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(54) Title: PROCESS FOR PREPARING SUBSTITUTED PYRAZOLES CONTAINING HALOALKOXY- AND HALOALKYLTHIO GROUPS FROM α,α-DIHALOALKYLAMINES AND KETIMINES

(57) Abstract: The present invention relates to a novel process for preparing 3,5 -bis substituted pyrazoles containing haloalkoxy- and haloalkylthio groups.

Process for preparing substituted pyrazoles containing haloalkoxy- and haloalkylthio groups from α,α-dihaloalkylamines and ketimines

The present invention relates to a novel process for preparing 3,5-bis substituted pyrazoles containing haloalkoxy- and haloalkylthio groups.

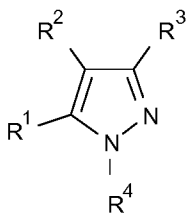
Polyfluoroalkylpyrazolylcarboxylic acid derivatives and 3,5-bis(haloalkyl)pyrazoles are valuable precursors of active fungicidal ingredients (WO 2003/070705, WO 2008/013925, WO 2012/025557) .

Pyrazolecarboxylic acid derivatives are typically prepared by reacting acrylic acid derivatives having two leaving groups with hydrazines (WO 2009/112157 and WO 2009/106230). WO 2005/042468 discloses a process for preparing 2-dihaloacyl-3-aminoacrylic esters by reacting acid halides with dialkylaminoacrylic esters and subsequent cyclization thereof with alkyl hydrazines. WO 2008/022777 describes a process for preparing 3-dihalomethylpyrazole-4-carboxylic acid derivatives by reacting α,α-difluoroalkylamines in the presence of Lewis acids with acrylic acid derivatives and subsequent reaction thereof with alkylhydrazines.

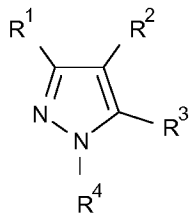
3,5-bis(fluoroalkyl)pyrazoles are prepared by reacting bisperfluoroalkyl diketones (e.g. 1,1,1,5,5,5-hexafluoroacetylacetone) with hydrazines (cf. *Pashkevich et al.*, Zhurnal Vsesoyuznogo Khimicheskogo Obshchestva im. D. I. Mendeleeva (1981), 26(1), 105-7), the yield being only 27 - 40%. The synthesis, isolation and purification of the polyfluoroalkyl diketones is very complex since the compounds are generally very volatile and highly toxic.

In the light of the prior art described above, it is an object of the present invention to provide a process that does not have the aforementioned disadvantages and hence gives a route to 3,5-bis(haloalkyl)pyrazole derivatives in high yields.

The object described above was achieved by a process for preparing 3,5-bis(haloalkyl)pyrazoles of the formula **(Ia)** and **(Ib)**,



(Ia)



(Ib)

in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

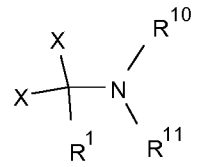
R^4 is selected from H, C_1-C_8 alkyl, aryl, pyridyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

characterized in that in step (A1), α,α-dihaloalkylamines of the formula **(II)**,



(II)

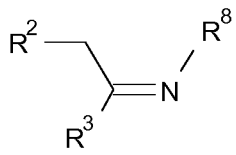
in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

X is independently selected from F, Cl or Br,

R^{10} and R^{11} are each independently selected from C_{1-6}-alkyl, C_{3-8}-cycloalkyl,

are reacted in the presence of Lewis Acid with compounds of the formula **(III)**,



(III)

in which

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

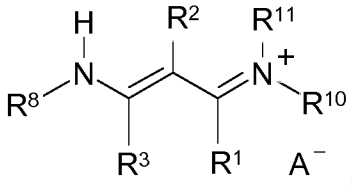
R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

to form the compound of formula **(V-1),**



(V-1)

wherein A^- is BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl;

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl;

R^{10} and R^{11} are each independently selected from C_{1-6}-alkyl, C_{3-8}-cycloalkyl,

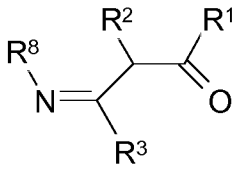
and that in step (B) in the presence of hydrazine

H_2N-NHR^4 **(IV)** wherein

R^4 is selected from H, C_1-C_8 alkyl, aryl or pyridyl

a cyclization of **(V-1)** takes place to form **(Ia/Ib)**.

In another embodiment of the process according to the invention in a step (A2) compound **(V-1)** is further reacted with water to compound of formula **(V-2)**



(V-2)

in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl;

and that in step (B) in the presence of hydrazine

H_2N-NHR^4 **(IV)** wherein

R^4 is selected from H, C_1-C_8 alkyl, aryl or pyridyl

a cyclization of **(V-2)** takes place to form **(Ia/Ib)**.

Preferred is a process according to the invention, where the radicals in formula **(Ia), (Ib), (II), (III), (IV), (V-1)** and **(V-2)** are defined as follows:

R^1 is selected from $CHF\text{-}OCF_3$ (fluoro(trifluoromethoxy)methyl), $CHF\text{-}OC_2F_5$ (fluoro(pentafluoroethoxy)methyl), $CHF\text{-}SCF_3$ (fluoro(trifluorothiomethyl)methyl), $CHF\text{-}SC_2F_5$ fluoro(pentafluorothioethyl)methyl;

R^2 is selected from H, F, Cl, Br, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, CN and $CON(CH_3)_2$, $CON(C_2H_5)_2$;

R^3 is selected from difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, tetrafluoroethyl (CF_3CFH), pentafluoroethyl and 1,1,1-trifluoroprop-2-yl;

R^4 is selected from H, C_1-C_8 alkyl, aryl, pyridyl;

R^8 are each independently selected from methyl, ethyl, *n*-, *iso*-propyl, *n*-, *iso*-, *sec*- und *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenylethyl, C_{7-19}-alkylaryl, tolyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl;

X is independently selected from F or Cl;

R^{10} and R^{11} are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{7-19}-arylalkyl or

R^{10} and R^{11} together with the nitrogen atom to which they are bonded may form a five- membered ring.

More preferred is a process according to the invention, where the radicals in formula **(Ia), (Ib), (II), (III), (IV), (V-1)** and **(V-2)** are defined as follows:

R^1 is selected from fluoro(trifluoromethoxy)methyl, fluoro(pentafluoroethoxy)methyl;

R^2 is selected from H, Cl, CN, $COOC_2H_5$;

R^3 is selected from trifluoromethyl, difluoromethyl, difluorochloromethyl, pentafluoroethyl;

R^4 is selected from H, methyl, ethyl, n-, isopropyl, n-, iso-, sec- and t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, aryl;

R^8 is selected from methyl, ethyl, *n*-, *iso*-propyl, *n*-, *iso*-, *sec*- und *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, C_{7-19}-alkylaryl;

X is independently selected from F or Cl;

R^{10} and R^{11} are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl.

Even more preferred is a process according to the invention, where the radicals in formula **(Ia), (Ib), (II), (III), (IV), (V-1)** and **(V-2)** are defined as follows:

R^1 is $CHFOCF_3$, $CHFOC_2F_5$;

R^2 is selected from H or $COOC_2H_5$;

R^3 are CF_2H, CF_3;

R^4 is selected form H, methyl, ethyl, phenyl;

R^8 is selected from ethyl, *n*-, *iso*-propyl, *n*-, cyclopentyl, cyclohexyl, benzyl;

X is F;

R^{10} and R^{11} are each independently selected from C_{1-12}-alkyl.

Most preferred is a process according to the invention, where the radicals in formula **(Ia), (Ib), (II), (III), (IV), (V-1)** and **(V-2)** are defined as follows:

R^1 is $CHFOCF_3$;

R^2 is H;

R^3 are CF_2H, CF_3;

R^4 is selected from H, methyl;

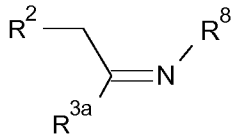
R^8 is benzyl;

X is F;

R^{10} and R^{11} are each independently selected from methyl, ethyl.

The pyrazoles of the formula (I) can be prepared under the inventive conditions with good yields and in high purity, which means that the process according to the invention overcomes the abovementioned disadvantages of the preparation processes previously described in the prior art.

A further aspect of the present invention are compounds of formula **(III-a):**



(III-a)

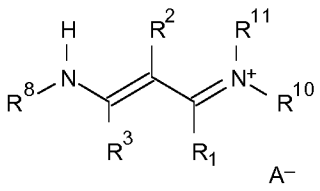
in which

R^2 is H,

R^{3a} is HCF_2, CF_3;

R^8 is benzyl.

A further aspect of the present invention are compounds of formula **(V-1):**



(V-1)

in which the radicals are as defined above

and

A^- is selected from BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl.

Preferred are compounds of formula **(V-1)** in which

R^1 is selected from $CHFOCF_3$;

R^2 is H;

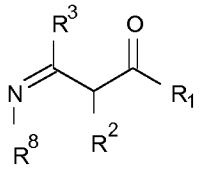
R^3 is selected from CF_2H, CF_3;

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl and benzyl;

R^{10} and R^{11} are each independently selected from C_{1-5} alkyl;

A^- is selected from BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl.

A further aspect of the present invention are compounds of formula **(V-2):**



(V-2)

in which the radicals are as defined above.

Preferred are compounds of formula **(V-2)** in which

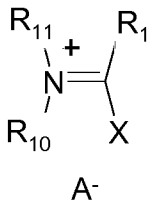
R^1 is selected from $CHFOCF_3$;

R^2 is H;

R^3 is selected from CF_2H, CF_3;

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl and benzyl.

A further aspect of the present invention are compounds of formula **(II-1):**



in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

X is independently selected from F, Cl or Br,

R^{10} and R^{11} are each independently selected from C_{1-6}-alkyl, C_{3-8}-cycloalkyl and

A^- is selected from BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl.

General definitions

In the context of the present invention, the term "halogen" (**Hal**), unless defined differently, comprises those elements which are selected from the group comprising fluorine, chlorine, bromine and iodine, preferably fluorine, chlorine and bromine, more preferably fluorine and chlorine.

Optionally substituted groups may be mono- or polysubstituted, where the substituents in the case of polysubstitutions may be the same or different.

Haloalkyl: straight-chain or branched alkyl groups having 1 to 6 and preferably 1 to 3 carbon atoms (as specified above), where some or all of the hydrogen atoms in these groups may be replaced by halogen atoms as specified above, for example (but not limited to) C_1-C_3-haloalkyl such as chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, pentafluoroethyl and 1,1,1-trifluoroprop-2-yl. This definition also applies to haloalkyl as part of a composite substituent, for example haloalkylaminoalkyl etc., unless defined elsewhere. Preference is given to alkyl groups substituted by one or more halogen atoms, for example trifluoromethyl (CF_3), difluoromethyl (CHF_2), CF_3CH_2, CF_2Cl or CF_3CCl_2.

Alkyl groups in the context of the present invention, unless defined differently, are linear or branched saturated hydrocarbyl groups. The definition C_1-C_{12}-alkyl encompasses the widest range defined herein for an alkyl group. Specifically, this definition encompasses, for example, the meanings of methyl, ethyl, n-, isopropyl, n-, iso-, sec- and t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl or n-dodecyl.

Alkenyl groups in the context of the present invention, unless defined differently, are linear or branched hydrocarbyl groups containing at least one single unsaturation (double bond). The definition C_2-C_{12}-alkenyl encompasses the widest range defined herein for an alkenyl group. Specifically, this definition encompasses, for example, the meanings of vinyl; allyl (2-propenyl), isopropenyl (1-methylethenyl); but-1-enyl (crotyl), but-2-enyl, but-3-enyl; hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hex-5-enyl; hept-1-enyl, hept-2-enyl, hept-3-enyl, hept-4-enyl, hept-5-enyl, hept-6-enyl; oct-1-enyl, oct-2-enyl, oct-3-enyl, oct-4-enyl, oct-5-enyl, oct-6-enyl, oct-7-enyl; non-1-enyl, non-2-enyl, non-3-enyl, non-4-enyl, non-5-enyl, non-6-enyl, non-7-enyl, non-8-enyl; dec-1-enyl, dec-2-enyl, dec-3-enyl, dec-4-enyl, dec-5-enyl, dec-6-enyl, dec-7-enyl, dec-8-enyl, dec-9-enyl; undec-1-enyl, undec-2-enyl, undec-3-enyl, undec-4-enyl, undec-5-enyl, undec-6-enyl, undec-7-enyl, undec-8-enyl, undec-9-enyl, undec-10-enyl; dodec-1-enyl, dodec-2-enyl, dodec-3-enyl, dodec-4-enyl, dodec-5-enyl, dodec-6-enyl, dodec-7-enyl, dodec-8-enyl, dodec-9-enyl, dodec-10-enyl, dodec-11-enyl; buta-1,3-dienyl or penta-1,3-dienyl.

Alkynyl groups in the context of the present invention, unless defined differently, are linear, branched or cyclic hydrocarbyl groups containing at least one double unsaturation (triple bond). The definition C_2-C_{12}-alkynyl encompasses the widest range defined herein for an alkynyl group. Specifically, this definition encompasses, for example, the meanings of ethynyl (acetylenyl); prop-1-ynyl and prop-2-ynyl.

Cycloalkyl: monocyclic, saturated hydrocarbyl groups having 3 to 8 and preferably 3 to 6 carbon ring members, for example (but not limited to) cyclopropyl, cyclopentyl and cyclohexyl. This definition also applies to cycloalkyl as part of a composite substituent, for example cycloalkylalkyl etc., unless defined elsewhere.

Aryl groups in the context of the present invention, unless defined differently, are aromatic hydrocarbyl groups which may have one, two or more heteroatoms selected from O, N, P and S. The definition C_{6-18}-aryl encompasses the widest range defined herein for an aryl group having 5 to 18 skeleton atoms, where the carbon atoms may be exchanged for heteroatoms. Specifically, this definition encompasses, for example, the meanings of phenyl, cycloheptatrienyl, cyclooctatetraenyl, naphthyl and anthracenyl; 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl and 1,3,4-triazol-2-yl; 1-pyrrolyl, 1-pyrazolyl, 1,2,4-triazol-1-yl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,3,4-triazol-1-yl; 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 1,3,5-triazin-2-yl and 1,2,4-triazin-3-yl.

Arylalkyl groups (aralkyl groups) in the context of the present invention, unless defined differently, are alkyl groups which are substituted by aryl groups, may have one C_{1-8}-alkylene chain and may have, in the aryl skeleton, one or more heteroatoms selected from O, N, P and S. The definition C_{7-19}-aralkyl group encompasses the widest range defined herein for an arylalkyl group having a total of 7 to 19 atoms in the skeleton and alkylene chain. Specifically, this definition encompasses, for example, the meanings of benzyl and phenylethyl.

Alkylaryl groups (alkaryl groups) in the context of the present invention, unless defined differently, are aryl groups which are substituted by alkyl groups, may have one C_{1-8}-alkylene chain and may have, in the aryl skeleton, one or more heteroatoms selected from O, N, P and S. The definition C_{7-19}-alkylaryl group encompasses the widest range defined herein for an alkylaryl group having a total of 7 to 19 atoms in the skeleton and alkylene chain. Specifically, this definition encompasses, for example, the meanings of tolyl or 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl.

The term *intermediate* used in the context of the present invention describes the substances which occur in the process according to the invention and are prepared for further chemical processing and are consumed or used therein in order to be converted to another substance. The intermediates can often be isolated and intermediately stored or are used without prior isolation in the subsequent reaction step. The term "intermediate" also encompasses the generally unstable and short-lived intermediates which occur

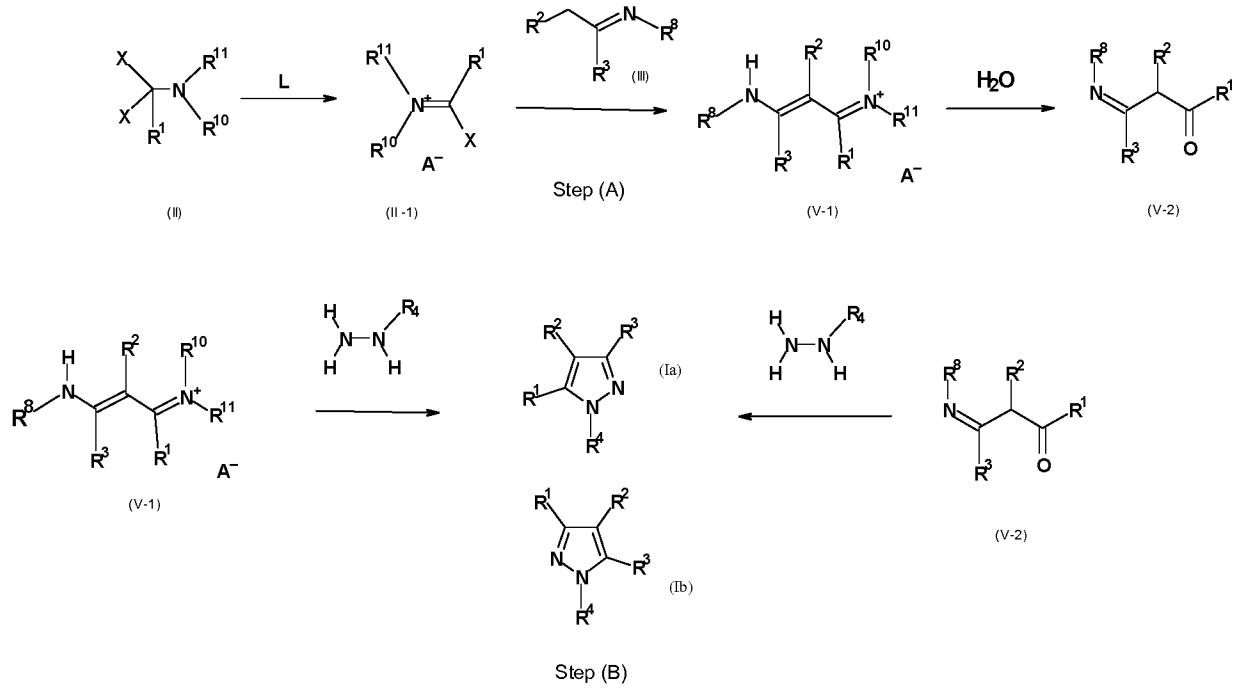
transiently in multistage reactions (staged reactions) and to which local minima in the energy profile of the reaction can be assigned.

The inventive compounds may be present as mixtures of any different isomeric forms possible, especially of stereoisomers, for example E and Z isomers, threo and erythro isomers, and optical isomers, but if appropriate also of tautomers. Both the E and the Z isomers are disclosed and claimed, as are the threo and erythro isomers, and also the optical isomers, any mixtures of these isomers, and also the possible tautomeric forms.

Process description

The process is illustrated in Scheme 1:

Scheme 1:



Step (A)

In step (A), α,α-dihaloalkylamines of the formula (II) are first reacted, in the presence of a Lewis acid [L], with compounds of the formula (III) to form compounds of formula (II-1). Compounds of formula (II-1) are new.

Preferred compounds of the general formula (II) are *N*,*N*-dimethyl-1,1,2-trifluoro-2-(trifluoromethoxy)-ethanamine, *N*,*N*-diethyl-1,1,2-trifluoro-2-(trifluoromethoxy)-ethanamine, *N*,*N*-dimethyl-1,1,2-trifluoro-2-(pentafluoroethoxy)-ethanamine, *N*,*N*-diethyl-1,1,2-trifluoro-2-(pentafluoroethoxy)-ethanamine, *N*,*N*-

dimethyl-1,1,2-trifluoro-2-(trifluorothiomethyl)-ethanamine, and *N*,*N*-diethyl-1,1,2-trifluoro-2-(trifluorothiomethyl)-ethanamine.

Compounds of the general formula (II) are used as aminoalkylating agents. Preference is given to *N*,*N*-dimethyl-1,1,2-trifluoro-2-(trifluoromethoxy)-ethanamine, *N*,*N*-diethyl-1,1,2-trifluoro-2-(trifluoromethoxy)-ethanamine. These α,α-dihaloamines can be prepared (cf. Maslennikov, I. G.; Eremin, K. I. *Russ. J. Gen. Chem.* 2011, 81, 1741-1742, CAN 155:509447).

In a preferred embodiment of the process according to the invention, the α,α-dihaloalkylamine is first reacted with Lewis acid [L], for example BF_3, $AlCl_3$, AlF_2Cl_2, AlF_3Cl and then the mixture of the compound of the formula (III) is added in substance or dissolved in a suitable solvent (cf. WO 2008/022777).

α,α-Dihaloalkylamines are reacted with Lewis acids (preparation of the iminium salts of the formula (II-1) according to the teaching of WO 2008/022777. According to the invention, the reaction is effected at temperatures of –20°C to +40°C, preferably at temperatures of –20°C to +30°C, more preferably at -10 to 20°C and under standard pressure. Due to the hydrolysis sensitivity of the α,α-dihaloalkylamines, the reaction is conducted in anhydrous apparatus under inert gas atmosphere.

The reaction time is not critical and may, according to the batch size and temperature, be selected within a range between a few minutes and several hours.

According to the invention, 1 mol of the Lewis acid [L] is reacted with equimolar amounts of the α,α-dihaloalkylamine of the formula (II).

For the process according to the invention 1 to 2 mol, preferred 1 to 1,5 mol, most preferred 1 to 1,2 mol of the α,α-dihaloalkylamine of the formula (II) is reacted with 1 mol compound of formula (III).

Suitable solvents are, for example, aliphatic, alicyclic or aromatic hydrocarbons, for example petroleum ether, n-hexane, n-heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin, and halogenated hydrocarbons, for example chlorobenzene, dichlorobenzene, dichloromethane, chloroform, tetrachloromethane, dichloroethane or trichloroethane, ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, methyl tert-amyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane or anisole; nitriles such as acetonitrile, propionitrile, n- or isobutyronitrile or benzonitrile; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylformanilide, N-methylpyrrolidone or hexamethylphosphoramide; sulphoxides such as dimethyl sulphoxide or sulphones such as sulpholane. Particular preference is given, for example, to THF, acetonitriles, ethers, toluene, xylene, chlorobenzene, n-hexane, cyclohexane or methylcyclohexane, and very particular preference, for example, to acetonitrile, THF, ether or dichloromethane.

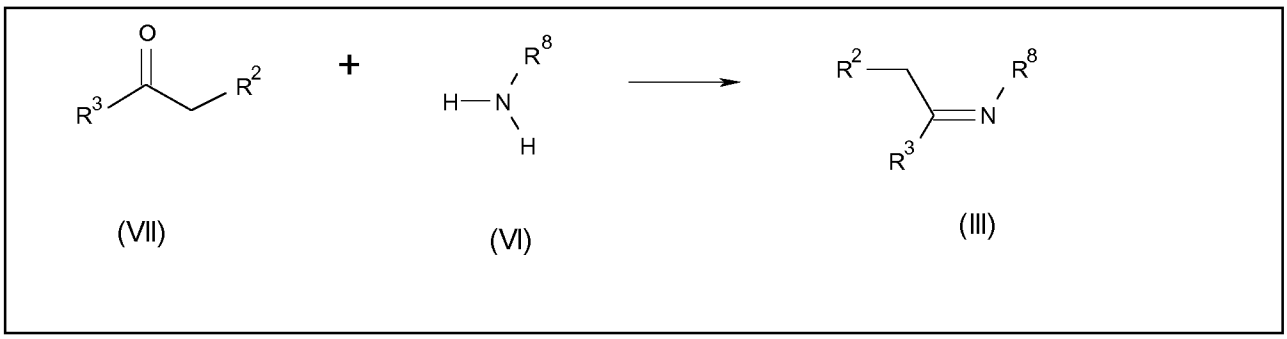
The intermediates of the formula (V-1) can be used in the cyclization step without prior workup.

Alternatively, the intermediates (V-1) can be isolated by suitable workup steps, characterized and optionally further purified or transformed into enaminoketones (V-2).

Compounds (V-2) are formed during the treatment of compounds (V-1) with water. In order to achieve the full transformation of (V-1) into (V- 2), 1 mol to 50 mol, preferably 2 to 20 mol of the water for 1 mol of the compound of formula (V-1) is used. This transformation proceeds without solvent exchange. Compounds (V-2) could also be isolated and additionally purified, or directly converted in step (B) to the pyrazole of Formula (I) upon their treatment with hydrazine of the formula NH_2-NHR^4.

Starting ketimines (III) can be prepared from ketones (VII) and amines (VI).

Scheme 2:



The reaction of compound (VII) and (VI) according to the invention is effected at temperatures of -40 °C to +120 °C, preferably at temperatures of +20 °C to +100 °C, more preferably at 20 °C to +60 °C and under standard pressure.

For the process according to the invention 0,9 to 2 mol, preferred 1 to 1,8 mol, most preferred 1 to 1,5 mol of the compound of the formula (VI) is reacted with 1 mol compound of the formula (VII).

The reaction time is not critical and may, according to the batch size and temperature, be selected within a range between a few and many hours.

Suitable solvents are, for example, aliphatic, alicyclic or aromatic hydrocarbons, for example petroleum ether, n-hexane, n-heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin, and halogenated hydrocarbons, for example chlorobenzene, dichlorobenzene, dichloromethane, chloroform, tetrachloromethane, dichloroethane or trichloroethane, ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, methyl tert-amyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane

or anisole; nitriles such as acetonitrile, propionitrile, n- or isobutyronitrile or benzonitrile; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylformanilide, N-methylpyrrolidone or hexamethylphosphoramide; sulphoxides such as dimethyl sulphoxide or sulphones such as sulpholane, alkohols such as methanol, ethanol, isopropanolm butanol. Particular preference is given, for example, to THF, acetonitriles, ethers, toluene, xylene, chlorobenzene, n-hexane, cyclohexane or methylcyclohexane, ethanol and very particular preference, for example, to acetonitrile, THF, ether, dichloromethane, ethanol.

Step (B)

According to the invention, 1 mol to 2 mol, preferably 1 to 1.5 mol of the hydrazine of the formula NH_2-NHR for 1 mol of the compound of formula (V-1 or V-2) is used.

The cyclization in step (B) of the compound of formula (V-1 ord V-2) is effected at temperatures of -40 °C to +80 °C, preferably at temperatures of +20 °C to +70 °C, more preferably at 30°C to +60 °C and under standard pressure.

The reaction time is not critical and may, according to the batch size, be selected within a relatively wide range.

Typically, the cyclization step (B) is effected without changing the solvent.

Typically the cyclization of compound of the formula (V-1 and V-2) proceeds under acidic condition.

Preference is given to mineral acids, for example H_2SO_4, HCl, HF, HBr, HI, H_3PO_4 or organic acids, for example CH3COOH, CF_3COOH, p-toluenesulphonic acid, methanesulphonic acid, trifluoromethanesulphonic acid.

According to the invention, 0.1 mol to 2 mol, preferably 0.1 to 1.5 mol of the acid for 1 mol of the compound of formula (V-I, V-II) is used. Suitable solvents are, for example, aliphatic, alicyclic or aromatic hydrocarbons, for example petroleum ether, n-hexane, n-heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin, and halogenated hydrocarbons, for example chlorobenzene, dichlorobenzene, dichloromethane, chloroform, tetrachloromethane, dichloroethane or trichloroethane, ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, methyl tert-amyl ether, dioxane, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-diethoxyethane or anisole; alcohols such as methanol, ethanol, isopropanol or butanol, nitriles such as acetonitrile, propionitrile, n- or isobutyronitrile or benzonitrile; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylformanilide, N-methylpyrrolidone or hexamethylphosphoramide; sulphoxides such as dimethyl sulphoxide or sulphones such as sulpholane. Particular preference is given, for example, to acetonitrilestoluene, xylene,

chlorobenzene, n-hexane, cyclohexane or methylcyclohexane, and very particular preference, for example, to acetonitriles, THF, toluene or xylene. After the reaction has ended, for example, the solvents are removed and the product is isolated by filtration, or the product is first washed with water and extracted, the organic phase is removed and the solvent is removed under reduced pressure.

The compounds of the formula (Iab) where $R^2 = COOR^4$ can then be converted to pyrazole acids of the formula (I) $R^2 = COOH$.

The inventive compounds (Ia) and (Ib) are used for preparation of active fungicidal ingredients.

Example 1

***N,N*-dimethyl-1,1,2-trifluoro-2-(trifluoromethoxy)-ethanamine (II-1)**

1,1,2-trifluoro-2-(trifluoromethoxy)ethene (0.44 mL, 3.97 mmol) was liquefied at -78 °C into a sealed tube equipped with a magnetic stirbar under inert atmosphere using a dry ice/acetone bath. A solution of dimethylamine (2M in THF, 2 mL, 4 mmol) was added via syringe, the mixture was raised to max. 20 °C over 20min to avoid polymerization of THF. The formed product was used for further transformation without purification.

Example 2

3-(fluoro(trifluoromethoxy)methyl)-5-(trifluoromethyl)-1*H*-pyrazole (I-1).

To the mixture solution of the ***N,N*-dimethyl-1,1,2-trifluoro-2-(trifluoromethoxy)-ethanamine (II-1) (3.95 mmol)** was added BF_3-Et_2O (0.5 mL, 3.95 mmol) *via* syringe. The solution was vigorously stirred for 15min. The resulting biphasic mixture was then added onto a solution of *N*-benzyl-1,1,1-trifluoropropan-2-imine (660 mg, 3.28 mmol) in distilled THF (4 mL) under inert atmosphere into a Schlenk vessel *via* syringe. The mixture was stirred at room temperature for 30min. Hydrazine hydrate (0.24 mL, 4.89 mmol) was added *via* syringe, rapidly followed by conc. H_2SO_4 (0.08 mL, 1.5 mmol), both *via* syringe. The mixture was further stirred 1h at room temperature. The mixture was then evaporated *in vacuo* (>200mbar, 45 °C max).

The crude product was purified by flash chromatography (Et_2O in pentane 0 to 20%).

Yield: 500mg, 60%; brown oil.

^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 12.2 (s.br, N*H*), 6.78 (d, C*H*FOCF_3, $^2J_{H\text{-}F}$ = 57.5 Hz), 6.77 (s, CH_{arom}), ppm.

^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -60.0 (d, CHFOCF_3, $^4J_{H\text{-}F}$ = 5 Hz), -62.3 (s, CF_3), -121.7 (qd, CH*F*OCF_3, $^2J_{H\text{-}F}$ = 57 Hz, $^4J_{H\text{-}F}$ = 5 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 140.8 (m, *C*CF_3 and *C*CHFOCF_3), 120.3 and 121.0 (*C*F_3 and O*C*F_3, $^1J_{C\text{-}F}$ = 269 and 262 Hz), 104.0 (*C*H_{arom}), 99.1 (dd, *C*H$FOCF_3$, $^1J_{C\text{-}F}$ = 230 Hz, $^3J_{C\text{-}F}$ = 3.5 Hz) ppm.

HRMS (ESI) calcd for $C_6H_4F_7N_2O$ [M+H]: 253.0206. Found: 253.0213.

Example 3

3-(fluoro(trifluoromethoxy)methyl)-5-(perfluoroethyl)-1*H*-pyrazole (I-2). (preparation see Example 2 using *N*-benzyl-3,3,4,4,4-pentafluorobutan-2-imine (500 mg, 1.73 mmol) and **II-1** (2.08 mmol)).

Yield: 99% (by ^{19}F NMR); yellow oil.

^1H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 12.59 (s.br, N*H*), 6.82 (s, CH_{arom}), 6.79 (d, C*H*FOCF_3, $^2J_{H-F}$ = 57.5 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -59.9 (d, CHFOCF_3, $^4J_{H-F}$ = 5 Hz), -85.1 (s, CF_2CF_3), -113.6 (s, CF_2CF_3), -121.8 (dq, CH*F*OCF_3, $^2J_{H-F}$ = 57.4 Hz, $^4J_{H-F}$ = 4.9 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 140.9 and 139.2 (m, *C*CHFOCF_3 and *C*C_2F_5), 120.7 (q, CHFO*C*F_3, J = 263 Hz), 118.4 (qt, CF_2CF_3, $^1J_{C-F}$ = 286 Hz, $^2J_{C-F}$ = 40 Hz), 109.8 (tq, *C*F_2CF_3, $^1J_{C-F}$ = 252 Hz, $^2J_{C-F}$ = 40 Hz), 105.2 (*C*H_{arom}), 98.8 (dd, *C*HFOCF_3, $^1J_{C-F}$ = 230 Hz, $^3J_{C-F}$ = 2.5 Hz) ppm.

HRMS (ESI) calcd for $C_7H_4F_9N_2O$ [M+H]: 303.0174. Found: 303.0168. b.p. 80-82°C.

Example 4

Mixture 3-(difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole and 5-(difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1*H*-pyrazole (7:3). (preparation see Example 2, using *N*-benzyl-1,1-difluoropropan-2-imine (3.35 mmol) and **II-1** (3.97 mmol))

Yield: 84% (by ^{19}F NMR, 7/3 **I-3**:**I-4**, both isomers separated by chromatography); both yellow oils.

*3-(difluoromethyl)-5-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**I-3**).*

^1H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 6.71 (dt, C*H*F_2, $^2J_{H-F}$ = 53.5 Hz, $^4J_{H-F}$ = 1.2 Hz), 6.70 (d, C*H*FOCF_3, $^2J_{H-F}$ = 57 Hz), 4.00 (s, NCH_3), 6.68 (s, CH_{arom}) ppm.

^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -59.3 (m, OCF_3), -113.4 (m, CHF_2, $^2J_{H-F}$ = 53.5 Hz), -119.8 (d, CH*F*OCF_3, $^2J_{H-F}$ = 57.5 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 144.8 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 29 Hz), 136.9 (t, *C*CHF_2, $^2J_{C-F}$ = 26 Hz), 121.1 (q, OCF_3, $^1J_{C-F}$ = 261 Hz), 108.3 (t, *C*HF_2, $^1J_{C-F}$ = 237 Hz), 105.3 (t, *C*H_{arom}), 101.0 (qd, *C*HFOCF3, $^1J_{C-F}$ = 227 Hz, $^3J_{C-F}$ = 4 Hz), 38.5 (N*C*H_3), ppm.

HRMS (ESI) calcd for $C_7H_7F_6N_2O$ [M+H]: 249.0457. Found: 249.0460.

*5-(difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1-methyl-1H-pyrazole (**I-4**).*

^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 6.76 (d, C*H*FOCF_3, $^2J_{H-F}$ = 56 Hz), 6.68 (s, CH_{arom}), 6.64 (t, C*H*F_2, $^2J_{H-F}$ = 55 Hz), 3.98 (s, NCH_3) ppm.

^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -59.6 (d, OCF_3, $^4J_{H-F}$ = 5.5 Hz), -112.2 (d, CH*F*$_2$, $^2J_{H-F}$ = 55 Hz), -121.6 (qd, CH*F*OCF_3, $^2J_{H-F}$ = 56 Hz, $^4J_{H-F}$ = 5.5 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 145.7 (t, *C*CHF_2, $^2J_{C-F}$ = 30 Hz), 135.5 (d, *C*CHFOCF_3, $^2J_{C-F}$ = 26 Hz), 120.8 (q, OCF_3, $^1J_{C-F}$ = 263 Hz), 110.5 (t, *C*HF_2, $^1J_{C-F}$ = 234 Hz), 104.8 (*C*H_{arom}), 98.5 (qd, *C*HFOCF_3, $^1J_{C-F}$ = 228 Hz, $^3J_{C-F}$ = 4 Hz), 38.5 (N*C*H_3), ppm.

HRMS calcd for $C_7H_7F_6N_2O$ [M+H]: 249.0457. Found: 249.0458.

Example 5

3-(fluoro(trifluoromethoxy)methyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrazole (I-5). (preparation according to example 2, using *N*-benzyl-1,1,1-trifluoropropan-2-imine (3.35 mmol) and **II-1** (3.97 mmol))

Yield: 66% (by ^{19}F NMR); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 6.84 (s, CH_{arom}), 6.71 (d, C*H*FOCF_3, $^2J_{H-F}$ = 57 Hz), 4.02 (s, NCH_3) ppm.

^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -59.3 (d, CHFOC*F*$_3$, $^4J_{H-F}$ = 5 Hz), -60.9 (s, C*F*$_3$), -120.1 (qd, CH*F*OCF_3, $^2J_{H-F}$ = 57 Hz, $^4J_{H-F}$ = 5.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 144.8 (d, *C*CHFOCF_3, $^1J_{C-F}$ = 30 Hz), 133.6 (*C*CF_3, $^2J_{C-F}$ = 40 Hz), 121.0 and 119.6 (q, O*C*F_3 and *C*F_3, $^1J_{C-F}$ = 261 and 269 Hz), 105.8 (*C*H_{arom}), 100.8 (qd, CHFO*C*F_3, $^1J_{C-F}$ = 227 Hz, $^3J_{C-F}$ = 4 Hz), 38.6 (N*C*H_3) ppm.

HRMS (ESI) calcd for $C_7H_6F_7N_2O$ [M+H]: 267.0363. Found: 267.0347.

Example 6

3-(fluoro(trifluoromethoxy)methyl)-1-methyl-5-(perfluoroethyl)-1*H*-pyrazole (I-6). (preparation according to example 2, using *N*-benzyl-1,1,1-trifluoropropan-2-imine (3.35 mmol) and **II-1** (3.97 mmol))

Yield: 81% (by ^{19}F NMR); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 6.84 (s, CH_{arom}), 6.72 (d, $CHFOCF_3$, $^{2}J_{H-F}$ = 57.2 Hz), 4.04 (s, NCH_3) ppm.

^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -59.3 (d, $CHFOCF_3$, $^{2}J_{H-F}$ = 5.4 Hz), -83.9 (s, CF_2CF_3), -110.7 (CF_2CF_3), -120.3 (dq, $CHFOCF_3$, $^{2}J_{H-F}$ = 57.2 Hz, $^{4}J_{H-F}$ = 5.3 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 145.2 (d, $CCHFOCF_3$, $^{2}J_{C-F}$ = 29.5 Hz), 131.6 (t, CC_2F_5, $^{2}J_{C-F}$ = 28.7 Hz), 121.1 (q, $CHFOCF_3$, $^{1}J_{C-F}$ = 262 Hz), 118.6 (qt, CF_2CF_3, $^{1}J_{C-F}$ = 286.3 Hz, $^{2}J_{C-F}$ = 37.2 Hz), 109.9 (tq, CF_2CF_3, $^{1}J_{C-F}$ = 253.5 Hz, $^{2}J_{C-F}$ = 40 Hz), 107.4 (CH_{arom}), 100.7 (dd, $CHFOCF_3$, $^{1}J_{C-F}$ = 227.4 Hz, $^{4}J_{C-F}$ = 4.3 Hz), 39.5 (NCH_3) ppm.

HRMS (ESI) calcd for $C_8H_6F_9N_2O$ [M+H]: 317.0331. Found: 317.0298.

Example 7

(*E/Z*)-*N*-(4-(benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-ylidene)-N-methylmethanaminium tetrafluoroborate (V-1-1).

1,1,2-trifluoro-2-(trifluoromethoxy)ethene (0.44 mL, 3.97 mmol) was liquefied at -78 °C into a sealed tube equipped with a magnetic stirbar under inert atmosphere using a dry ice/acetone bath. A solution of dimethylamine (2M in THF, 2 mL, 4 mmol) was added via syringe, the mixture was raised to max. 20 °C over 20min. BF_3-Et_2O (0.51 mL, 4.02 mmol) was added *via* syringe, the solution was vigorously stirred for 15min. The resulting biphasic mixture was then added onto a solution of *N*-benzyl-1,1-difluoropropan-2-imine (728 mg, 3.97 mmol) in distilled THF (0.8-1 mol/L) under inert atmosphere into a Schlenk vessel *via* syringe. The mixture was stirred at room temperature for 30min. The mixture was directly concentrated *in vacuo*, to yield the vinamidinium intermediate as thick orange oil (1.62 g, 92%).

^{1}H NMR (400 MHz, CD_3CN; Me_4Si): δ = 8.33 (s.br, N*H*), 7.47 to 7.35 (m, 5H, arom), 6.81 (d, $CHFOCF_3$, $^{2}J_{H-F}$ = 54.1 Hz), 6.64 (t, CHF_2, $^{2}J_{H-F}$ = 52.6 Hz), 5.14 (s, $CHCN(Me)_2$), 4.56 (d, CH_2NH), 3.35 (s.br, $C=N(CH_3)_2$) ppm.

^{19}F NMR (376 MHz, CD_3CN; $CFCl_3$): δ = -59.8 (d, $CHFOCF_3$, $^{4}J_{H-F}$ = 4.8 Hz), -120.6 (d, CHF_2, $^{2}J_{H-F}$ = 53.1 Hz), -129.1 (d, $CHFOCF_3$, $^{2}J_{H-F}$ = 54.5 Hz), -151.5 (s, BF_4^-) ppm.

^{13}C NMR (100 MHz, CD_3CN; Me_4Si): δ = 164.6 (d, $COCHFOCF_3$, $^{2}J_{C-F}$ = 25.4 Hz), 159.9 (t, $CCHF_2$, $^{2}J_{C-F}$ = 23.3 Hz), 135.4, 130.0, 129.5, 129.0 (arom.), 121.6 (q, OCF_3, $^{1}J_{C-F}$ = 263.3 Hz), 111.0 (td, CHF_2, $^{1}J_{C-F}$ = 244.8 Hz, $^{5}J_{C-F}$ = 4.3 Hz), 100.9 (d, $CHFOCF_3$, $^{1}J_{C-F}$ = 238.3 Hz), 87.3 ($CHCN^{+}(Me)_2$), 49.8 (CH_2NH) ppm.

Example 8

(*E/Z*)-4-(benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-one (V-2-1).

(*E/Z*)-*N*-(4-(benzylamino)-1,5,5-trifluoro-1-(trifluoromethoxy)pent-3-en-2-ylidene)-*N*-methylmethanaminium tetrafluoroborate (**V-1-1)** (1.62 g, 3.66 mmol) was dissolved in 10 ml of Et_2O before 1 ml of water and 1 mL of 1N HCl were added followed by a vigorous stirring of the mixture (pH of the soluton between 3-4). The mixture was stirred for 1 h at RT, and the organic layer was separated, dried over Na_2SO_4, filtered and evaporated *in vacuo*, to yield (V-2-1) as orange oil (1.08 g, 3.30 mmol, 83 %).

^{1}H NMR (400 MHz, $CDCl_3$; Me_4Si): δ = 10.64 (s.br, N*H*), 7.40 to 7.28 (m, 5H, arom), 6.18 (t, C*H*F_2, $^2J_{H\text{-}F}$ = 53.2 Hz), 5.81 (d, C*H*FOCF_3, $^2J_{H\text{-}F}$ = 56.9 Hz), 5.68 (s, C*H*CO), 4.65 (d, CH_2NH) ppm.

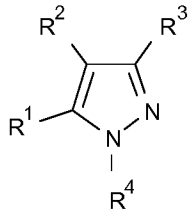
^{19}F NMR (376 MHz, $CDCl_3$; $CFCl_3$): δ = -59.3 (d, CHFOCF_3, $^4J_{H\text{-}F}$ = 4.7 Hz), -119.3 (d, CHF_2, $^2J_{H\text{-}F}$ = 53.1 Hz), -135.5 (dq, CH*F*OCF_3, $^2J_{H\text{-}F}$ = 56.6 Hz, $^4J_{H\text{-}F}$ = 4.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$; Me_4Si): δ = 185.5 (d, *C*=O, $^2J_{C\text{-}F}$ = 25.3 Hz), 157.3 (t, *C*CHF_2, $^2J_{C\text{-}F}$ = 22.0 Hz), 136.1, 129.2, 128.4, 127.3 (arom), 121.2 (q, O*C*F_3, $^1J_{C\text{-}F}$ = 261 Hz), 111.0 (t, *C*HF_2, $^1J_{C\text{-}F}$ = 245 Hz), 101.3 (dq, *C*H$FOCF_3$, $^1J_{C\text{-}F}$ = 245 Hz, $^3J_{C\text{-}F}$ = 2.5 Hz), 87.8 (t, *C*HCO, $^3J_{C\text{-}F}$ = 77.2 Hz), 48.1 (*C*H_2NH) ppm.

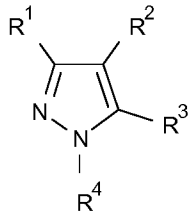
An interaction of (V-2-1) with hydrazine-hydrate according to the example 2 gave 5-(difluoromethyl)-3-(fluoro(trifluoromethoxy)methyl)-1H-pyrazole in 85 % yield.

Claims:

1. Process for preparing 3,5-bis(haloalkyl)pyrazoles of the formula **(Ia)** and **(Ib)**,



(Ia)



(Ib)

in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

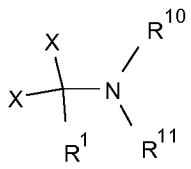
R^4 is selected from H, C_1-C_8 alkyl, aryl, pyridyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

characterized in that in step (A1), α,α-dihaloalkylamines of the formula **(II)**,



(II)

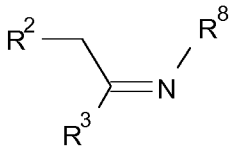
in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

X is independently selected from F, Cl or Br,

R^{10} and R^{11} are each independently selected from C_{1-6}-alkyl, C_{3-8}-cycloalkyl,

are reacted in the presence of Lewis Acid with compounds of the formula **(III)**,



(III)

in which

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

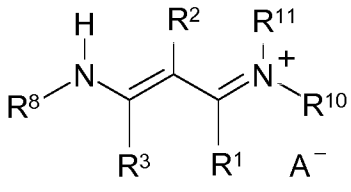
R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

to form the compound of formula **(V-1),**



(V-1)

wherein A^- is BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl;

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl;

R^{10} and R^{11} are each independently selected from C_{1-6}-alkyl, C_{3-8}-cycloalkyl,

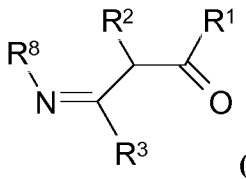
and that in step (B) in the presence of hydrazine

H_2N-NHR^4 **(IV)** wherein

R^4 is selected from H, C_1-C_8 alkyl, aryl or pyridyl

a cyclization of **(V-1)** takes place to form **(Ia/Ib)**.

2. Process according to claim 1, characterized in that in a step (A2) compound **(V-1)** is further reacted with water to compound of formula **(V-2)**



(V-2)

in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

R^2 is selected from H, halogen, COOH, $(C=O)OR^5$, CN and $(C=O)NR^6R^7$;

R^3 are each independently selected from C_1-C_6-haloalkyl alkyl;

R^5 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl;

R^6 and R^7 are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl, C_{7-19}-arylalkyl and C_{7-19}-alkylaryl, or where

R^6 and R^7 together with the nitrogen atom to which they are bonded may form a four-, five- or six-membered ring

R^8 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl;

and that in step (B) in the presence of hydrazine

H_2N-NHR^4 **(IV)** wherein

R^4 is selected from H, C_1-C_8 alkyl, aryl or pyridyl

a cyclization of **(V-2)** takes place to form **(Ia/Ib)**.

3. Process according to claim 1 or 2, characterized in that the radicals in formula **(Ia), (Ib), (II), (III), (IV), (V-1)** and **(V-2)** are

R^1 is selected from CHF-OCF_3 (fluoro(trifluoromethoxy)methyl), CHF-OC_2F_5 (fluoro(pentafluoroethoxy)methyl), CHF-SCF_3 (fluoro(trifluorothiomethyl)methyl), CHF-SC_2F_5 fluoro(pentafluorothioethyl)methyl;

R^2 is selected from H, F, Cl, Br, $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$, CN and $CON(CH_3)_2$, $CON(C_2H_5)_2$;

R^3 is selected from difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, tetrafluoroethyl (CF_3CFH), pentafluoroethyl and 1,1,1-trifluoroprop-2-yl;

R^4 is selected from H, C_1-C_8 alkyl, aryl, pyridyl;

R^8 are each independently selected from methyl, ethyl, *n*-, *iso*-propyl, *n*-, *iso*-, *sec*- und *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenylethyl, C_{7-19}-alkylaryl, tolyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl;

X is independently selected from F or Cl;

R^{10} and R^{11} are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{7-19}-arylalkyl or

R^{10} and R^{11} together with the nitrogen atom to which they are bonded may form a five- membered ring.

4. Process according to claim 1 or 2, characterized in that the radicals in formula **(Ia), (Ib), (II), (III), (IV), (V-1)** and **(V-2)** are

R^1 is selected from fluoro(trifluoromethoxy)methyl, fluoro(pentafluoroethoxy)methyl;

R^2 is selected from H, Cl, CN, $COOC_2H_5$;

R^3 is selected from trifluoromethyl, difluoromethyl, difluorochloromethyl, pentafluoroethyl;

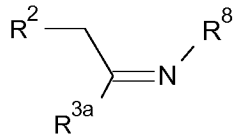
R^4 is selected from H, methyl, ethyl, n-, isopropyl, n-, iso-, sec- and t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, aryl;

R^8 is selected from methyl, ethyl, *n*-, *iso*-propyl, *n*-, *iso*-, *sec*- und *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, C_7-C_{19}-alkylaryl;

X is independently selected from F or Cl;

R^{10} and R^{11} are each independently selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl.

5. Compounds of formula **(III-a)**



(III-a)

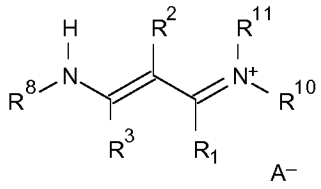
in which

R^2 is H,

R^{3a} is HCF_2, CF_3;

R^8 is benzyl.

6. Compounds of formula **(V-1)**



(V-1)

in which

R^1 is selected from $CHFOCF_3$;

R^2 is H;

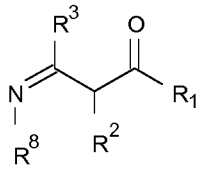
R^3 is selected from CF_2H, CF_3;

R^8 is selected from C_1-C_{12}-alkyl, C_3-C_8-cycloalkyl and benzyl;

R^{10} and R^{11} are each independently selected from C_1-C_5- alkyl;

A^- is selected from BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl.

7. Compounds of formula **(V-2)**



(V-2)

in which

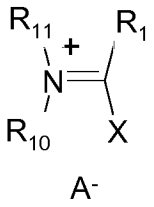
R^1 is selected from $CHFOCF_3$;

R^2 is H;

R^3 is selected from CF_2H, CF_3;

R^8 is selected from C_1-C_{12}-alkyl, C_3-C_8-cycloalkyl and benzyl.

8. Compounds of formula **(II-1):**



in which

R^1 is selected from C_1-C_6-haloalkyl-ethers or C_1-C_6-haloalkyl-thioethers;

X is independently selected from F, Cl or Br,

R^{10} and R^{11} are each independently selected from C_{1-6}-alkyl, C_{3-8}-cycloalkyl and

A^- is selected from BF_4, $AlCl_3F$, AlF_2Cl_2, AlF_3Cl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/064320

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/16 C07C251/26
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 C07C

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

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Y	WO 2014/033164 A1 (BAYER CROPSCIENCE AG [DE]; CENTRE NAT RECH SCIENT [FR]) 6 March 2014 (2014-03-06) cited in the application	1-4,8
A	Scheme 2 page 9 - Preparation of 3,5-dihaloalkyl-4-carboxy-pyrazoles Claims 1-15 Decarboxylation of 3,5-dihaloalkyl-4-carboxy-pyrazoles; claims 1-15	5-7

Y	WO 2008/022777 A2 (BAYER CROPSCIENCE AG [DE]; PAZENOK SERGIY [DE]; NORBERT LUI [DE]; NEEF) 28 February 2008 (2008-02-28) cited in the application	1-4,8
A	Pages 8 to 10 - Acylsäurederivate Pages 10-12 - a -Fluoroamine; claims 1-9	5-7

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

[X] See patent family annex.

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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)

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2016	26/07/2016

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	Sotoca Usina, E

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/064320

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/113829 A1 (BAYER CROPSCIENCE AG [DE]; CENTRE NAT RECH SCIENT [FR]) 8 August 2013 (2013-08-08)	1-4,8
A	claims 1-11	5-7
A	US 2010/274049 A1 (LUI NORBERT [DE] ET AL) 28 October 2010 (2010-10-28) Scheme 1; claims 1-10	1-8
A	EP 2 628 722 A1 (BAYER CROPSCIENCE AG [DE]; CENTRE NAT RECH SCIENT [FR]) 21 August 2013 (2013-08-21) cited in the application claims 1-11	1-8
A	PASHKEVICH ET AL: "3,5-Bis(fluoroalkyl)pyrazoles by reacting bisperfluoroalkyl diketones with hydrazines", ZHURNAL VSESOYUZNOGO KHIMICHESKOGO OBSHCHESTVA,, vol. 26, no. 1, 1 January 1981 (1981-01-01), pages 105-107, XP009179740, cited in the application Page 105 - Scheme	1-8
A	WO 2009/028727 A1 (SUMITOMO CHEMICAL CO [JP]; KUMAMOTO KOJI [JP]; MIYAZAKI HIROYUKI [JP]) 5 March 2009 (2009-03-05) Pages 37-60 Porduction Processes 1-10 : Preparation of the compounds by alkylation of sulfides.; claims 1-9	1-8

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/064320

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Information on patent family members

International application No
PCT/EP2016/064320

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