkyl group. R4 is C_1-C_8-alkyl, benzyl or phenyl.

The terms, used in the definition of the variables, for organic groups, such as, for example, the term "halogen", are collective terms representing the

individual members of these groups of organic moieties.

The prefix C_x-C_y denotes the number of possible carbon atoms in the case in question. C_1-C_4-Alkyl includes, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl.

The term "halogen" denotes in each case fluorine, bromine, chlorine or iodine, especially fluorine, chlorine or bromine.

The term "C_1-C_4-alkoxy-C_1-C_4-alkyl", as used herein, describes C_1-C_4-alkyl radicals where one carbon atom is attached to a C_1-C_4-alkoxy radical. Examples of these are CH_2-OCH_3, CH_2-OC_2H_5, n-propoxymethyl, CH_2-$OCH(CH_3)_2$, n-butoxymethyl, (1-methylpropoxy)methyl, (2-methylpropoxy)methyl, CH_2-$OC(CH_3)_3$, 2-(methoxy)ethyl, 2-(ethoxy)ethyl, 2-(n-propoxy)ethyl, 2-(1-methylethoxy)ethyl, 2-(n-butoxy)ethyl, 2-(1-methylpropoxy)ethyl, 2-(2-methylpropoxy)ethyl, 2-(1,1-dimethylethoxy)ethyl, 2-(methoxy)propyl, 2-(ethoxy)propyl, 2-(n-propoxy)propyl, 2-(1-methylethoxy)propyl, 2-(n-butoxy)propyl, 2-(1-methylpropoxy)propyl, 2-(2-methylpropoxy)propyl, 2-(1,1-dimethylethoxy)propyl, 3-(methoxy)propyl, 3-(ethoxy)propyl, 3-(n-propoxy)propyl, 3-(1-methylethoxy)propyl, 3-(n-butoxy)propyl, 3-(1-methylpropoxy)propyl, 3-(2-methylpropoxy)propyl, 3-(1,1-dimethylethoxy)propyl, 2-(methoxy) butyl, 2-(ethoxy)butyl, 2-(n-propoxy)butyl, 2-(1-methylethoxy)butyl, 2-(n-butoxy)butyl, 2-(1-methylpropoxy)butyl, 2-(2-methylpropoxy)butyl, 2-(1,1-dimethylethoxy)butyl, 3-(methoxy)butyl, 3-(ethoxy)butyl, 3-(n-propoxy)butyl, 3-(1-methylethoxy)butyl, 3-(n-butoxy)butyl, 3-(1-methylpropoxy)butyl, 3-(2-methylpropoxy)butyl, 3-(1,1-dimethylethoxy)butyl, 4-(methoxy)butyl, 4-(ethoxy)butyl, 4-(n-propoxy)butyl, 4-(1-methylethoxy)butyl, 4-(n-butoxy)butyl, 4-(1-methylpropoxy)butyl, 4-(2-methylpropoxy) butyl, 4-(1,1-dimethylethoxy)butyl.

The term "C_2-C_8-alkenyl", as used herein, describes straight-chain and branched unsaturated hydrocarbon radicals having 2 to 8 carbon atoms and at least one carbon-carbon double bond, such as, for example, ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-methyl-1-butenyl, 2-methyl-1-butenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-

hexenyl, 5-hexenyl, 1-methyl-1-pentenyl, 2-methyl-1-pentenyl, 3-methyl-1-pentenyl, 4-methyl-1-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-1-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-1-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-1-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 3,3-dimethyl-1-butenyl, 3,3-dimethyl-2-butenyl, 1-ethyl-1-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-1-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl, 1-ethyl-2-methyl-1-propenyl and 1-ethyl-2-methyl-2-propenyl, 1-heptenyl, 2-heptenyl, 1-octenyl or 2-octenyl.

In a preferred embodiment of the process according to the invention, R1 is H, C_1-C_4-alkyl or benzyl, in particular methyl, ethyl, n-propyl or isopropyl; R1 is especially ethyl; and

R2 is H or C_1-C_4-alkyl; R2 is especially methyl; R3 is selected from a group consisting of fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, and chlorodifluoromethyl; R3 is especially difluoromethyl. R4 is selected from the group consisting of C_1-C_4-alkyl and benzyl and in particular from the group consisting of methyl, ethyl, isopropyl and benzyl; R4 is especially ethyl.

The hydrazine of formula (III) used in the process according to the invention, can be used in anhydrous or hydrate form. The hydrazine of formula (III) can be used for example as an anhydrous solution or an aqueous solution.

In one embodiment, the hydrazine of formula (III) is used as an aqueous hydrazine solution.

In this embodiment, the aqueous hydrazine solution is preferably added to a reaction solution comprising compound (II) and an organic solvent which comprises at least one halogen thereby forming a two-phase reaction mixture.

In another more preferred embodiment, the hydrazine of formula (III) is in the form of an anhydrous solution.

If desired, the anhydrous hydrazine of formula (III) can be dissolved in an organic solvent, for example an organic solvent which comprises at least one halogen in such as described above in the context of the invention.

In one aspect of this preferred embodiment, the hydrazine compound (III)

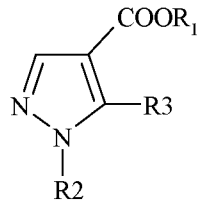
in anhydrous form is added to a reaction solution comprising compound (II) and an organic solvent which comprises at least one halogen.

In another aspect of this preferred embodiment, the hydrazine compound (III) dissolved in an organic solvent, in particular the organic solvent which comprises at least one halogen, is added to the reaction solution comprising compound (II) and the organic solvent which comprises at least one halogen.

In yet another aspect of this preferred embodiment, the compound (II) is added to the hydrazine compound (III), preferably dissolved in the organic solvent which comprises at least one halogen.

In an alternative and more preferred aspect of this preferred embodiment, the compound (II) present in the organic solvent which comprises at least one halogen is added to the hydrazine compound (III), preferably dissolved in the organic solvent which comprises at least one halogen.

In general, the reaction of the compound of formula (II) and the hydrazine of formula (III) can form the undesired pyrazole derivative of formula (IV)



(IV)

wherein R1, R2 and R3 are as defined above. Said pyrazole of formula (IV) is a regioisomer of the ester of 1-H-pyrazole-4-carboxylic acid of formula (I).

Surprisingly, it has been found that the selectivity of the reaction of the compound of formula (II) and the hydrazine of formula (III) to form the desired ester of a 1-H-pyrazole-4-carboxylic acid of formula (I) can be increased by carrying out said reaction in an organic solvent which comprises at least one halogen, preferably at least one fluorine atom.

In the present invention, the organic solvent which comprises at least one halogen is generally selected from the group consisting of hydrochlorocarbons, chlorocarbons, hydrofluorocarbons, fluorocarbons, fluoroalcohols, fluoroethers, hydrochlorofluorocarbons, and amides comprising at least one halogen. In an especially preferred embodiment, the organic solvent comprises at least one fluorine atom and is for instance selected from the group consisting of hydrofluorocarbons, fluorocarbons, fluoroalcohols, fluoroethers, hydrochlorofluorocarbons, and amides comprising at least one fluorine atom,

more particularly from hydrofluorocarbons, fluorocarbons, fluoroalcohols, fluoroethers, most particularly hydrofluorocarbons.

Suitable hydrochlorocarbons are selected, for example from dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1,3,3-pentachlorobutane.

Suitable chlorocarbons are selected, for example from carbon tetrachloride.

Suitable hydrofluorocarbons are selected, for example from 1,1,1,3,3-pentafluorobutane, 1,1,1,2,3,4,4,5,5,5-decafluoropentane.

Suitable fluoroalcohols are selected, for example from hexafluoroisopropanol, trifluoroethanol, trifluoroisopropanol, and 2,2,3,4,4,4-hexafluorobutanol.

Suitable fluoroethers are selected, for example from perfluorobutyl-methyl ether and perfluorobutyl-ethyl ether.

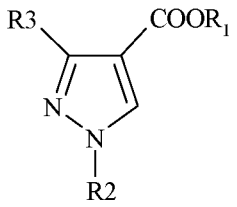
Suitable fluorocarbons are selected, for example from C4-as well as from C3-series.

Suitable hydrochlorofluorocarbons are selected, for example from 1,1-dichloro-1,3,3-trifluorobutane, 1,3-dichloro-1,1,3-trifluorobutane, 3,3-dichloro-1,1,1-trifluorobutane, 1-chloro-1,3,3,3-tetrafluorobutane, 3-chloro-1,1,3,3-tetrafluorobutane,

Preferably, the organic solvent comprising at least one halogen is selected from the group consisting of dichloromethane, 1,1-dichloro-1,3,3-trifluorobutane, 1,3-dichloro-1,1,3-trifluorobutane, 3,3-dichloro-1,1,1-trifluorobutane, 1-chloro-1,3,3,3-tetrafluorobutane, 3-chloro-1,1,3,3-tetrafluorobutane, 1,1,1,3,3-pentafluorobutane, hexafluoroisopropanol, and trifluoroethanol. More preferably, the organic solvent comprising at least one halogen is selected from the group consisting of 1,1,1,3,3-pentafluoropropane, 1,1,1,3,3-pentafluorobutane, hexafluoroisopropanol, trifluoroethanol. Good results are obtained using 1,1,1,3,3-pentafluorobutane.

The use of a hydrofluorocarbon, in particular 1,1,1,3,3-pentafluorobutane as organic solvent which comprises at least one halogen allows for particularly efficient formation of the esters of 1-H-pyrazole-4-carboxylic acid of formula (I) in very high regioselectivities. Said use also allows for an environmentally beneficial formation of the esters of 1-H-pyrazole-4-carboxylic acid of formula (I).

In a specific embodiment, the invention concerns a process for the manufacture of an ester of a 1-H-pyrazole-4-carboxylic acid of formula (I)

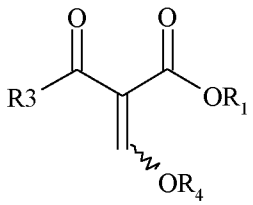


(I)

wherein

- R1 is H or an organic residue
- R2 is H or an organic residue
- R3 is H, an alkyl group, an halogenated alkyl group, an aralkyl group, an aryl group, a halogen.

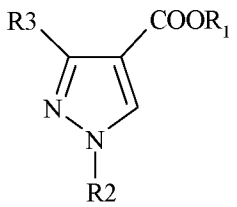
which comprises reacting a compound of formula (II):



(II)

wherein R4 is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkenyl, benzyl or phenyl,R1 and R3, are as defined above with a hydrazine of formula (III): $R2NHNH_2$ (III) wherein R2 is as defined above, in the presence of a hydrofluorocarbon solvent.

In another specific embodiment, the invention concerns a process for the manufacture of an ester of a 1-H-pyrazole-4-carboxylic acid of formula (I)

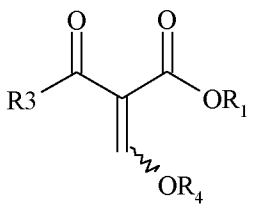


(I)

wherein

- R1 is H or an organic residue
- R2 is H or an organic residue
- R3 is H, an alkyl group, an halogenated alkyl group, an aralkyl group, an aryl group, a halogen.

which comprises reacting a compound of formula (II):



(II)

wherein R4 is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkenyl, benzyl or phenyl,R1 and R3, are as defined above with a hydrazine of formula (III): $R2NHNH_2$ (III) wherein R2 is as defined above, in the presence of 1,1,1,3,3-pentafluorobutane.

The definitions and preferences described above for the compounds used in the process according to the invention equally apply to the specific embodiments of the process according to the invention.

In a preferred aspect of the process of the present invention, the organic solvent which comprises at least one halogen, is substantially free of water.

For the purpose of the present invention, the term "solvent substantially free of water" denotes in particular that the content of water is equal to or lower than 1 wt % by weight relative to the total weight of solvent, preferably equal to lower than 7000 ppm, more preferably equal to lower than 5000 ppm, most preferably equal to lower than 2000 ppm. The solvent substantially free of water generally contains at least 1ppm by weight of water, oftent at least 10 ppm by weight of water relative to the total weight of solvent. Solvents which are substantially free of water allow to maintain a high reaction rate and the formation of phase separation and consequently, in general, no additional phase transfer catalysts are required.

If appropriate, the organic solvent which comprises at least one halogen, is used usually in an amount of from 50 to 99 by weight, preferably from 60 to 99 % by weight, more preferably from 75 to 99% by weight of the solvent relative to the total weight of the reaction medium.

If desired, the process of the present invention optionally may be carried out in the presence of a base. If a base is used, it may be an inorganic base or an organic base. When an inorganic base is used, it may be suitably selected from the group consisting of alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, alkaline earth metal hydroxides such as calcium hydroxide, barium hydroxide, magnesium hydroxide, strontium hydroxide, and basic alkali metal salts such as sodium carbonate, sodium hydrogencarbonate, potassium carbonate and potassium hydrogencarbonate. Preferred bases are sodium hydroxide and potassium hydroxide. Most preferred base is potassium hydroxide. When an organic base is used, it may be suitably from the group consisting of nitrogen-containing heterocyclic compounds such as pyridine, quinoline or picoline; and tertiary bases such as triethylamine, dimethylaniline, diethylaniline and 4-dimethylaminopyridine. Among them, pyridine, triethylamine, dimethylaniline,

diethylaniline and 4-dimethylaminopyridine are preferred. A single base can be used or a mixture of several bases.

In the process according to the invention, the reaction is generally carried out at a temperature from - 20°C to 60°C, preferably from 0°C to 50°C, more preferably from 10 °C to 40 °C. In a specific embodiment, an initial reaction temperature is set and the reaction temperature is changed during the reaction. Typical initial reaction temperatures range from -60 to 0 °C, in particular from -60 to -20° C. Good results were obtained with the temperature set from -30 to -20° C. If appropriate, during the reaction the reaction mixture is warmed to a temperature of from 0 to 60° C, in particular from 10 to 40° C.

The compound of formula (II) can be produced for example by the reaction of a β-ketocarboxylate of formula (V) $R3C(O)CH_2C(O)OR1$ (V) wherein R1 and R3 are defined as above, with an orthoformate of formula (VI): $HC(OR4)_3$ (VI) wherein R4 is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkenyl, benzyl or phenyl, in the presence of an anhydride of a carboxylic acid, for example a C_1-C_4-alkanecarboxylic acid, such as acetic anhydride. The formation of the compound of formula (II) can be carried out, for example, analogously to the reaction described in WO 2008/053043 and in the patent application EP - 10170633.1.

Some of the compounds of formula (V): $R3C(O)CH_2C(O)OR1$ (V) wherein R1 and R3 are defined as above, are commercially available or can be prepared according to known synthetic methods. For instance, the compounds of formula (V) can be prepared by Claisen condensation of the corresponding fluorine containing carboxylate and acetate. A more preferred route for the preparation of compounds of formula (V) is described in WO-A-2009/021987.

According to this reference, the compounds of formula (V) can be obtained, by addition of fluorine containing carboxylic acid chlorides to ketene followed by esterification. The preparation of the compounds of general formula (V) using the ketene technology allows to avoid excessive waste formation and does not need expensive bases. The used raw materials, such as difluorochloroacetyl chloride are available in industrial scale and can be produced by environmental friendly technologies (e.g. photochemical oxidation of 1,1-difluoro-1,2,2-trichloroethane with oxygen).

If appropriate, the isolation of the compound of formula (I) and the purification thereof can be carried out by purification methods, such as for example extraction, chromatography (e.g. thin layer or column), distillation. When a distillation is carried out, a solid distillation is suitably used. It is

preferred to subject the reaction mixture obtained in the process according to the invention to an aqueous extraction, followed by a distillation, in particular a solid distillation.

For the purpose of the present invention the term "solid distillation" denotes in particular a distillation of a compound of formula (I) having a melting point equal to or higher than 20°C, particularly a compound having a melting point equal to or higher than 30°C. The solid distillation is generally carried out so as to keep the parts of the distillation apparatus which are in contact with compound of formula (I) at a temperature higher than the melting point of the compound. Typically, at least the part of boiler and cooler of the distillation apparatus which are in contact with compound of formula (I) are kept at a temperature higher than the melting point of the compound. Possible means of keeping such parts at the desired temperature include, for example, thermal insulation and heating. In a particular aspect, the recovery of purified compound of formula (I) from the solid distillation is carried out at a temperature below the melting point of the compound. In this case, the purified compound is suitably recovered in solid form.

If appropriate, the solid distillation can be carried out under atmospheric pressure or, preferably, under vacuum.

The invention also concerns a method for the purification of the compound of formula (I) which comprises a solid distillation of the compound of formula (I).

In a most preferred aspect of the invention described herein, the compound of formula (I) is an ester of 1-methyl-3-difluoromethyl-pyrazole-4-carboxylic acid, in particular the ethyl ester.

In this especially preferred process of the present invention, the 1-methyl-3-difluoromethyl-pyrazole-4-carboxylic acid as compound of formula (I), in particular the ethyl ester, can be obtained from the reaction of an ester of 2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoic acid as compound of formula (II), in particular the ethyl ester, with methylhydrazine as compound of formula (III).

The invention also concerns a method for the manufacture of an agrochemically or pharmaceutically active compound which comprises the steps of

(a) manufacturing a compound of formula (I) according to the process according to the invention, as described above

(b) further reacting said compound of formula (I) as intermediate in the manufacture of the agrochemically or pharmaceutically active compound.

An example of further reaction according to step (b) is illustrated in WO 2005/123690, the respective content of which is incorporated by reference into the present patent application.

Should the disclosure of any patents, patent applications, and publications which are incorporated herein by reference conflict with the description of the present application to the extent that it might render a term unclear, the present description shall take precedence.

The following example is intended to further explain the invention without limiting it.

In these examples and throughout this specification the abbreviations employed are defined as follows: ECDFAA is ethyl 4,4-difluoro-4-chloro-3-oxobutanoic acid (or ethyl 4,4-difluoro-4-chloroacetoacetate), EMEDFAA is ethyl 2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate (or ethyl 2-ethoxymethylene-4,4-difluoroacetoacetate), EMECDFAA is ethyl 2-(ethoxymethylene)-4,4-difluoro-4-chloro-3-oxobutanoate (or ethyl 2-ethoxymethylene-4,4-difluoro-4-chloroacetoacetate), DFMMP is ethyl 1-methyl-3-difluoromethyl-pyrazole-4-carboxylate, i-DFMMP is ethyl 1-methyl-5-difluoromethyl-pyrazole-4-carboxylate, c-DFMMP is ethyl 1-methyl-3-chlorodifluoromethyl-pyrazole-4-carboxylate, i-CDFMMP is ethyl 1-methyl-5-chlorodifluoromethyl-pyrazole-4-carboxylate, MTBE is methyl t-butyl ether, EMIMOTf is 1-ethyl-3-methyl-imidazolium trifluormethane sulfonate, BMIMOTf is 1-butyl-3-methyl-imidazolium trifluormethane sulfonate, EMIM-n-butyl sulfate is 1-ethyl-3-methyl-imidazolium n-butyl sulfate, BMIM-octyl sulfate is 1-butyl-3-methylimidazolium octyl sulfate, HFIP is hexafluoroisopropyl. The hydrofluoroalkane Solkane®365 mfc is 1,1,1,3,3-pentafluorobutane,

Example 1: Preparation of ethyl 4,4-difluoro-4-chloro-3-oxo-butanoic acid (ECDFAA) using the ketene technology.

In a three-neck round bottom flask, chlorodifluoroacetyl chloride (148.92g, 1 mol) was dissolved in methylene chloride (500 mL) and the solution was cooled to -30°C. During 2 hours, ketene from a ketene generator (at a rate of *ca.* 930 mmol/h) was passed through the solution of chlorodifluoroacetyl chloride. The reaction mixture was warmed up to 0 °C and kept for 1 hour at 0 °C. Ethanol (61.98 g, 1.94 mol) was added dropwise to the solution while keeping the

temperature below 5°C. The solution was stirred for another 0.5 hour. The reaction mixture was transferred to a 2-liter flask and concentrated on a rotary evaporator under reduced pressure (30 °C, 300 mBar). The residue (282.78 g) was further distilled over a 60-cm Vigreux column under a pressure of 30 mBar. Ethyl- 4,4-difluoro-4-chloro 3-oxo-butanoic acid was recovered at a temperature of 58-65 °C as a colorless liquid. The yield was 85 % of the theoretical yield, and a purity of 98.0 % was obtained.

Example 2: Preparation of ethyl 4,4-difluoro-4-chloro-3-oxobutanoic acid (ECDFAA) using a Claissen reaction.

n-Butyllithium (85.3 g, 308 mmol) in n-hexane (2.5 M solution) was added dropwise within 30 min to a solution of diisopropylamine (32.7 g, 323 mmol) in THF (200 mL) cooled at -30 to -60 °C. The solution was allowed to warm up to 0 °C, then cooled down to -70 °C and ethyl acetate (26.4 g, 300 mol) was added dropwise during 30 min whilst keeping the temperature at about -60 °C. Subsequently, ethyl chlorodifluoroacetate (24.3 g) was added dropwise during 30 min at the same temperature, the mixture was stirred at -65 to -70 °C for 3 h, then allowed to warm to room temperature. The mixture was poured onto ice and 4 N HCl (150 mL) is added. The organic phase was separated and the aqueous phase extracted twice with MTBE. The combined organic phases were washed with 2 N HCl (100 mL) and saturated sodium chloride solution (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. Ethyl 4-chloro-4,4-difluoro-3-oxo-butanoate (19 g, 61 %) was obtained by distillation (92-94 °C; 30 mbar) along with a further mixed fraction.

Example 3: Preparation of ethyl 2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate (EMEDFAA).

A solution of ethyl 4,4-difluoro-3-oxobutanoate (500 g, 3.01 mol), triethyl orthoformate (923 g, 6.23 mmol) and acetic anhydride (784 g, 7.68 mmol) were mixed in a dry glass flask equipped with a small distillation bridge and refluxed at 135 °C until no more ethanol is distilled. This procedure was repeated three times; fractionation thus yielded 1575g of EMEDFAA (distillation temperature 106°C at 0 mbar) with a yield of 78.5 % and a purity of > 99%.

Example 4: General procedure for the preparation of ethyl 1-methyl-3-difluoromethyl-pyrazole-4-carboxylate (DFMMP).

EMEDFAA (294g, 1.3 mol) was dissolved in the respective solvent (indicated in Table 1) (under N_2 as inert gas) and cooled to 0°C. Then anhydrous methyl hydrazine (67.1 mL, 1.3 mol) was slowly added from a dropping funnel;

the reaction was exothermic. After the addition, the reaction mixture was allowed to come to room temperature; 1N HCl was added, the phases were separated. The ratio of ethyl 1-methyl-3-difluoromethyl-pyrazole-4-carboxylate (DFMMP) to ethyl 1-methyl-5-difluoromethyl-pyrazole-4-carboxylate (i-DFMMP) was determined using ^{1}H NMR (see Table 1). The further purification was carried out by first drying the organic phase with Na_2SO_4, and then the solvent was evaporated followed by a precision distillation in a solid distillation apparatus.

This general procedure was carried out in different solvents (shown in Table 1) in order to evaluate the influence of the different solvents on the selectivity of the reaction. The experimental data are summarized in Table 1. The last column shows the ratio of DFMMP to i-DFMMP. The entire purification was only carried out in the experiments described below, for which the table also lists the yields (as isolated).

Table 1:

Example	Solvent	Molar ratio[d] DFMMP : i-DFMMP	Isolated yield of DFMMP
4a	Ethanol[a]	60:40	~60%
4b	Methanol	80:18	
4c	Toluene[b]	100:0	~50%
4d	Toluene[c]	26:10	
4e	BMIM OTf	65:35	
4f	EMIM-n-Butylsulfate	70:30	
4g	EMIM-OTf	57:43	
4h	BMIM octyl sulfate	65:22	
4i	Acetonitrile	65:35	
4j	Acetic acid	mixture	
4k	Pentane	77:22	
4l	HFIP	85:13	
4m	Trifluoroethanol	87:13	
4n	Solkane®365 mfc solvent	92:2 – 85:15	~80%
4o	CH_2Cl_2	80:20	

([a]) cooled until -40 °C

([b]) in the presence of KOH aq.

([c]) in the presence of HCl aq.

([d]) the molar ratio were measured by GC analyses.

Example 5: Preparation of ethyl 1-methyl-3-difluoromethyl-pyrazole-4-carboxylate (DFMMP) in the hydrofluoralkane Solkane®365 mfc.

EMEDFAA (294g, 1.3 mol) was dissolved in the hydrofluoralkane Solkane®365 mfc (under N_2 inert gas) and cooled to 0°C. Then anhydrous methyl hydrazine (67.1 mL, 1.3 mol) was slowly added from a dropping funnel; the reaction is exothermic. After the addition the reaction mixture was allowed to come to room temperature; 1N HCl was added, the phases were separated and after drying with Na_2SO_4 and evaporation of the solvent the product was fractionated in a solid distillation apparatus to isolate the DFMMP. The isomer i-DFMMP was distilled at 0 mbar, at 80°C, the desired isomer DFMMP was distilled at 115°C, 0 mbar. The yield of isolated DFMMP was 80%, its purity > 99.9 % (^{1}H NMR).

Example 6:

EMEDFAA (1g, 4.5 mmol) was dissolved in the hydrofluoralkane Solkane®365 mfc (4 ml) (under N_2 inert gas) and cooled to -20 °C. Then anhydrous methyl hydrazine (0.24 ml, 4.55 mmol) was added drop wise. After aging for 3 hours the reaction mixture was poured into 1N HCl. The organic phase was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure yielding 872 mg (95%) of a yellowish material;

GC-analysis showed that DFMMP and i-DFMMP were present in a molar ratio of 89:11.

Example 7:

To a solution of anhydrous methyl hydrazine (0.238 ml, 4.55 mmol) in the hydrofluoralkane Solkane®365 mfc (3 ml) was added drop wise a solution of EMEDFAA (1g, 4.5 mmol) in the hydrofluoralkane Solkane®365 mfc (2 ml) at -20 to -30 °C. After aging for 3 hours the reaction mixture was poured into 1N HCl. The organic phase was washed with water, dried with Na2SO4, filtered and concentrated under reduced pressure yielding 878mg (96%) of a yellowish solid;

GC-analysis showed that DFMMP and i-DFMMP were present in a molar ratio of 95:5.

Example 8:

To a solution of anhydrous methyl hydrazine (0.238 ml, 4.55 mmol) in the hydrofluoralkane Solkane®365 mfc (3 ml) was added drop wise a solution of EMEDFAA (1g, 4.5 mmol) in the hydrofluoralkane Solkane®365 mfc (2 ml) at 0 °C. After aging for 3 hours the reaction mixture was poured into 1N HCl. The organic phase was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure yielding 872mg (95%) of a yellowish solid;

GC-analysis showed that DFMMP and i-DFMMP were present in a molar ratio of 92.5:7.5.

Example 9: Preparation of ethyl 2-(ethoxymethylene)-4,4-difluoro-4-chloro-3-oxobutanoate (EMECDFAA).

A solution of ethyl 4,4-difluoro-4-chloro-3-oxobutanoate (401 g, 2 mol), triethyl orthoformate (593 g, 4 mmol) and acetic anhydride (612 g, 6 mmol) were mixed in a dry glass flask equipped with a small distillation bridge and refluxed at 125 °C until no more ethanol is distilled (about 6h). Reaction mixture was further heated at 110° and vacuum was slowly applied up to 1 mbar to remove all light boiling components. The residue was further distilled by 0.8 mbar at 92°C yielding 452g of yellow oil with a yield of 88% and a purity of 97% (GC).

Example 10: General procedure for the preparation of ethyl 1-methyl-3-chlorodifluoromethyl-pyrazole-4-carboxylate (CDFMMP).

EMECDFAA (1g, 3.89 mmol) was dissolved in the respective solvent (indicated in Table 2) (under N_2 as inert gas) and cooled to 0°C. Then anhydrous methyl hydrazine (179 mg, 3.89 mmol) was slowly added from a syringe; the reaction was exothermic. After the addition, the reaction mixture was allowed to come to room temperature. The ratio of ethyl 1-methyl-3-chlorodifluoromethyl-pyrazole-4-carboxylate (CDFMMP) to ethyl 1-methyl-5-clorodifluoromethyl-pyrazole-4-carboxylate (i-CDFMMP) was determined using GC (see Table 2). The further purification was carried out by extraction of product with DCM, drying the organic phase with Na_2SO_4, and then the solvent was evaporated followed by a precision distillation in a vacuum distillation apparatus.

This general procedure was carried out in different solvents (shown in Table 2) in order to evaluate the influence of the different solvents on the selectivity of the reaction. The experimental data are summarized in Table 2. The last column shows the ratio of CDFMMP to i-CDFMMP. The entire purification was only carried out in the experiments described below, for which the table also lists the yields (as isolated).

Table 2:

Example	Solvent	Molar ratio[b] CDFMMP : i-CDFMMP	Isolated yield of CDFMMP
10a	Acetic acid (10ml)	31:69	
10b	TFA+365 (5+5ml)	13:87	
10c	Solkane®365 mfc solvent (3ml)	87:13	74%
10d	Solkane®365 mfc solvent[a] (3ml)	75:25	
10e	NEt_3+365 (2+3ml)	75:25	

([a]) 1g Molecular sieves 3A was added

([b]) The molar ratio was measured by GC analyses.

Example 11: Preparation of ethyl 1-methyl-3-clorodifluoromethyl-pyrazole-4-carboxylate (CDFMMP) in the hydrofluoralkane Solkane®365 mfc.

Anhydrous methyl hydrazine (7.35 g, 0.16 mol) was dissolved in 80ml hydrofluoralkane Solkane®365 mfc and cooled to 0°C. EMECDFAA (41g, 0.16 mol) was dissolved in 40 mL hydrofluoralkane Solkane®365 mfc, and slowly added from a dropping funnel maintaining reaction temperature at 0°C; the reaction is exothermic. After the addition, the reaction mixture was allowed to come to room temperature; water was added, the phases were separated and after drying with Na_2SO_4 and evaporation of the solvent, the product was fractionated in a vacuum distillation apparatus to isolate the CDFMMP. The isomer i-CDFMMP was distilled at at 75-90°C, 0.13 mbar. The desired isomer CDFMMP was distilled at 101°C, 0.13 mbar. Light yellow oil or crystals were obtained, mp. 27.3-27.5°C. The yield of isolated CDFMMP was 74%, its purity 99 % (^{1}H NMR, GC).

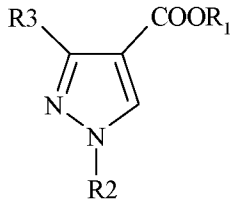
Example 12 (Comparative example): Preparation of ethyl 1-methyl-3-difluoromethyl-pyrazole-4-carboxylate (DFMMP) in water according to Example 24 in patent application US2008/0154045-A.

A 35% by weight aqueous solution of methylhydrazine (5,45ml, 4.8g; 104mmol) was added to a solution of sodium hydroxide (0.9g; 22.5 mmol) in 50ml of water with stirring. To the solution, ethyl 2-ethoxymethylene-4,4,difluoroacetoacetate (5g, 22.5 mmol) was added drop wise under ice-cooling, followed by stirring for 1 hour at ambient temperature. To the reaction mixture, 1N hydrochloric acid was added to neutralize it, and a saturated aqueous solution of sodium chloride was further added, followed by extraction with chloroform

(by GC-analysis of the extract it was found that ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate and ethyl 5-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate were present in a ratio of 99.4% to 0.6%). The organic layer was dried over anhydrous sodium sulphate, and the desiccant was separated by filtration. Then, the filtrate was evaporated to dryness under reduced pressure, thereby obtaining a white solid 3.3g (72%).

CLAIMS

1. A process for the manufacture of an ester of a 1-H-pyrazole-4-carboxylic acid of formula (I)

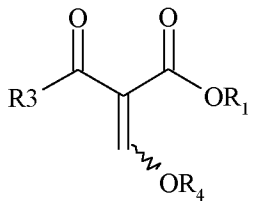


(I)

wherein

- R1 is H or an organic residue
- R2 is H or an organic residue
- R3 is H, an alkyl group having from 1 to 12 carbon atoms, an halogenated alkyl group having from 1 to 12 carbon atoms, an aralkyl group, an aryl group, a halogen.

which comprises reacting a compound of formula (II):



(II)

wherein R4 is C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkenyl, benzyl or phenyl,R1 and R3, are as defined above with a hydrazine of formula (III): $R2NHNH_2$ (III) wherein R2 is as defined above, in the presence of an organic solvent comprising at least one halogen.

2. The process according to claim 1, wherein the organic solvent comprising at least one halogen is selected from the group consisting of hydrochlorocarbons, chlorocarbons, hydrofluorocarbons, fluorocarbons, fluoroalcohols, fluoroethers, hydrochlorofluorocarbons, and amides comprising at least one halogen, preferably from hydrofluorocarbons, fluorocarbons, fluoroalcohols, fluoroethers, hydrochlorofluorocarbons, and amides comprising at least one fluorine atom, more particularly from hydrofluorocarbons, fluorocarbons, fluoroalcohols, and fluoroethers.

3. The process according to claim 2, wherein the organic solvent comprising at least one halogen is a hydrofluorocarbon.

4. The process according to anyone of claims 1 to 3, wherein the organic solvent comprising at least one halogen is selected from the group consisting of hexafluoroisopropanol, trifluoroethanol, 1,1,1,3,3-pentafluorobutane.

5. The process according to claim 4, wherein the hydrofluorcarbon is 1,1,1,3,3-pentafluorobutane .

6. The process according to anyone of claims 1-5, wherein the organic solvent is substantially free of water.

7. The process according to anyone of claims 1 to 6, wherein R1 is selected from the group consisting of H, linear or branched alkyl or alkylene groups, cycloalkyl or cycloalkylene groups, heterocycles and aromatic systems, optionally containing heteroatoms, double bonds, triple bonds, functional groups and mixtures thereof; preferably from H, C_1-C_8 alkyl, C_3-C_8-cycloalkyl, C_1-C_4 alkoxy C_1-C_4 alkyl, C_3-C_8 cycloalkoxy C_1-C_4 alkyl, C_2-C_8 alkenyl, and benzyl optionally substituted by 1, 2 or 3 substituents R^{Y1} independently of one another selected from C_1-C_4 alkyl, C_1-C_4 alkoxy and nitro; more preferably from H, C_1-C_4 alkyl, and benzyl; most preferably from methyl, ethyl and propyl.

8. The process according to claim 7, wherein R1 is ethyl.

9. The process according to anyone of claims 1 to 8, wherein R2 is selected from the group consisting of H, linear or branched alkyl or alkylene groups, cycloalkyl or cycloalkylene groups, heterocycles and aromatic systems, optionally containing heteroatoms, double bonds, triple bonds, functional groups and mixtures thereof; preferably from H, C_1-C_4 alkyl, benzyl and phenyl, where benzyl and phenyl may be optionally substituted by 1, 2 or 3 substituents R^{Y2} independently of one another selected from halogen, nitrile, nitro, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy and C_1-C_4 haloalkoxy; more preferably from H and C_1-C_4 alkyl; most preferably methyl.

10. The process according to anyone of claims 1 to 9, wherein R3 is an halogenated alkyl group; preferably a fluorinated alkyl group selected from the group consisting of fluoromethyl, difluoromethyl, trifluoromethyl,

chlorofluoromethyl, dichlorofluoromethyl, and chlorodifluoromethyl; more preferably difluoromethyl.

11. The process according to anyone of claims 1 to 10, wherein R4 is selected from the group consisting of C_1-C_8 alkyl, benzyl and phenyl; in particular C_1-C_4 alkyl and benzyl; more particularly from methyl, ethyl, isopropyl and benzyl; especially ethyl.

12. The process according to any one of claims 1 to 11, wherein the temperature of the reaction is from -20 °C to 60°C, preferably from 0°C to 50°C, more preferably from 10 °C to 40 °C.

13. The process according to claim 12, wherein the temperature of the reaction is initially set from – 60 to 0°C.

14. A method for the manufacture of an agrochemically or pharmaceutically active compound which comprises the steps of

(a) manufacturing a compound of formula (I) according to the process according to the claims 1 to 13

(b) further reacting said compound of formula (I) as intermediate in the manufacture of the agrochemically or pharmaceutically active compound.

15. A method for the purification of the compound of formula (I) which comprises a solid distillation of the compound of formula (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/064339

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/14
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 practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 854 788 A1 (SAGAMI CHEM RES [JP]; JAPAN FINECHEM COMPANY INC [JP]) 14 November 2007 (2007-11-14)	1-14
A	paragraph [0001] page 4, line 43 - page 4, line 45 paragraph [0032] - paragraph [0033] examples 22,23	15

X	DE 39 34 924 A1 (HUELS CHEMISCHE WERKE AG [DE]) 25 April 1991 (1991-04-25)	1,2, 7-12,15
A	column 2, line 3 - column 2, line 29 example 5 Distillation of products: column 2, lines 28-33 and examples 2, 7 and 9	3-6,13, 14

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sarakinos, Georgios

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