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Eljárás 3-halogénalkilpirazol-származékok előállítására

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(54) **PROCESS FOR THE PREPARATION OF 3-HALOALKYLPYRAZOLES**

VERFAHREN ZUR HERSTELLUNG VON 3-HALOALKYLPYRAZOLEN

PROCÉDÉS DE PRÉPARATION D'HALOALKYLPYRAZOLES

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(56) References cited:
**WO-A1-2006/045504 WO-A1-2008/003452
WO-A1-2008/141020 WO-A1-2008/145257
WO-A1-2009/147167**

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Description

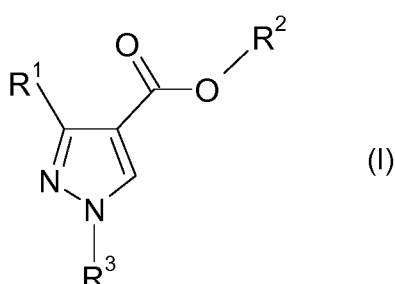
[0001] The present invention relates to N-alkylation of substituted pyrazoles. In particular, the invention relates to the isomerisation of N-alkylated substituted pyrazoles and to the preparation of selected isomers of N-alkylated substituted pyrazoles.

[0002] Fungicides for use in crop protection are produced on a very large scale, e.g. thousands of tons per year. Given the scale on which fungicides are produced, any improvement in the production process can represent significant cost savings.

[0003] N-alkylated substituted pyrazoles, for example ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE), are valuable intermediates in the preparation of a number of fungicides, including Sedaxane, Isopyrazam and others. In DFPE only one of the nitrogen atoms in the pyrazole ring is alkylated.

[0004] According to WO 2006/045504, regioselective N-alkylation of substituted pyrazoles may be achieved by reacting the corresponding substituted pyrazoles with trialkyl phosphates or trialkylphosphonates. However, it would be desirable to increase the yield of the non-iso isomer in order to reduce costs and wastage in commercial production.

[0005] In a first aspect, the invention provides a process for the preparation of a compound of formula I:

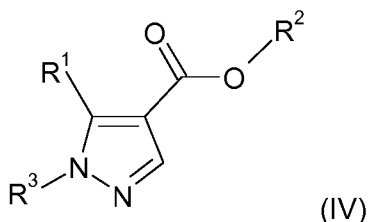


wherein R¹ is C₁-C₄haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

R³ is methyl or ethyl;

comprising reacting a compound of formula IV:



wherein R¹, R² and R³ are as defined for the compound of formula I;

with a methylating or ethylating agent in the presence of an amide.

[0006] The compound of formula IV is referred to herein as the "iso" isomer with respect to compounds of formula I.

[0007] The alkyl groups appearing in the above substituent definitions may be straight-chain or branched and are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl, preferably methyl or ethyl. Halogen is generally fluorine, chlorine, bromine or iodine, preferably fluorine. C₁-C₄haloalkyl groups are derived from the mentioned C₁-C₄alkyl groups and are preferably difluoromethyl or trifluoromethyl.

[0008] Aryl refers to aromatic hydrocarbon ring systems which may be a single ring or multiple rings which are fused together or linked covalently. Examples of aryl groups are phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl, anthracenyl, phenanthrenyl and biphenyl.

[0009] Heteroaryl refers to aromatic ring systems comprising mono-, bi- or tricyclic systems wherein at least one oxygen, nitrogen or sulfur atom is present as a ring member. Examples are furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, benzothiophenyl, benzofuranyl, benzimidazolyl, indazolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl and naphthyridinyl.

[0010] R² for example may be optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl.

This means that the alkyl, aryl and heteroaryl groups may or may not carry one or more identical or different substituents. Normally not more than three substituents are present at the same time. Examples of substituents are: halogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkenyl, haloalkenyl, cycloalkenyl, alkynyl, haloalkynyl, alkoxy, haloalkoxy, cycloalkoxy, alkenyloxy, haloalkenyloxy, alkynyloxy, haloalkenyloxy, alkylthio, haloalkylthio, cycloalkylthio, alkenylthio, alkynylthio, alkylcarbonyl, haloalkylcarbonyl, cycloalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkoxyalkyl, cyano, nitro, hydroxy, mercapto, amino, alkylamino and dialkylamino.

[0011] Preferred optional substituents are C₁-C₈alkyl, halo-C₁-C₈alkyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkyl-C₁-C₈alkyl, C₂-C₈ alkenyl, halo-C₂-C₈ alkenyl, C₃-C₈ cyclo-C₂-C₈ alkenyl, C₂-C₈ alkynyl, halo-C₂-C₈ alkynyl, C₁-C₈ alkoxy, halo-C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, C₂-C₈ alkenyloxy, halo-C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, halo-C₂-C₈ alkynyloxy, C₁-C₈ alkylthio, halo-C₁-C₈ alkylthio, C₃-C₈ cycloalkylthio, C₂-C₈ alkenylthio, C₂-C₈ alkynylthio, C₁-C₈ alkylcarbonyl, halo-C₁-C₈ alkylcarbonyl, C₃-C₈ cycloalkylcarbonyl, C₂-C₈ alkenylcarbonyl, C₂-C₈ alkynylcarbonyl, C₁-C₈ alkoxy-C₁-C₈ alkyl, cyano, nitro, hydroxy, mercapto, amino, C₁-C₈ alkylamino and C₁-C₈ dialkylamino.

[0012] More preferred optional substituents are C₁-C₄ alkyl, halo-C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl-C₁-C₄ alkyl, C₂-C₄ alkenyl, halo-C₂-C₄ alkenyl, C₃-C₆ cyclo-C₂-C₄ alkenyl, C₂-C₄ alkynyl, halo-C₂-C₄ alkynyl, C₁-C₄alkoxy, halo-C₁-C₄alkoxy, C₃-C₆ cycloalkoxy, C₂-C₄ alkenyloxy, halo-C₂-C₄ alkenyloxy, C₂-C₄ alkynyloxy, halo-C₂-C₄ alkynyloxy, C₁-C₄ alkylthio, halo-C₁-C₄ alkylthio, C₃-C₆ cycloalkylthio, C₂-C₄ alkenylthio, C₂-C₄ alkynylthio, C₁-C₄ alkylcarbonyl, halo-C₁-C₄ alkylcarbonyl, C₃-C₆ cycloalkylcarbonyl, C₂-C₄ alkenylcarbonyl, C₂-C₄ alkynylcarbonyl, C₁-C₄ alkoxy-C₁-C₄ alkyl, cyano, nitro, hydroxy, mercapto, amino, C₁-C₄ alkylamino and C₁-C₄ dialkylamino.

[0013] More preferred optionally substituted substituents are C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, halo-C₁-C₄ alkoxy, halogen, hydroxy, cyano, nitro and amino.

[0014] Typical examples for optionally substituted aryl include 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,3-dicyanophenyl, 2,4-dicyanophenyl, 2,5-dicyanophenyl, 2,6-dicyanophenyl, 3,4-dicyanophenyl, 3,5-dicyanophenyl, 2,3-bis(trifluoromethyl)phenyl, 2,4-bis(trifluoromethyl)phenyl, 2,5-bis(trifluoromethyl)phenyl, 2,6-bis(trifluoromethyl)phenyl, 3,4-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, 2,3-bis(trifluoromethoxy)phenyl, 2,4-bis(trifluoromethoxy)phenyl, 2,5-bis(trifluoromethoxy)phenyl, 2,6-bis(trifluoromethoxy)phenyl, 3,4-bis(trifluoromethoxy)phenyl, 3,5-bis(trifluoromethoxy)phenyl, 2-chloro-5-fluorophenyl, 2-fluoro-5-methylphenyl, 2-fluoro-5-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-methylphenyl, 2-chloro-5-methoxyphenyl, 5-fluoro-2-methylphenyl, 5-chloro-2-methylphenyl, 5-methoxy-2-methylphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-methoxyphenyl and 2-methoxy-5-methylphenyl.

[0015] Typical examples for optionally substituted heteroaryl include 5-methyl-3-trifluoromethylpyrazol-1-yl, 3-methyl-5-trifluoromethylpyrazol-1-yl, 3,5-bis-trifluoromethylpyrazol-1-yl, 3,5-dimethylpyrazol-1-yl, 5-ethyl-3-trifluoromethylpyrazol-1-yl, 5-methyl-3-trifluoromethoxypyrazol-1-yl, 2-methyl-4-trifluoromethylimidazol-1-yl, 4-methyl-2-trifluoromethylimidazol-1-yl, 2,4-bis-trifluoromethylimidazol-1-yl, 2,4-dimethylimidazol-1-yl, 2-ethyl-4-trifluoromethylimidazol-1-yl, 2-methyl-4-trifluoromethoxyimidazol-1-yl, 5-methyl-3-trifluoromethyl[1,2,4]triazol-1-yl, 3-methyl-5-trifluoromethyl[1,2,4]triazol-1-yl, 3,5-bis-trifluoromethyl[1,2,4]triazol-1-yl and 3,5-dimethyl[1,2,4]triazol-1-yl, 5-ethyl-3-trifluoromethyl[1,2,4]triazol-1-yl, and 5-methyl-3-trifluoromethoxy[1,2,4]triazol-1-yl.

[0016] Cycloalkyl on its own or as part of another substituent is, depending upon the number of carbon atoms mentioned, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0017] Alkoxy on its own or as part of another substituent is, depending upon the number of carbon atoms mentioned, for example methoxy, ethoxy, 1-propoxy, 2-propoxy, n-butoxy, 2-n-butoxy, or 2-tert-butoxy.

[0018] Alkenyl on its own or as part of another substituent is, depending upon the number of carbon atoms mentioned, for example, ethenyl, allyl, propen-1-yl, buten-2-yl, buten-3-yl, penten-1-yl, penten-3-yl, hexen-1-yl or 4-methyl-penten-3-yl.

[0019] Alkynyl on its own or as part of another substituent is, depending upon the number of carbon atoms mentioned, for example, ethynyl, propyn-1-yl, propyn-2-yl, butyn-1-yl, butyn-2-yl, 1-methyl-2-butyne, hexyn-1-yl or 1-ethyl-2-butyne.

[0020] Preferably, R¹ is difluoromethyl or trifluoromethyl;

[0021] Preferably R² is C₁-C₈ alkyl, phenyl, or phenyl-C₁-C₈ alkyl, wherein the alkyl, phenyl and phenylalkyl are each optionally substituted with one or more of, e.g. 1 to 3, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, halo-C₁-C₄ alkoxy, halogen, hydroxy, cyano, nitro and amino. More preferably R² is C₁-C₈ alkyl or C₁-C₈ haloalkyl, phenyl or benzyl, wherein the phenyl and benzyl are each optionally substituted with halogen, e.g. 1 to 3 halogen atoms. Even more preferably

R² is C₁-C₆ alkyl, e.g. C₁-C₄ alkyl. Most preferably R² is methyl or ethyl.

[0022] Preferably R³ is methyl.

[0023] The processes according to the invention are suitable preferably for the preparation of compounds of formula I wherein R¹ is difluoromethyl or trifluoromethyl; R² is C₁-C₆ alkyl, e.g. ethyl; and R³ is methyl.

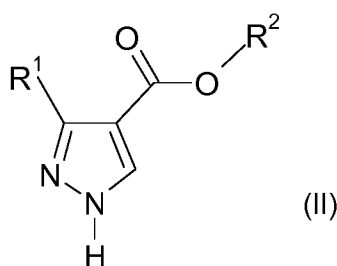
[0024] The processes according to the invention are especially suitable for the preparation of compounds of formula I wherein R¹ is difluoromethyl.

[0025] The processes according to the invention are very especially suitable for the preparation of compounds of formula I wherein R¹ is difluoromethyl, R² is ethyl, and R³ is methyl.

[0026] The processes according to the invention are also very especially suitable for the preparation of compounds of formula I wherein R¹ is trifluoromethyl; R² is ethyl, and R³ is methyl.

[0027] The compound of formula IV may be provided as a mixture comprising the compound of formula IV and the compound of formula I. For example, compounds of formula IV may be produced by N-alkylating the corresponding pyrazole. This will generally result in a mixture of compounds of formula IV and formula I. The present invention provides a process for increasing the proportion of the compound of formula I in a mixture comprising a compound of formula I and a compound of formula IV.

[0028] The compound of formula IV may be provided as a mixture comprising a compound of formula I and a compound of formula IV, and wherein said mixture is prepared by N-alkylating a compound of formula II:

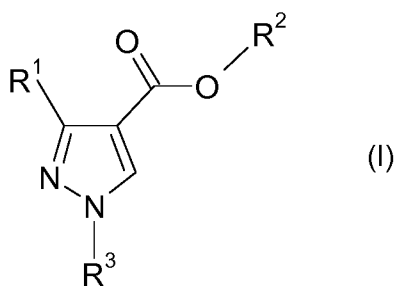


wherein R¹ and R² are as defined for the compound of formula I;

e.g. thereby producing a mixture comprising a compound of formula I and a compound of formula IV.

[0029] It may be advantageous in some cases to N-alkylate the corresponding substituted pyrazole and isomerise any compound of formula IV produced from the alkylation substantially at the same time, e.g. simultaneously. The reaction may be performed in one step.

[0030] Accordingly, in a further aspect, the invention provides a process, e.g. a regioselective process, for the preparation of a compound of formula I:

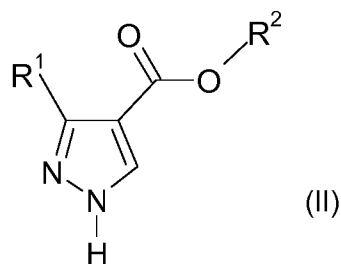


wherein R¹ is C₁-C₄haloalkyl;

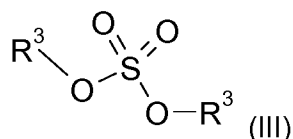
R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

R³ is methyl or ethyl;

comprising reacting a compound of formula II:



wherein R¹ and R² are as defined for the compound of formula I;
with an alkylating agent and an amide wherein the alkylating agents is a compound of formula III



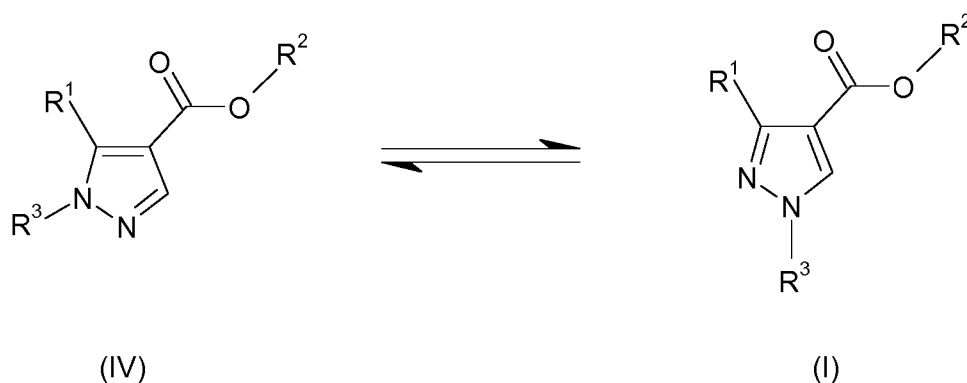
Where R³ is methyl or ethyl.

[0031] Preferred definitions of R¹, R² and R³ are the same as those given above. Most preferably R¹ is difluoromethyl, R² is C₁-C₆ alkyl e.g. ethyl and R³ is methyl.

[0032] Without being bound by theory, it is thought that the alkylating agent and the amide act as a catalyst to inter-convert the compound of formula I and the compound of formula IV, thereby promoting the proportions of the compounds of formula I and IV to thermodynamic equilibrium.

[0033] Also disclosed is a process for inter-converting a compound of formula IV and a compound of formula I according to Scheme I:

Scheme I



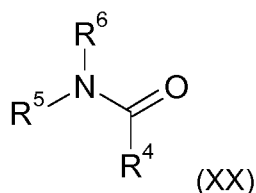
wherein R¹ is C₁-C₄haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and
R³ is methyl or ethyl;

using an alkylating agent and an amide as inter-conversion reagents.

[0034] Preferred definitions of R¹, R² and R³ are the same as those given above. Most preferably R¹ is difluoromethyl, R² is C₁-C₆ alkyl, e.g. ethyl, and R³ is methyl.

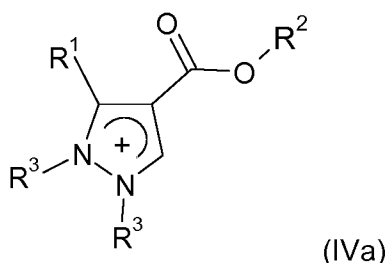
[0035] Preferably the amide is a tertiary amide, e.g. a compound of formula XX:



wherein R⁴ is H or C₁-C₄ alkyl;
 R⁵ is C₁-C₄ alkyl;
 R⁶ is C₁-C₄ alkyl;
 or R⁴ and R⁵ are together C₂-C₅ alkyene;
 or R⁵ and R⁶ are together C₂-C₅ alkyene.

[0036] More preferably R⁴ is H or C₁-C₄ alkyl; R⁵ is C₁-C₄ alkyl; or R⁴ and R⁵ are together C₂-C₅ alkyene; and R⁶ is C₁-C₄ alkyl. Most preferably the amide is N, N-dimethylformamide, N, N-dimethylacetamide or N-methyl-2-pyrrolidone.

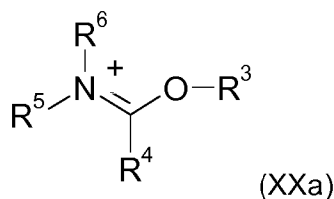
[0037] Without being bound by theory it is understood that inter-conversion of the compound of formula I and IV proceeds via the pyrazolium cation. The alkylating agent is preferably a strong alkylating agent, e.g. one that is capable of alkylating a compound of formula IV to form the corresponding pyrazolium cation, e.g. a compound of formula IVa



wherein R¹, R² and R³ are as defined for a compound of formula IV.

[0038] The alkylating agent and amide are present simultaneously in the reactions of the invention, e.g. as a mixture comprising the alkylating agent and amide. They may be added separately or simultaneously. When added simultaneously, if desired, they may be added as a salt, e.g. formed by alkylation of the amide by the alkylating agent. Similarly, the amide and alkylating agent may form ions *in situ* arising from alkylation of the amide by the alkylating agent, thereby creating an "ionic liquid". In other words, the reactions of the invention may comprise a non-aqueous phase containing dispersed ions arising from alkylation of the amide by the alkylating agent.

[0039] The alkylating agent may be one that is capable of alkylating an amide, preferably a tertiary amide, e.g. to form a compound of formula XXa



wherein R⁴, R⁵ and R⁶ are as defined for a compound of formula XX and R³ is methyl or ethyl.

[0040] Preferably the reactions of the invention employ a methylating agent or ethylating agent, more preferably a methylating agent, e.g. a methylating agent that is capable of methylating a compound of formula IV and/or an amide such as a tertiary amide, e.g. a compound of formula XX. More preferably the methylating agent is a compound of formula III in which R³ is methyl, e.g. dimethylsulphate.

[0041] In one embodiment the alkylating agent is dimethylsulphate and the amide is N, N-dimethylformamide. In another embodiment the alkylating agent is dimethylsulphate and the amide is N, N-dimethylacetamide. In another embodiment the alkylating agent is dimethylsulphate and the amide is N-methyl-2-pyrrolidone.

[0042] The reaction according to the invention can be carried out in an inert solvent, preferably an anhydrous inert solvent. Suitable solvents are, for example, xylene, mesitylene, tert-butyl benzene, chlorobenzene, 1,2-dichlorobenzene,

Decalin, dibutyl ether, dipentyl ether, diphenyl ether and anisole. The reaction according to the invention is preferably carried out neat, e.g. without an additional solvent.

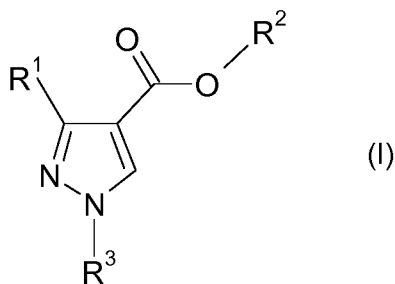
[0043] The temperature of the reaction in which the compound of formula IV is converted into the compound of formula I may be carried out at a temperature of e.g. 50 to 250°C, e.g. 100 to 200°C, e.g. 140 to 180°C. Preferably the reaction is performed at least 100°C, at least 120°C, at least 140°C, at least 160°C. A person skilled in the art would be able to optimise the reaction to find the most suitable temperature.

[0044] The alkylating agent may be present in the reaction at 0.05 molar equivalents to 5 molar equivalents. We have found that increasing the concentration of alkylating agent increases the rate at which inter-conversion takes place, however larger amount of alkylating agent can affect yield. The amount of alkylating agent is preferably less than 1 molar equivalent. Preferably the alkylating agent is 0.2 molar equivalents to 0.7 molar equivalents, most preferably 0.3 molar equivalents to 0.5 molar equivalents. Equivalents are relative to the molar amount of the compound of formula IV or the compound of formula IV and compound of formula I when both are present.

[0045] The amide may be present in the reaction at 0.1 molar equivalents to 10 molar equivalents, preferably 0.2 molar equivalents to 2 molar equivalents, most preferably 0.5 molar equivalents to 1.5 molar equivalents. Equivalents are relative to the molar amount of the compound of formula IV or the compound of formula IV and the compound of formula I when both are present. In one embodiment the alkylating agent and amide are present in a catalytic amount.

[0046] WO 2008/145257 describes synthesis routes to N-alkylated substituted pyrazoles using methylhydrazine. The use of methylhydrazine instead of hydrazine allows synthesis of N-alkylated substituted pyrazoles in which a methyl group is placed on the desired pyrazole nitrogen atom thereby avoiding the need for a separate step for alkylation. The present invention now provides an alkylation step that allows synthesis of the non-iso isomers with high regioselectivity. This makes a route involving hydrazine more feasible.

[0047] In a further aspect, the invention provides a process, e.g. a regioselective process, for the preparation of a compound of formula I:



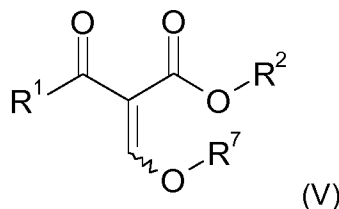
wherein R¹ is C₁-C₄haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

R³ is methyl or ethyl;

comprising

a. reacting a compound of formula V:

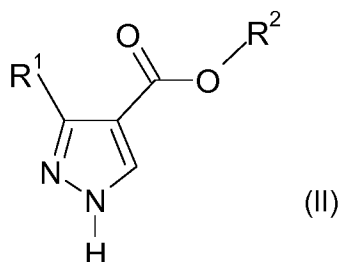


wherein R¹ is C₁-C₄ haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

R⁷ is hydrogen, optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

with hydrazine to produce a compound of formula II:

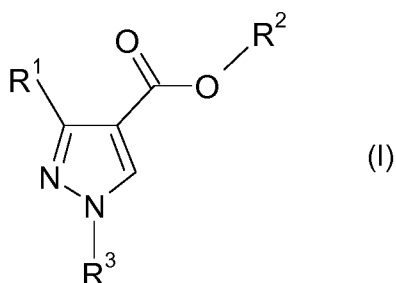


wherein R¹ and R² are as defined for formula I; and

b. reacting the compound of formula II with an alkylating agent in the presence of an amide.

[0048] Preferred definitions of R¹, R² and R³ are the same as those given above and R⁷ is preferably hydrogen or C₁-C₆ alkyl. Most preferably R¹ is difluoromethyl, R² is C₁-C₆ alkyl e.g. ethyl, R³ is methyl and R⁷ is hydrogen or C₁-C₆ alkyl e.g. ethyl. Preferably the alkylating agent and amide are as described above.

[0049] In a further aspect alkylation of a compound of formula II and isomerisation may be carried out in separate steps. Accordingly, in a further aspect the invention provides a process, e.g. a regioselective process, for the preparation of a compound of formula I:



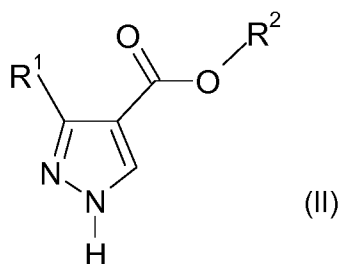
wherein R¹ is C₁-C₄haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

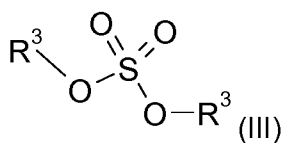
R³ is methyl or ethyl;

comprising

b1. reacting a compound of formula II:

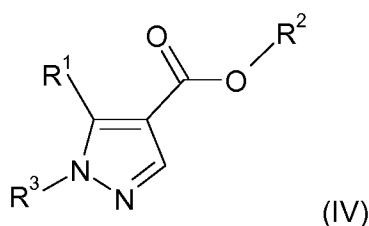


wherein R¹ and R² are as defined for the compound of formula I; with an alkylating agent of formula III;



wherein R³ is methyl or ethyl,

to produce a mixture comprising a compound of formula I and a compound of formula IV



wherein R^1 , R^2 and R^3 are as defined for the compound of formula I; and

b2. reacting the mixture from b1. with an alkylating agent of Formula III in the presence of an amide.

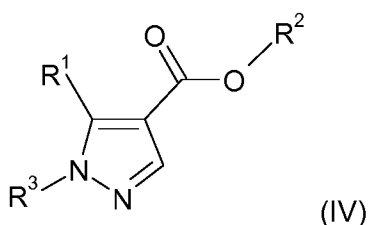
[0050] Preferred definitions of R^1 , R^2 and R^3 are the same as those given above. Most preferably R^1 is difluoromethyl, R^2 is C_1 - C_6 alkyl e.g. ethyl and R^3 is methyl.

[0051] The alkylating agent used in step b1. may or may not be the same as the alkylating agent used in step b2.

[0052] Alkylation may be performed in the presence of a base. Suitable bases are for example hydroxides and carbonates, e.g. of alkali metals. Methods of alkylating compounds of formula II are described for example in WO 2006/045504.

[0053] The compounds of formula II are known or can be prepared using hydrazine analogously to processes known in the literature. For example, such compounds can be prepared from the 3-oxo-carboxylic acid esters on which they are based by means of a two-step synthesis by reaction with trimethyl orthoformate and subsequent reaction with hydrazine. Such reactions are described, for example, in JP-2000-044541. A further synthesis route for the preparation of compounds of formula II is described in JP-2001-322983, wherein, for example, 3-trifluoromethyl-1 H-pyrazole-4-carboxylic acid ethyl ester is prepared starting from 3-chloro-4,4,4-trifluoro-2-formyl-2-butenic acid ethylester by reaction with hydrazine. Also, WO 2006/045504 discusses procedures that may be employed for producing compounds of formula II from compounds of formula V using hydrazine. Compounds of formula III and XX are commercially available.

[0054] In a further aspect of the invention, there is provided use of an alkylating agent and an amide, e.g. as catalyst, in the conversion of a compound of formula IV:

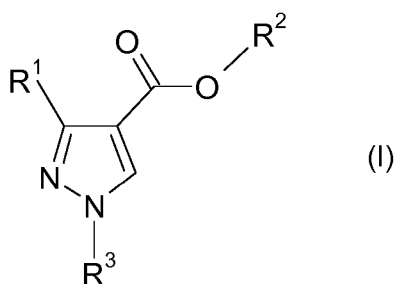


wherein R^1 is C_1 - C_4 haloalkyl,

R^2 is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

R^3 is methyl or ethyl;

into a compound of formula I:

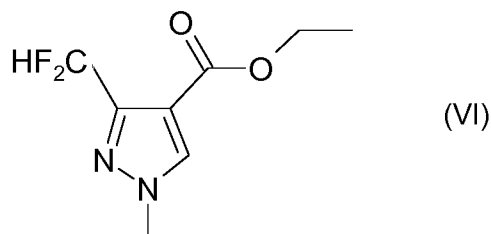


wherein R^1 , R^2 and R^3 are as defined for the compound of formula IV.

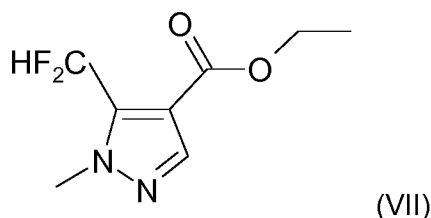
[0055] Preferred definitions of R^1 , R^2 , and R^3 are the same as those given above. Most preferably R^1 is difluoromethyl, R^2 is C_1 - C_6 alkyl e.g. ethyl and R^3 is methyl. Preferably the alkylating agent and amide are as described above.

[0056] In a further aspect there is provided a catalyst, e.g. for converting a compound of formula IV to a compound of formula I, comprising an alkylating agent and an amide. Preferably the alkylating agent and amide are as described above. Such a catalyst will usually exist as an ionic liquid.

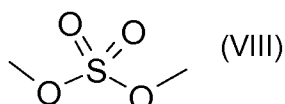
[0057] In a further aspect of the invention there is provided a process, e.g. a regioselective process, for preparing a compound of formula VI:



comprising reacting a compound of formula VII:

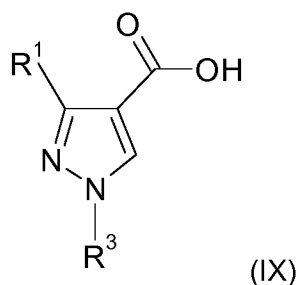


with a compound of formula VIII:



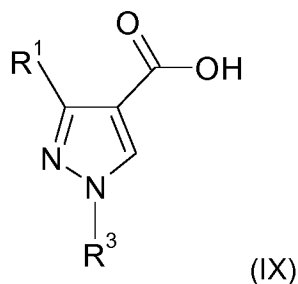
in the presence of an amide selected from dimethylformamide, N, N-dimethylacetamide and N-methyl-2-pyrrolidone.

[0058] Compounds of formula I may be subsequently converted into the corresponding acid. Such compounds may also be useful intermediates in the production of fungicides, see e.g. WO 2008/145257. For example, compounds of formula I may be converted into compounds of formula IX:



wherein R^1 and R^3 are as defined for the compound of formula I; by hydrolysing the compound of formula I.

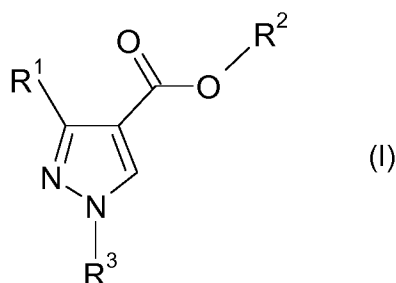
[0059] Accordingly, the invention provides a process for the preparation of a compound of formula IX:



wherein R^1 is C_1 - C_4 haloalkyl; and
 R^3 is methyl or ethyl;

comprising

1. preparing a compound of formula I:



wherein R^1 and R^3 are as defined for the compound of formula IX; and
 R^2 is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

according to the invention; and

2. hydrolysing the compound of formula I to produce the compound of formula IX.

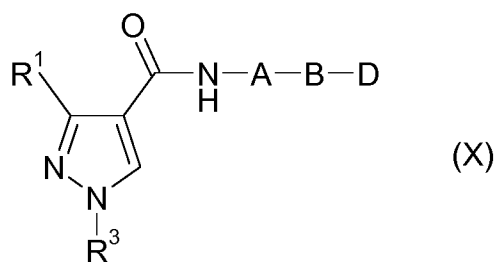
[0060] Preferred definitions of R^1 , R^2 , and R^3 are the same as those given above. Most preferably R^1 is difluoromethyl, R^2 is C_1 - C_6 alkyl e.g. ethyl and R^3 is methyl.

[0061] Hydrolysis of the compound of formula I may be achieved by performing the steps:

- i) saponifying that compound in situ leading to the formation of a compound of formula I by
- ii) adding a base to form the anion of the compound of formula IX;
- ii') adding an acid to form the compound of formula IX;

e.g. as described in WO 2008/145257.

[0062] In a further aspect the invention provides a process for the preparation of a compound of formula X:



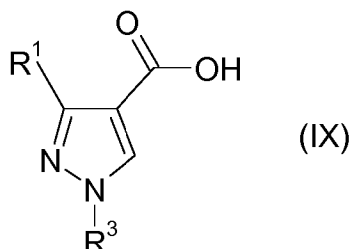
wherein R^1 is C_1 - C_4 haloalkyl;

R³ is methyl or ethyl;

A is thienyl, phenyl, or ethylene each optionally substituted by one to three groups independently selected from halogen, methyl and methoxy;

B is a direct bond, cyclopropylene, an annelated bicyclo[2.2.1]heptane- or bicyclo[2.2.1]heptene ring;

D is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₆ cycloalkyl, C₁-C₆ alkylidene, C₁-C₆ haloalkylidene, phenyl or phenyl optionally substituted by one to three substituents independently selected from halogen and trihalomethylthio; comprising providing a compound of formula IX:



wherein R¹ is C₁-C₄haloalkyl and R³ is methyl or ethyl;

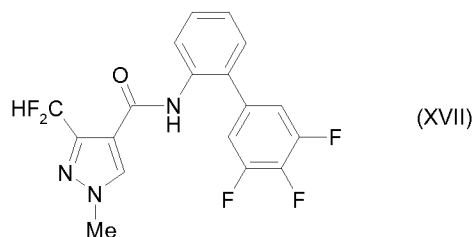
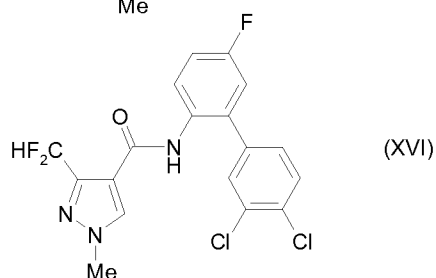
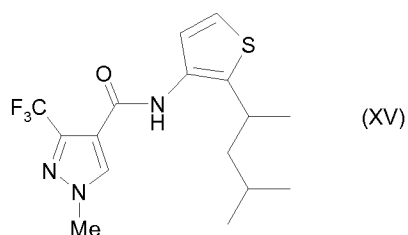
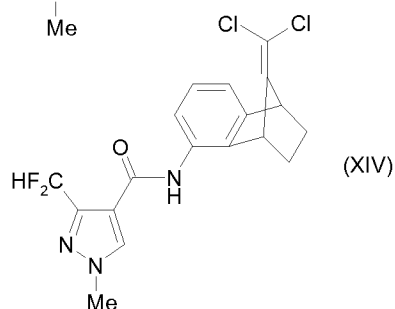
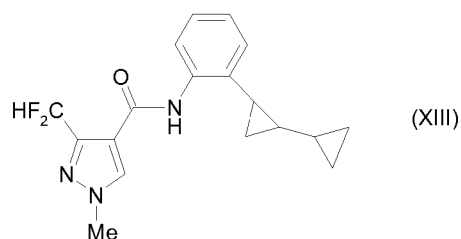
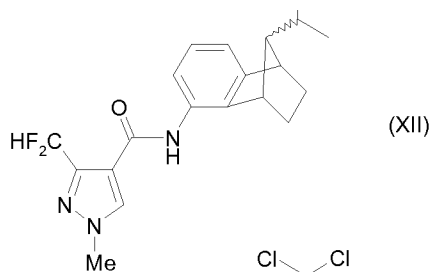
according to the processes described above; and

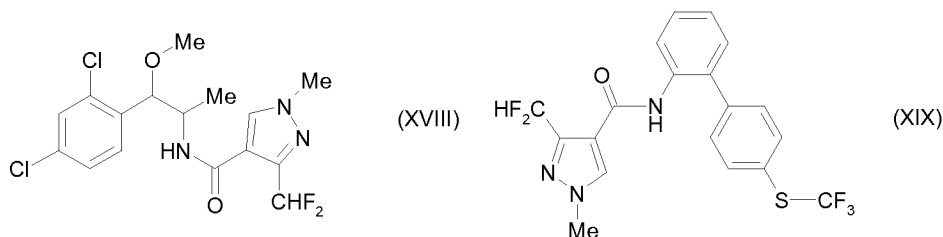
reacting the compound of formula IX or the corresponding acid-halide with a compound of formula XI:



wherein A, B and D are as defined for the compound of formula X.

[0063] The compound of formula X is preferably a compound of formula XII (Isopyrazam), a compound of formula XIII (Sedaxane), a compound of formula XIV, a compound of formula XV (Penthiopyrad), a compound of formula XVI (Bixafen), a compound of formula XVII (Fluxapyroxad), a compound of formula XVIII, or a compound of formula XIX:





[0064] The step of reacting the compound of formula IX or the corresponding acid-halide with a compound of formula XI may be performed according to known methods, e.g. as described in WO 2004/035589 or WO 2009/135860. For example, the compound of formula IX may be treated with a halogenating agent, such as thionyl chloride, oxalyl chloride, phosgene, SF₄, DAST, deoxofluor or thionylbromide to provide the acid-halogen, e.g. the acid chloride, which may then be reacted with the compound of formula XI in the presence of a suitable base, e.g. LiOH, KOH, NaOH, NEt₃, NaHCO₃, KHCO₃, Na₂CO₃ or K₂CO₃, e.g. in a solvent such as toluene, xylenes, dichloromethane, ethyl acetate or DMF, e.g. at -10°C to 30°C.

[0065] Isopyrazam, Sedaxane, Penthiopyrad, Fluxapyroxad and Bixafen are known fungicides. The compound of formula XIV is known, e.g. from WO 2007/048556, the compound of formula XVIII is known e.g. from WO 2010/000612, the compound of formula XIX is known e.g. from WO 2008/053044.

[0066] We have found that the compounds of formula I and IV have different boiling points which may be exploited to separate the compound of formula I from the compound of formula IV. Thus, the process may comprise separating a mixture of compounds of formula I and IV by distillation. For example, iso-DFPE has a boiling point of approximately 95°C/10mbar, whereas DFPE has a boiling point of approximately 120°C/1mbar. This separation step may be performed after completion of isomerisation or may be performed simultaneously with isomerisation, e.g. when the process is continuous. The compound of formula I may be purified by crystallisation.

[0067] Table 1 shows examples of compounds of formula I of the invention.

Table 1: Compounds of formula I

(I)			
Comp. No.	R ₁	R ₂	R ₃
A1	CF ₂ H	CH ₂ CH ₃	CH ₃
A2	CF ₂ H	CH ₃	CH ₃
A3	CF ₂ H	CH ₃	CH ₂ CH ₃
A4	CF ₂ H	CH ₂ CH ₃	CH ₂ CH ₃
A5	CF ₃	CH ₂ CH ₃	CH ₃
A6	CF ₃	CH ₃	CH ₃
A7	CF ₃	CH ₃	CH ₂ CH ₃
A8	CF ₃	CH ₂ CH ₃	CH ₂ CH ₃

[0068] The present invention will now be described by way of the following non-limiting Examples. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

[0069] All aspects and preferred features of the invention may be combined with each other, except where this is evidently not possible.

Figures**Figure 1**

[0070] Figure 1 shows that ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DFPE) reverts into ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) under conditions according to the invention. The Y axis indicates the amount of DFPE as a proportion of the combined amount of DFPE and iso-DFPE. The X axis indicates time.

[0071] Experimental details are described under Example 8. DMF is dimethylformamide, NMP is N-methyl-2-pyrrolidone, DMA is N, N-dimethylacetamide, DMS is dimethylsulphate. "DMF/DMS 0.5 equiv" means pre-formed DMF/DMS salt as described in Example 1, i.e., by treatment of 0.5 molar equivalents of DMF and 0.5 molar equivalents of DMS relative to the combined amount of DFPE and iso-DFPE.

Figure 2

[0072] Figure 2 shows that ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso DFPE) reverts into ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) under conditions according to the invention. The Y axis indicates the amount of DFPE as a proportion of the combined amount of DFPE and iso-DFPE. The X axis indicates time.

Experimental details are described under Example 9.

Examples**Example 1:**

[0073] Preparation of an amide/dimethylsulfate salt: dimethylsulfate (1 molar equivalent) and amide (1.2 molar equivalents), are heated to 70°C for 1.5 hours. Once cooled, the resulting solution is available for use.

Example 2:

[0074] A solution of ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DFPE) (~98%, 56.1 g, 0.27 mol) and dimethylformamide (27.1 g, 0.37 mol) was stirred at room temperature. Dimethylsulphate (12.1 g, 0.10 mol) was added. The resulting solution was heated gradually to 160°C and held for 4 hours. The solution was then heated gradually to 170°C over 30 minutes and held for additional 1.5 hours for a total reaction time of 6 hours at ≥160°C. Quantitative GC analysis of the reaction mass indicated the solution yields to be 49.8 g of ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) and 5.4 g of iso-DFPE.

Example 3:

[0075] A solution of ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DFPE) (>99%, 2.04 g, 0.01 mol), N, N-dimethylformamide /dimethylsulfate salt (1.00 g, 0.005 mol) and N, N-dimethylformamide (0.37 g, 0.005 mol) was stirred at room temperature. The resulting solution was heated gradually to 160°C and held for 7 hours. The conversion to ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) was approximately 95.7%.

Example 4:

[0076] A solution of ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DFPE) (>99%, 2.04 g, 0.01 mol), N-methyl-2-pyrrolidone/dimethylsulfate salt (1.12 g, 0.005 mol) and N-methyl-2-pyrrolidone (0.50 g, 0.005 mol) was stirred at room temperature. The resulting solution was heated gradually to 160°C and held for 7 hours. The conversion to ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) was approximately 93.5%.

Example 5:

[0077] A solution of ethyl 5-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylate (iso-DFPE) (>99%, 2.04 g, 0.01 mol), N,N-dimethylacetamide /dimethylsulfate salt (1.06 g, 0.005 mol) and N,N-dimethylacetamide (0.44 mg, 0.005 mol) was stirred at room temperature. The resulting solution was heated gradually to 160°C and held for 7 hours. The conversion to ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) was approximately 82.2%.

Example 6:

[0078] To 147.2 g of a crude mixture of ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DFPE) and ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE) (iso-DPFE: 50.1 g; DFPE: 85.3 g) was added 43.8 g of N,N-dimethylformamide and 12.6 g of dimethylsulfate. The resulting solution was heated gradually to 160°C and held for 4 hours. The solution was then heated gradually to 170°C over 30 minutes and held for an additional 1.5 hours for a total reaction time of 6 hours at ≥160°C. Quantitative GC analysis of the reaction mass indicated the solution yields to be 120.1 g of DFPE and 9.1 g of iso-DFPE. The unreacted iso-DFPE was then distilled out and recycled in the next batch. The crude product of DFPE from distillation bottom was dissolved in toluene and can be used directly for the next step, e.g. hydrolysis, without any further purification.

Example 7:

[0079] To 1.9 g of ethyl 3-difluoromethylpyrazole-4-carboxylate (NHDFPE) was added 2.5 g of N, N-dimethylformamide /dimethylsulfate salt. The mixture was heated to 160°C and stirred for 7 hours. The isomer ratio of ethyl 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (DFPE): ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DFPE) at end of reaction time based on GC analysis was 98:2.

Example 8:

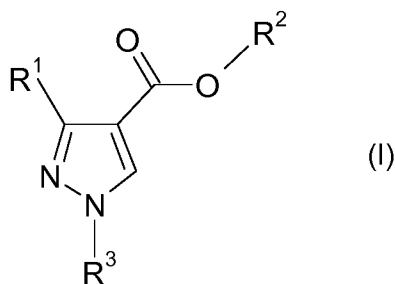
[0080] In each reactor of a multi-pot reaction block was placed 2.0 g (10 mmol) of ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DPFE) and amide/dimethylsulfate salt. The reaction block was heated to 170°C and stirred for 8 hours. Samples were taken periodically for GC analysis. Results are shown in Figure 1.

Example 9:

[0081] In each reactor of a multi-pot reaction block was placed 2.0 g (10 mmol) of ethyl 5-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylate (iso-DPFE), DMF/dimethylsulfate salt (1.0-2.5 mmol), and 0.7 g DMF (10 mmol). The reaction block was heated to 150°C and stirred for 8 hours. Samples were taken periodically for GC analysis. Results are shown in Figure 2.

Claims

1. A process for the preparation of a compound of formula I:

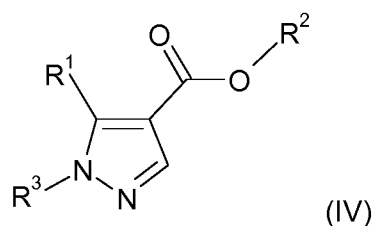


wherein R¹ is C₁-C₄haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

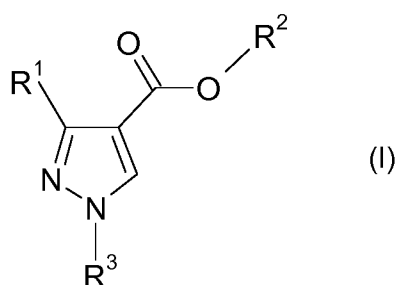
R³ is methyl or ethyl;

comprising reacting a compound of formula IV:



wherein R¹, R² and R³ are as defined for the compound of formula I;
with a methylating or ethylating agent in the presence of an amide.

2. A process according to claim 1, wherein the process is for increasing the proportion of a compound of formula I in a mixture comprising a compound of formula I and a compound of formula IV.
3. A process according to claim 1 or claim 2 wherein the amide is present in an amount of 0.1 molar equivalents to 10 molar equivalents relative to the amount of the compound of formula IV and the compound of formula I.
4. A process according to claim 1 for the preparation of a compound of formula I:

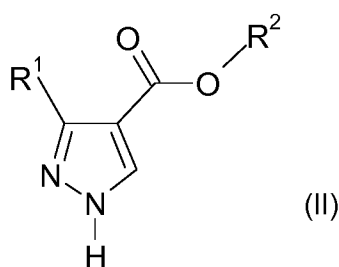


wherein R¹ is C₁-C₄haloalkyl;

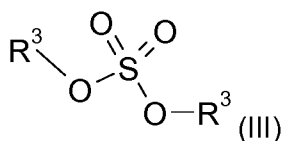
R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

R³ is methyl or ethyl;

comprising reacting a compound of formula II:

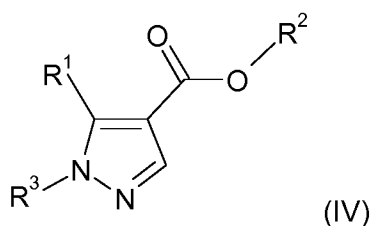


wherein R¹ and R² are as defined for the compound of formula I; with an alkylating agent and an amide;
wherein the alkylating agent is a compound of formula III:



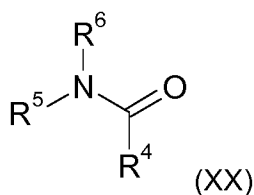
where R³ is methyl or ethyl;

wherein the process comprises *N*-alkylating the compound of formula II and isomerising the compound of formula IV



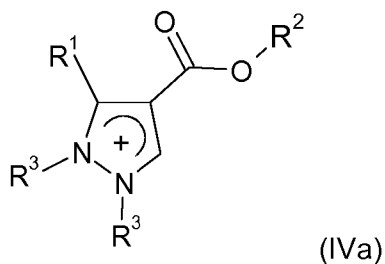
wherein R^1 , R^2 and R^3 are as defined for the compound of formula I;
 produced from the alkylation substantially at the same time;
 wherein the amide is present in an amount of 0.1 molar equivalents to 10 molar equivalents relative to the amount
 of the compound of formula IV and the compound of formula I.

5. A process according to any one of claims 1 to 4, wherein the amide is a compound of formula XX:



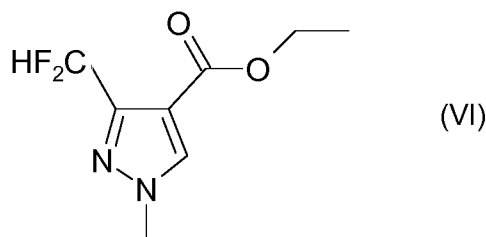
wherein R^4 is H or C_1 - C_4 alkyl;
 R^5 is C_1 - C_4 alkyl;
 R^6 is C_1 - C_4 alkyl;
 or R^4 and R^5 together are C_2 - C_5 alkyne;
 or R^5 and R^6 are together C_2 - C_5 alkyne.

6. A process according to any one of claims 1 to 5, wherein the amide is dimethylformamide, N-methyl-2-pyrrolidone
 or N, N-dimethylacetamide.
7. A process according to any one of claims 1 to 6, wherein the alkylating agent is capable of alkylating a compound
 of formula IV as defined in claim 1 to form a compound of formula IVa

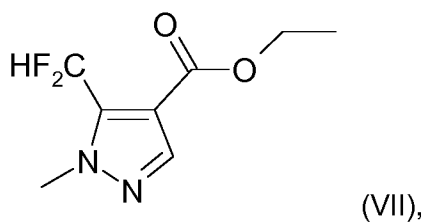


wherein R^1 , R^2 and R^3 are as defined for a compound of formula IV in claim 1.

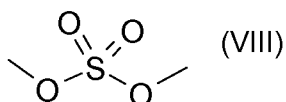
8. A process according to any one of claims 1 to 7, wherein the process is for preparing a compound of formula VI:



comprising reacting a compound of formula VII:

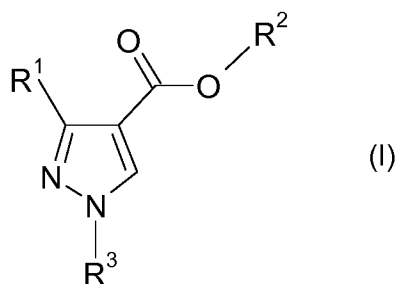


with a compound of formula VIII:



in the presence of an amide selected from dimethylformamide, N-methyl-2-pyrrolidone and N, N-dimethylacetamide.

9. A process according to claim 1 for the preparation of a compound of formula I:



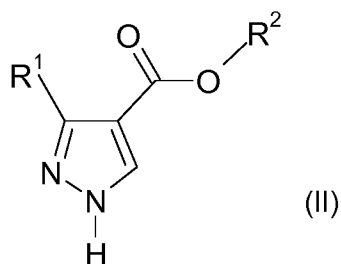
wherein R¹ is C₁-C₄haloalkyl;

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl; and

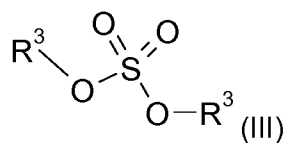
R³ is methyl or ethyl;

comprising

b1. reacting a compound of formula II:

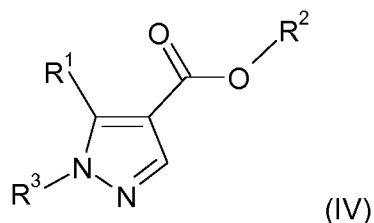


wherein R¹ and R² are as defined for the compound of formula I; with an alkylating agent of formula III:



wherein R³ is methyl or ethyl;

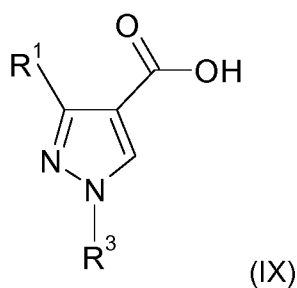
to produce a mixture comprising a compound of formula I and a compound of formula IV



wherein R¹, R² and R³ are as defined for the compound of formula I; and

b2. reacting the mixture from b1. with an alkylating agent of formula III in the presence of an amide.

10. A process for the preparation of a compound of formula IX:

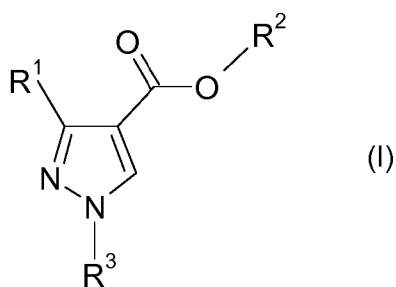


wherein R¹ is C₁-C₄haloalkyl, and

R³ is methyl or ethyl;

comprising

1. preparing a compound of formula I:



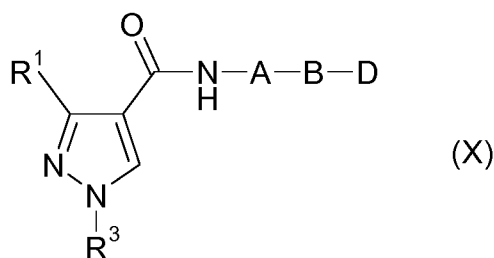
wherein R¹ and R³ are as defined for the compound of formula IX; and

R² is optionally substituted alkyl, optionally substituted aryl or optionally substituted heteroaryl;

as defined in any one of claims 1 to 9; and

2. hydrolysing the compound of formula I to produce the compound of formula IX.

11. A process for the preparation of a compound of formula X:



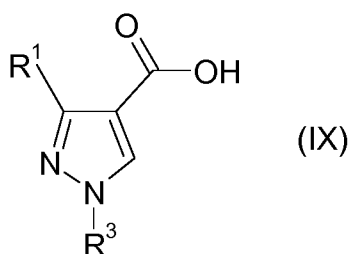
wherein R^1 is C_1 - C_4 haloalkyl;

R^3 is methyl or ethyl;

A is thienyl, phenyl, or ethylene each optionally substituted by one to three groups independently selected from halogen, methyl and methoxy;

B is a direct bond, cyclopropylene, an annulated bicyclo[2.2.1]heptane- or bicyclo[2.2.1]heptene ring;

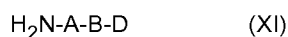
D is hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_3 - C_6 cycloalkyl, C_1 - C_6 alkylidene, C_1 - C_6 haloalkylidene, phenyl or phenyl optionally substituted by one to three substituents independently selected from halogen and trihalomethylthio; comprising providing a compound of formula IX:



wherein R^1 is C_1 - C_4 haloalkyl and R^3 is methyl or ethyl;

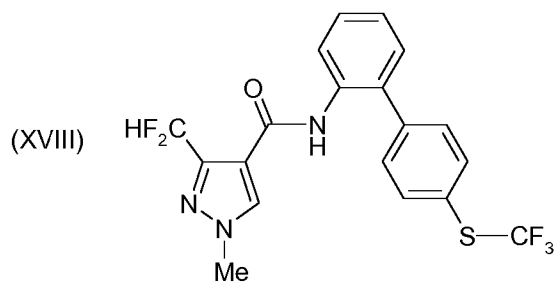
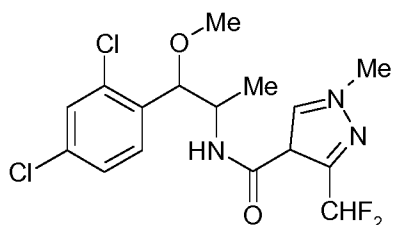
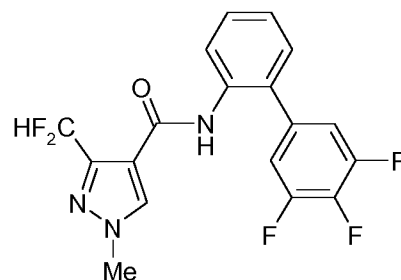
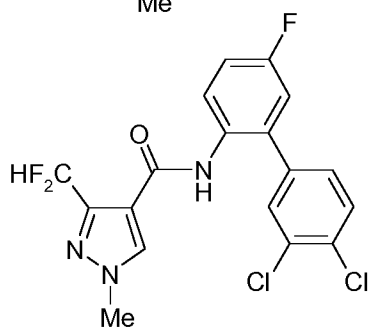
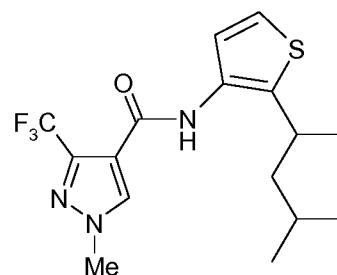
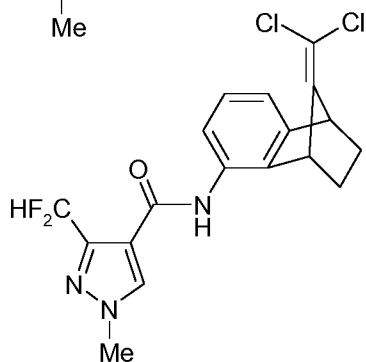
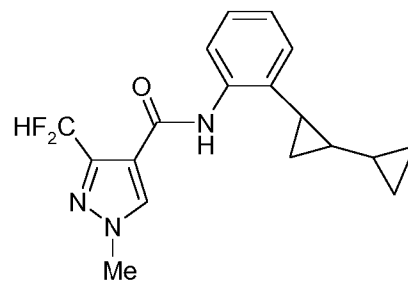
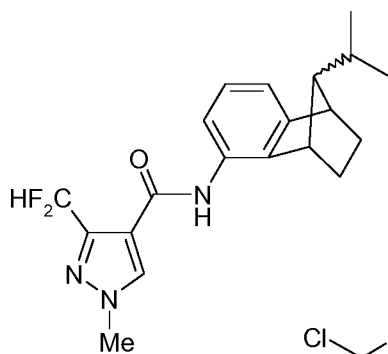
according to the process as defined in claim 10; and

reacting the compound of formula IX or the corresponding acid-halide with a compound of formula XI:



wherein A, B and D are as defined for the compound of formula X.

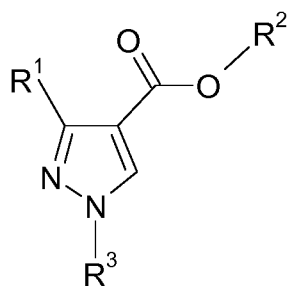
- 12.** A process according to claim 11, wherein the compound of formula X is a compound of formula XII (Isopyrazam), a compound of formula XIII (Sedaxane), a compound of formula XIV, a compound of formula XV (Penthiopyrad), a compound of formula XVI (Bixafen), a compound of formula XVII (Fluxapyroxad), a compound of formula XVIII, or a compound of formula XIX:



13. A process according to any one of claims 1 to 12, wherein
 R¹ is difluoromethyl or trifluoromethyl;
 R² is C₁-C₆ alkyl; and
 R³ is methyl.

Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel I:



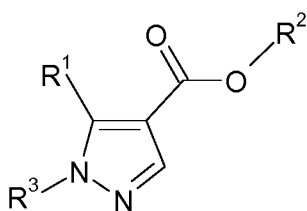
(I) ,

wobei R¹ für C₁-C₄-Halogenalkyl steht;

R² für gegebenenfalls substituiertes Alkyl, gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl steht; und

R³ für Methyl oder Ethyl steht;

bei dem man eine Verbindung der Formel IV:

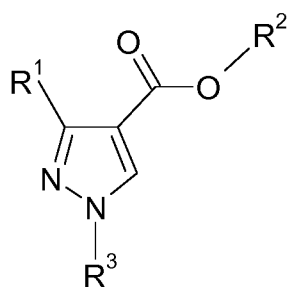


(IV) ,

wobei R¹, R² und R³ wie für die Verbindung der Formel I definiert sind;

in Gegenwart eines Amids mit einem Methylierungs- oder Ethylierungsmittel umgesetzt.

2. Verfahren nach Anspruch 1, bei dem das Verfahren zur Erhöhung des Anteils einer Verbindung der Formel I in einem Gemisch, das eine Verbindung der Formel I und eine Verbindung der Formel IV umfasst, dient.
3. Verfahren nach Anspruch 1 oder Anspruch 2, bei dem das Amid in einer Menge von 0,1 Moläquivalenten bis 10 Moläquivalenten, bezogen auf die Menge der Verbindung der Formel IV und die Verbindung der Formel I, vorliegt.
4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I:



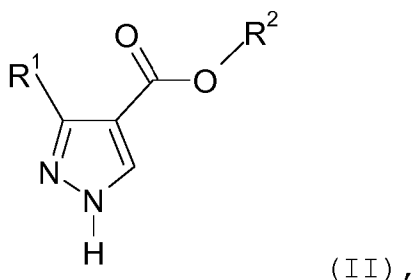
(I) ,

wobei R¹ für C₁-C₄-Halogenalkyl steht;

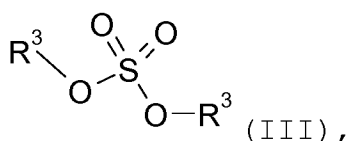
R² für gegebenenfalls substituiertes Alkyl, gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl steht; und

R³ für Methyl oder Ethyl steht;

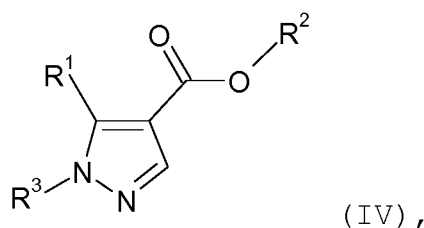
bei dem man eine Verbindung der Formel II:



10 wobei R¹ und R² wie für die Verbindung der Formel I definiert sind;
mit einem Alkylierungsmittel und einem Amid umgesetzt;
wobei es sich bei dem Alkylierungsmittel um eine Verbindung der Formel III handelt:

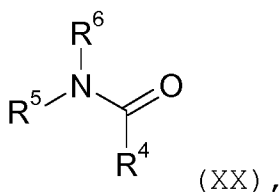


20 wobei R³ für Methyl oder Ethyl steht;
wobei man bei dem Verfahren die Verbindung der Formel II N-alkyliert und die bei der Alkylierung gebildete
Verbindung der Formel IV



30 wobei R¹, R² und R³ wie für die Verbindung der Formel I definiert sind;
zur gleichen Zeit isomerisiert;
wobei das Amid in einer Menge von 0,1 Moläquivalenten bis 10 Moläquivalenten, bezogen auf die Menge der
Verbindung der Formel IV und die Verbindung der Formel I, vorliegt.

35 5. Verfahren nach einem der Ansprüche 1 bis 4, wobei es sich bei dem Amid um eine Verbindung der Formel XX handelt:



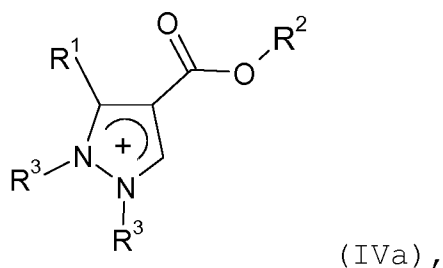
45

50 wobei R⁴ für H oder C₁-C₄-Alkyl steht;
R⁵ für C₁-C₄-Alkyl steht;
R⁶ für C₁-C₄-Alkyl steht;
oder R⁴ und R⁵ zusammen für C₂-C₅-Alkylen stehen;
oder R⁵ und R⁶ zusammen für C₂-C₅-Alkylen stehen.

55 6. Verfahren nach einem der Ansprüche 1 bis 5, wobei es sich bei dem Amid um Dimethylformamid, N-Methyl-2-pyrrolidon oder N,N-Dimethylacetamid handelt.

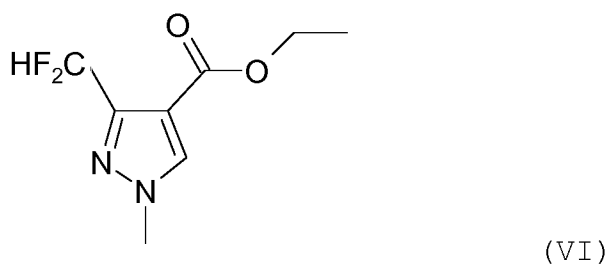
7. Verfahren nach einem der Ansprüche 1 bis 6, bei dem das Alkylierungsmittel zur Alkylierung einer Verbindung der

Formel IV gemäß Anspruch 1 zu einer Verbindung der Formel IVa

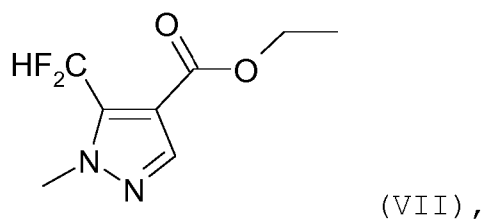


wobei R¹, R² und R³ wie für eine Verbindung der Formel IV in Anspruch 1 definiert sind, fähig ist.

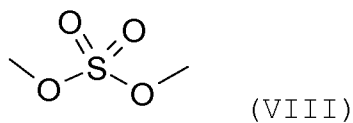
8. Verfahren nach einem der Ansprüche 1 bis 7, bei dem das Verfahren zur Herstellung einer Verbindung der Formel VI:



dient, wobei man eine Verbindung der Formel VII:

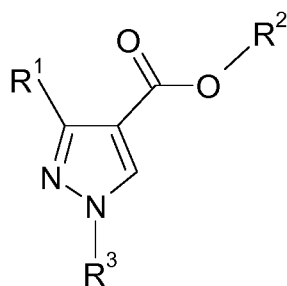


in Gegenwart eines aus Dimethylformamid, N-Methyl-2-pyrrolidon und N,N-Dimethylacetamid ausgewählten Amids mit einer Verbindung der Formel VIII:



umsetzt.

9. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel I:



(I) ,

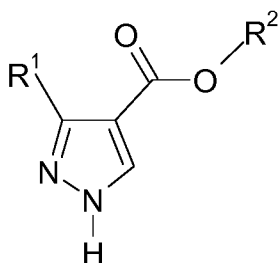
wobei R¹ für C₁-C₄-Halogenalkyl steht;

R² für gegebenenfalls substituiertes Alkyl, gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl steht; und

R³ für Methyl oder Ethyl steht;

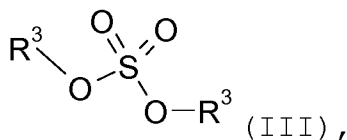
bei dem man

b1. eine Verbindung der Formel II:



(II) ,

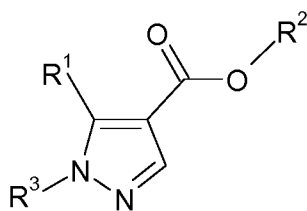
wobei R¹ und R² wie für die Verbindung der Formel I definiert sind; mit einem Alkylierungsmittel der Formel III:



(III) ,

wobei R³ für Methyl oder Ethyl steht;

umsetzt, wobei man ein Gemisch erhält, das eine Verbindung der Formel I und eine Verbindung der Formel IV

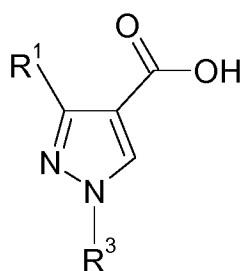


(IV) ,

wobei R¹, R² und R³ wie für die Verbindung der Formel I definiert sind, umfasst; und

b2. das Gemisch aus b1. in Gegenwart eines Amids mit einem Alkylierungsmittel der Formel III umsetzt.

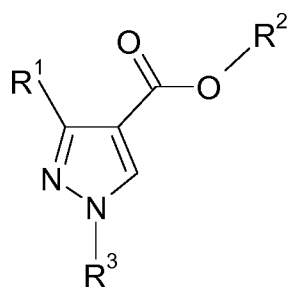
10. Verfahren zur Herstellung einer Verbindung der Formel IX:



(IX) ,

wobei R¹ für C₁-C₄-Halogenalkyl steht und R³ für Methyl oder Ethyl steht;
bei dem man

1. eine Verbindung der Formel I:



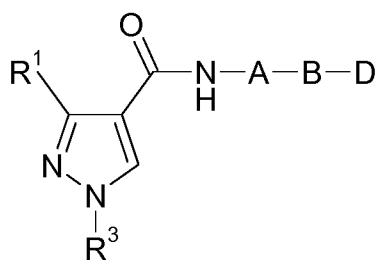
(I) ,

wobei R¹ und R³ wie für die Verbindung der Formel IX definiert sind; und
R² für gegebenenfalls substituiertes Alkyl, gegebenenfalls substituiertes Aryl oder gegebenenfalls substituiertes Heteroaryl steht;

gemäß einem der Ansprüche 1 bis 9 herstellt; und

2. die Verbindung der Formel I zu der Verbindung der Formel IX hydrolysiert.

11. Verfahren zur Herstellung einer Verbindung der Formel X:

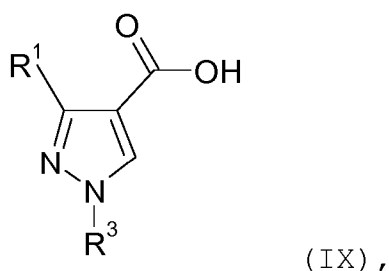


(X) ,

wobei R¹ für C₁-C₄-Halogenalkyl steht und
R³ für Methyl oder Ethyl steht;

A für Thienyl, Phenyl oder Ethylen steht, wobei jede dieser Gruppen gegebenenfalls durch eine bis drei Gruppen, die unabhängig aus Halogen, Methyl und Methoxy ausgewählt sind, substituiert ist;
B für eine direkte Bindung, Cyclopropylen, einen anellierten Bicyclo[2.2.1]heptan- oder Bicyclo-[2.2.1]heptenring steht;
D für Wasserstoff, Halogen, C₁-C₆-Alkyl, C₁-C₆-Halogenalkyl, C₁-C₆-Alkoxy, C₁-C₆-Halogenalkoxy, C₃-C₆-Cycloalkyl, C₁-C₆-Alkyliden, C₁-C₆-Halogen-alkyliden, Phenyl oder Phenyl, das gegebenenfalls durch einen bis drei Substituenten, die unabhängig aus Halogen und Trihalogenmethylthio ausgewählt sind, substituiert ist, steht;

bei dem man eine Verbindung der Formel IX:

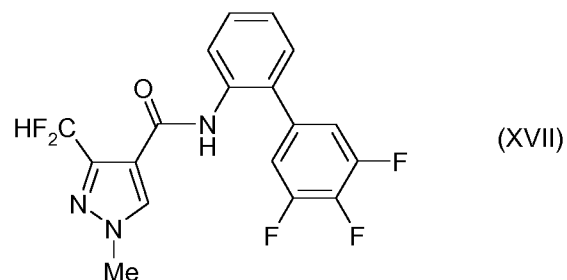
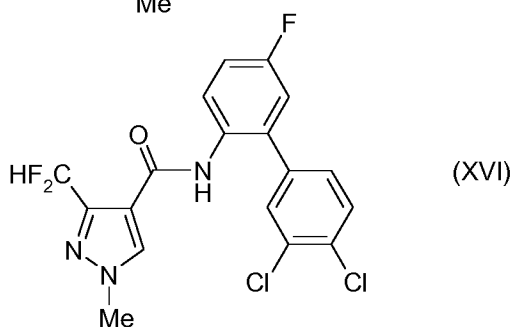
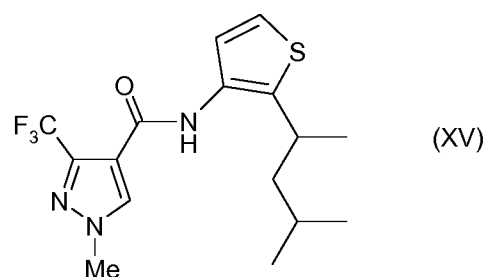
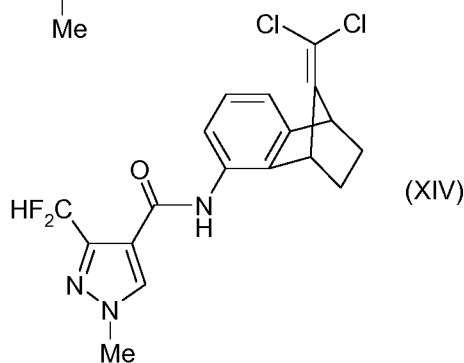
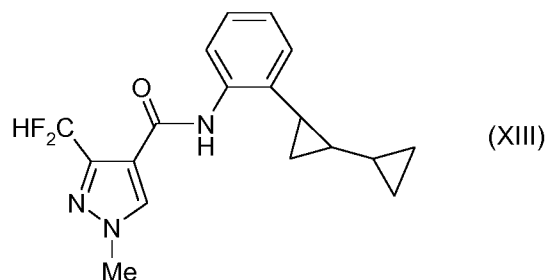
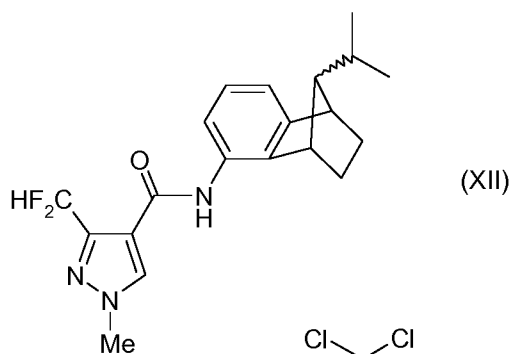


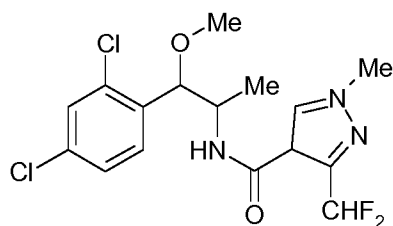
wobei R¹ für C₁-C₄-Halogenalkyl steht und R³ für Methyl oder Ethyl steht;
nach dem Verfahren gemäß Anspruch 10 bereitstellt; und
die Verbindung der Formel IX oder das entsprechende Säure Halogenid mit einer Verbindung der Formel XI:



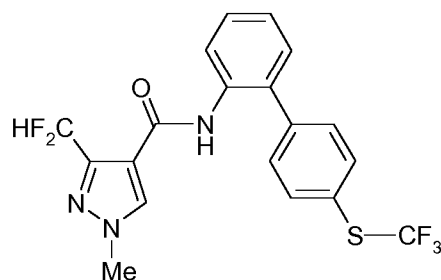
wobei A, B und D wie für die Verbindung der Formel X definiert sind;
umsetzt.

- 12.** Verfahren nach Anspruch 11, bei dem es sich bei der Verbindung der Formel X um eine Verbindung der Formel XII (Isopyrazam), eine Verbindung der Formel XIII (Sedaxan), eine Verbindung der Formel XIV, eine Verbindung der Formel XV (Penthiopyrad), eine Verbindung der Formel XVI (Bixafen), eine Verbindung der Formel XVII (Fluxapyroxad), eine Verbindung der Formel XVIII oder eine Verbindung der Formel XIX handelt:





(XVIII)

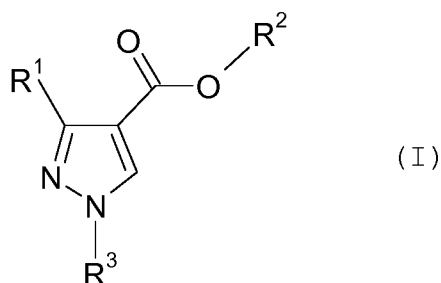


(XIX).

13. Verfahren nach einem der Ansprüche 1 bis 12, bei dem
 R^1 für Difluormethyl oder Trifluormethyl steht;
 R^2 für C_1 - C_6 -Alkyl steht; und
 R^3 für Methyl steht.

Revendications

1. Procédé de préparation d'un composé de formule I :



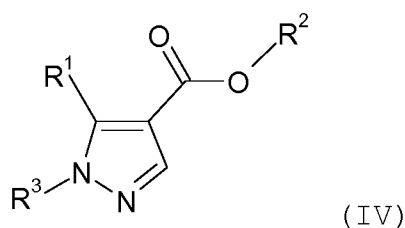
(I)

dans lequel R^1 est halogénoalkyle en C_1 - C_4 ;

R^2 est alkyle facultativement substitué, aryle facultativement substitué ou hétéroaryle facultativement substitué ;
 et

R^3 est méthyle ou éthyle ;

comprenant la réaction d'un composé de formule IV :

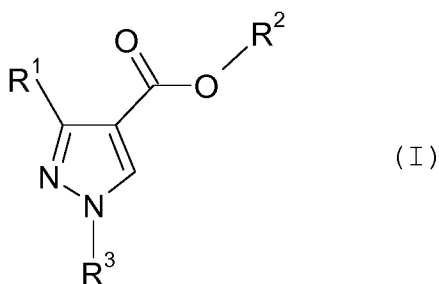


(IV)

dans lequel R^1 , R^2 et R^3 sont tels que définis pour le composé de formule I ;

avec un agent de méthylation ou d'éthylation en présence d'un amide.

2. Procédé selon la revendication 1, le procédé étant destiné à augmenter la proportion d'un composé de formule I dans un mélange comprenant un composé de formule I et un composé de formule IV.
3. Procédé selon la revendication 1 ou la revendication 2 dans lequel l'amide est présent en une quantité de 0,1 équivalent molaire à 10 équivalents molaires par rapport à la quantité du composé de formule IV et du composé de formule I.
4. Procédé selon la revendication 1 pour la préparation d'un composé de formule I :

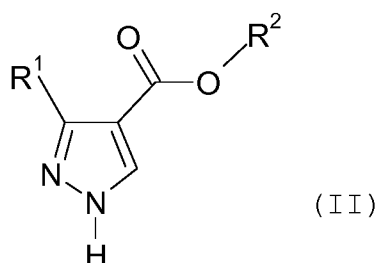


dans lequel R¹ est halogénoalkyle en C₁-C₄ ;

R² est alkyle facultativement substitué, aryle facultativement substitué ou hétéroaryle facultativement substitué ;
et

R³ est méthyle ou éthyle ;

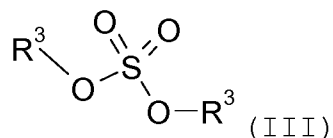
comprenant la réaction d'un composé de formule II :



dans lequel R¹ et R² sont tels que définis pour le composé de formule I ;

avec un agent d'alkylation et un amide ;

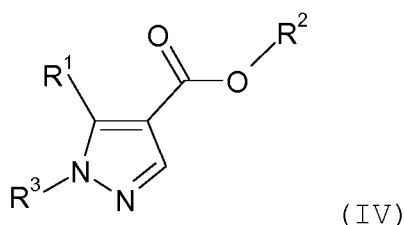
l'agent d'alkylation étant un composé de formule III :



dans lequel R³ est méthyle ou éthyle ;

le procédé comprenant la *N*-alkylation du composé de formule II et

l'isomérisation du composé de formule IV

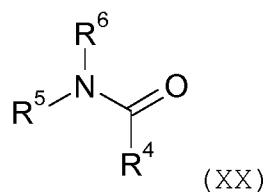


dans lequel R¹, R² et R³ sont tels que définis pour le composé de formule I ;

produit à partir de l'alkylation sensiblement en même temps ;

dans lequel l'amide est présent en une quantité de 0,1 équivalent molaire à 10 équivalents molaires par rapport
à la quantité du composé de formule IV et le composé de formule I.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel l'amide est un composé de formule XX :



dans lequel R^4 est H ou alkyle en $\text{C}_1\text{-C}_4$;

R^5 est alkyle en $\text{C}_1\text{-C}_4$;

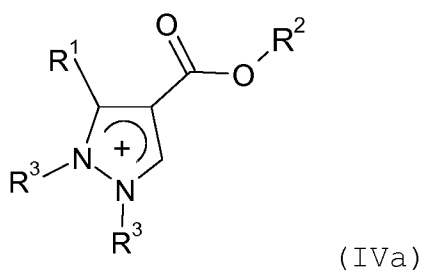
R^6 est alkyle en $\text{C}_1\text{-C}_4$;

ou R^4 et R^5 sont conjointement alkylène en $\text{C}_2\text{-C}_5$;

ou R^5 et R^6 sont conjointement alkylène en $\text{C}_2\text{-C}_5$.

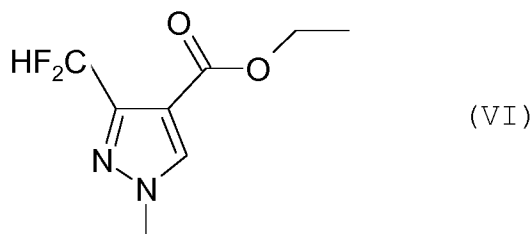
6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel l'amide est le diméthylformamide, la N-méthyl-2-pyrrolidone ou le N,N-diméthylacétamide.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel l'agent d'alkylation est capable d'alkyler un composé de formule IV tel que défini dans la revendication 1 pour former un composé de formule IVa

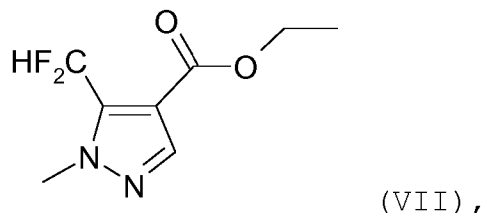


dans lequel R^1 , R^2 et R^3 sont tels que définis pour un composé de formule IV dans la revendication 1.

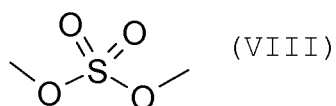
8. Procédé selon l'une quelconque des revendications 1 à 7, le procédé étant pour préparer un composé de formule VI :



comprenant la réaction d'un composé de formule VII :

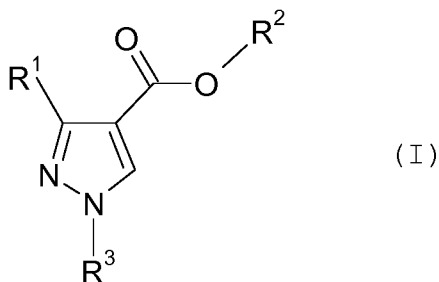


avec un composé de formule VIII :



en présence d'un amide choisi parmi le diméthylformamide, la N-méthyl-2-pyrrolidone et la N,N-diméthylacétamide.

9. Procédé selon la revendication 1 pour la préparation d'un composé de formule I :



dans lequel R¹ est halogénoalkyle en C₁-C₄ ;

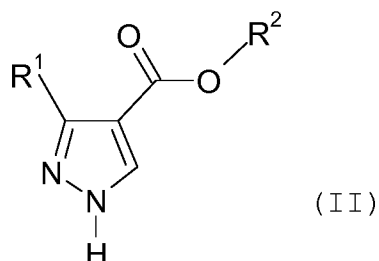
R² est alkyle facultativement substitué, aryle facultativement substitué ou hétéroaryle facultativement substitué ;

et

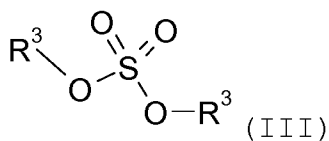
R³ est méthyle ou éthyle ;

comprenant

b1. la réaction d'un composé de formule II :

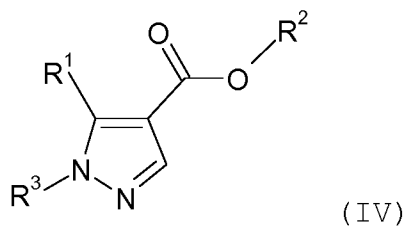


dans lequel R¹ et R² sont tels que définis pour le composé de formule I ; avec un agent d'alkylation de formule III :



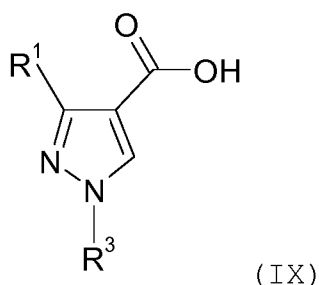
dans lequel R³ est méthyle ou éthyle ;

pour produire un mélange comprenant un composé de formule I et un composé de formule IV



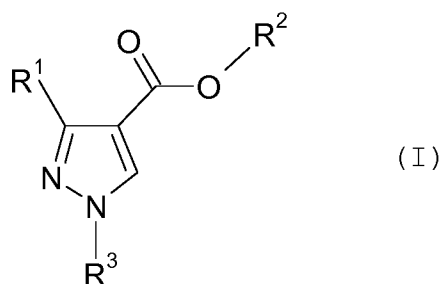
dans lequel R¹, R² et R³ sont tels que définis pour le composé de formule I ; et
b2. la réaction du mélange de b1. avec un agent d'alkylation de formule III en présence d'un amide.

10. Procédé de préparation d'un composé de formule IX :



dans lequel R¹ est halogénoalkyle en C₁-C₄, et R³ est méthyle ou éthyle ;
comprenant

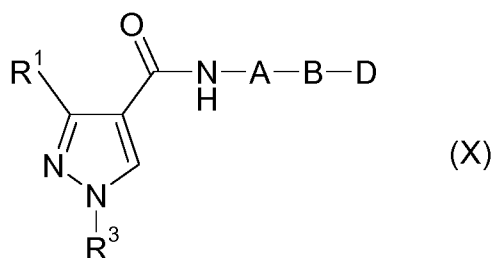
1. la préparation d'un composé de formule I :



dans lequel R¹ et R³ sont tels que définis pour le composé de formule IX ; et
R² est alkyle facultativement substitué, aryle facultativement substitué ou hétéroaryle facultativement substitué ;

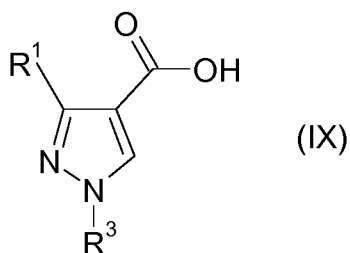
comme défini dans l'une quelconque des revendications 1 à 9 ; et
2. l'hydrolyse du composé de formule I pour produire le composé de formule IX.

11. Procédé de préparation d'un composé de formule X :

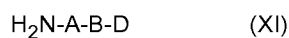


dans lequel R¹ est halogénoalkyle en C₁-C₄ ;
R³ est méthyle ou éthyle ;
A est thiényl, phényle ou éthylène chacun facultativement substitué par un à trois groupes indépendamment choisis parmi halogène, méthyle et méthoxy ;
B est une liaison directe, cyclopropylène, un cycle bicyclo[2.2.1]heptane ou bicyclo[2.2.1]heptène annelé ;
D est hydrogène, halogène, alkyle en C₁-C₆, halogénoalkyle en C₁-C₆, alcoxy en C₁-C₆, halogénoalcoxy en C₁-C₆, cycloalkyle en C₃-C₆, alkylidène en C₁-C₆, halogénoalkylidène en C₁-C₆, phényle ou phényle facultati-

vement substitué par un à trois substituants indépendamment choisis parmi halogène et trihalogénométhylthio ;
comprenant la fourniture d'un composé de formule IX :

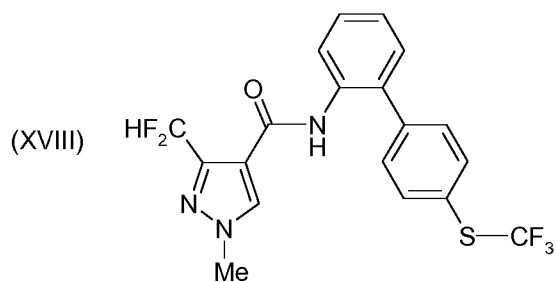
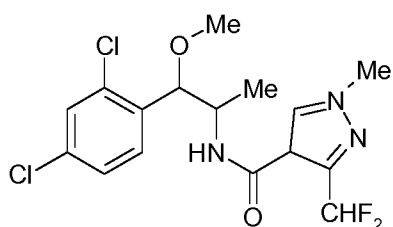
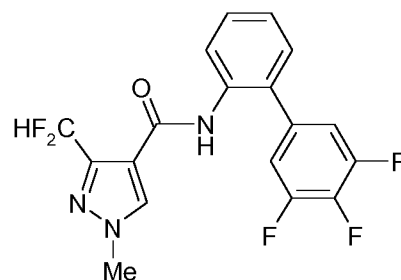
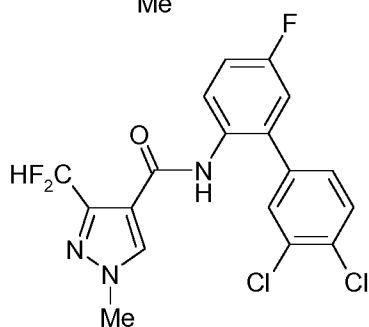
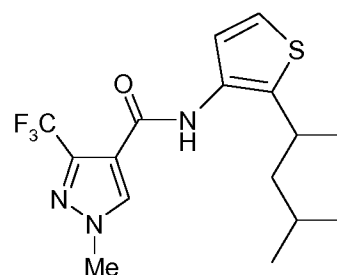
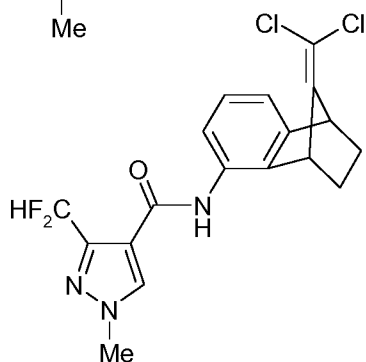
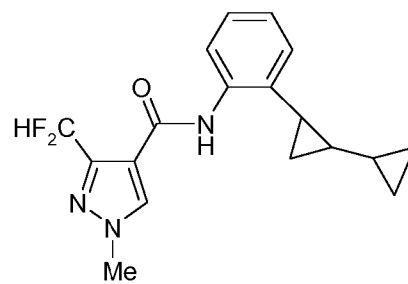
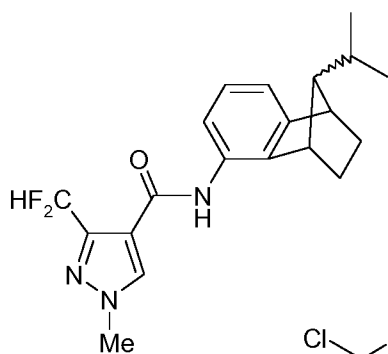


15 dans lequel R¹ est halogénoalkyle en C₁-C₄ et R³ est méthyle ou éthyle ;
selon le procédé tel que défini dans la revendication 10 ; et
la réaction du composé de formule IX ou de l'halogénure d'acide correspondant avec un composé de
formule XI :



dans lequel A, B et D sont tels que définis pour le composé de formule X.

- 25 **12.** Procédé selon la revendication 11, dans lequel le composé de formule X est un composé de formule XII (Isopyrazam),
un composé de formule XIII (Sedaxane), un composé de formule XIV, un composé de formule XV (Penthiopyrad),
un composé de formule XVI (Bixafen), un composé de formule XVII (Fluxapyroxad), un composé de formule XVIII,
ou un composé de formule XIX :



13. Procédé selon l'une quelconque des revendications 1 à 12, dans lequel
 R^1 est difluorométhyle ou trifluorométhyle ;
 R^2 est alkyle en C_1 - C_6 ; et
 R^3 est méthyle.

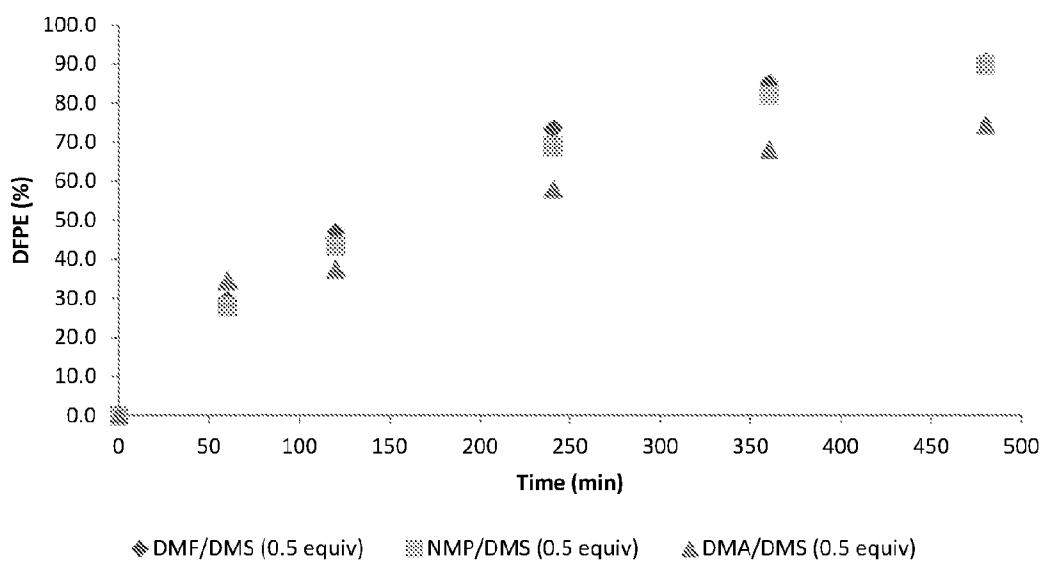


Figure 1

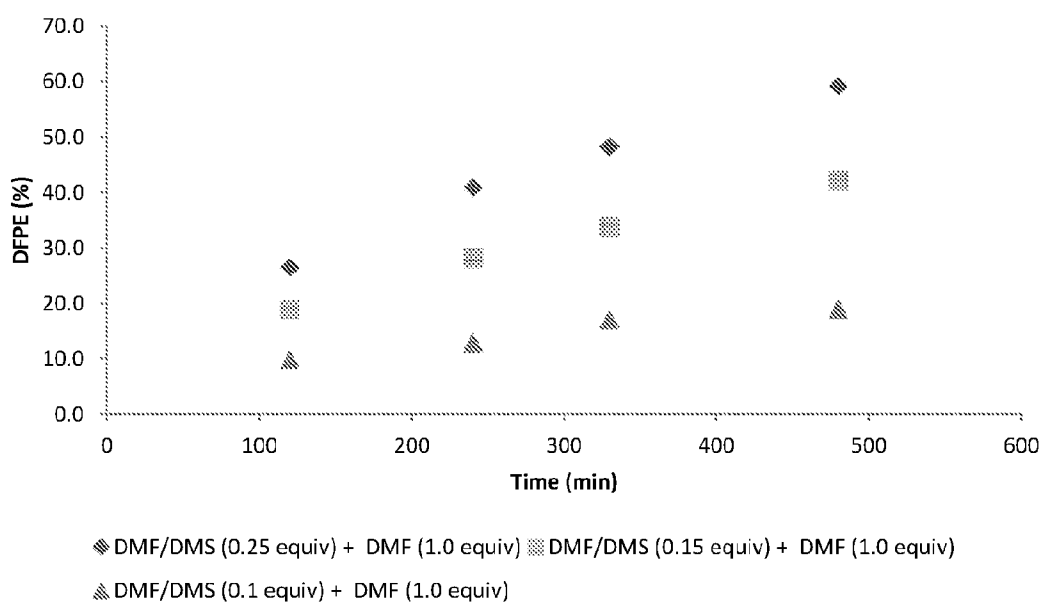


Figure 2

REFERENCES CITED IN THE DESCRIPTION

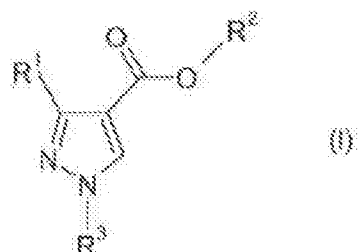
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- WO 2008053044 A [0065]

Szabadalmi igénypontok

1. Eljárás egy I képletű vegyület



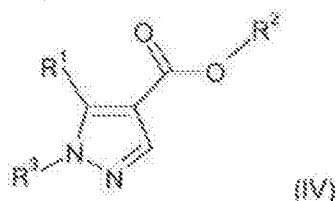
- a képletben

R^1 jelentése C_1 - C_4 halogénalkilcsoport;

R^2 jelentése adott esetben helyettesített alkil-, adott esetben helyettesített aril- vagy adott esetben helyettesített heteroarilcsoport; és

R^3 jelentése metil- vagy etilcsoport -

előállítására, amelynek során egy IV képletű vegyületet

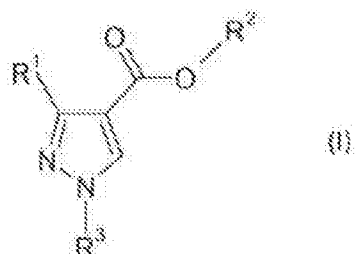


- a képletben R^1 , R^2 és R^3 jelentése az I képletű vegyületnél meghatározott - egy metilezőszerrel vagy etilezőszerrel reagáltatunk egy amid jelenlétében.

2. Az 1. igénypont szerinti eljárás, ahol az eljárás célja egy I képletű vegyület arányának növelése egy I képletű vegyületet és egy IV képletű vegyületet magában foglaló keverékben.

3. Az 1. vagy 2. igénypont szerinti eljárás, ahol az amid 0,1 mólekiválens és 10 mólekiválens közötti mennyiségben van jelen a IV képletű vegyület és az I képletű vegyület mennyiségére vonatkoztatva.

4. Az igénypont szerinti eljárás egy I képletű vegyület



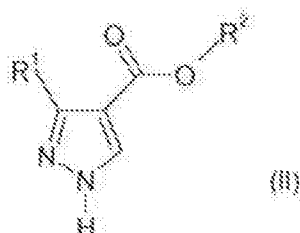
- a képletben

R^1 jelentése C_1 - C_4 halogénalkilcsoport;

R^2 jelentése adott esetben helyettesített alkil-, adott esetben helyettesített aril- vagy adott esetben helyettesített heteroarilcsoport; és

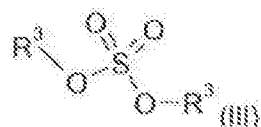
R^3 jelentése metil- vagy etilcsoport -

előállítására, amelynek során egy II képletű vegyületet



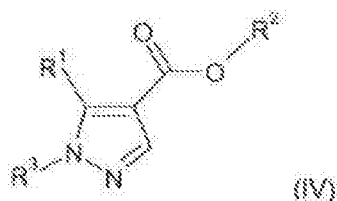
- a képletben R^1 , R^2 és R^3 jelentése az I képletű vegyületnél meghatározott -
egy alkilezőszerrel és egy amiddal reagáltatunk;

ahol az alkilezőszer egy III képletű vegyület



- a képletben R^3 jelentése metil- vagy etilcsoport -;

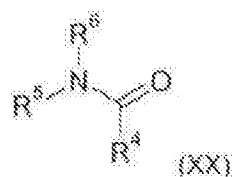
és ahol a II képletű vegyületet *N*-alkilezzük és az alkilezés során képződő IV képletű vegyületet



- a képletben R^1 , R^2 és R^3 jelentése az I képletű vegyületnél meghatározott -
lényegében egyidejűleg izomerizáljuk; és

ahol az amid 0,1 mólekivalens és 10 mólekivalens közötti mennyiségben van jelen a IV képletű vegyület és az I képletű vegyület mennyiségére vonatkoztatva.

5. Az 1 – 4. igénypontok bármelyike szerinti eljárás, ahol az amid egy XX képletű vegyület



- a képletben

R^4 jelentése H vagy C_1 - C_4 alkilcsoport;

R^5 jelentése C_1 - C_4 alkilcsoport;

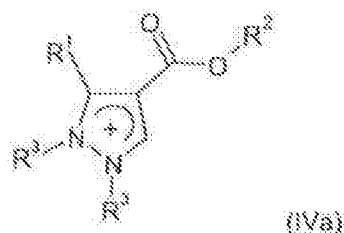
R^6 jelentése C_1 - C_3 alkilcsoport;

vagy R^4 és R^5 jelentése együtt C_2 - C_5 alkilénecsoport;

vagy R^5 és R^6 jelentése együtt C_2 - C_5 alkilénecsoport.

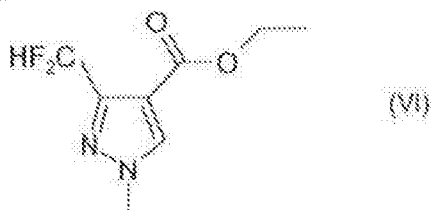
6. Az 1 – 5. igénypontok bármelyike szerinti eljárás, ahol az amid dimetilformamid, *N*-metil-2-pirrolidon vagy *N,N*-dimetilacetamid.

7. Az 1 – 6. igénypontok bármelyike szerinti eljárás, ahol az alkilezőszer képes egy, az 1. igénypontban definiált IV képletű vegyületet alkilezve egy IVa képletű vegyület

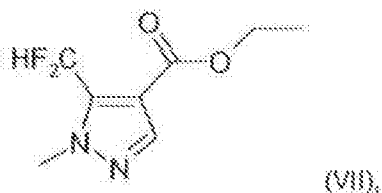


- a képletben R^1 , R^2 és R^3 jelentése az 1. igénypontban a IV képletű vegyületnél meghatározott - előállítására.

8. Az 1 – 7. igénypontok bármelyike szerinti eljárás, ahol az eljárás a VI képletű vegyület



előállítására irányul és abban áll, hogy a VII képletű vegyületet

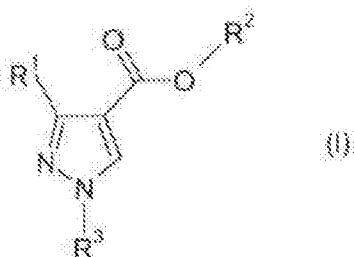


a VIII képletű vegyülettel



reagáltatjuk egy, dimetilformamid, N-metil-2-pirrolidon és N, N-dimetilacetamid közül megválasztott amid jelenlétében.

9. Az 1. igényponi szerinti eljárás egy I képletű vegyület



- a képletben

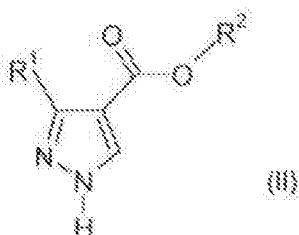
R^1 jelentése C_1 - C_4 halogénalkilcsoport;

R^2 jelentése adott esetben helyettesített alkil-, adott esetben helyettesített aril- vagy adott esetben helyettesített heteroarilcsoport; és

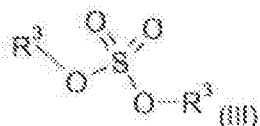
R^3 jelentése metil- vagy etilcsoport –

előállítására, amelynek során

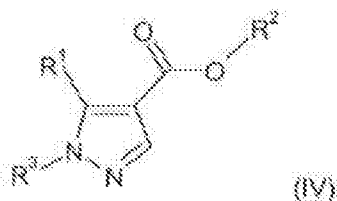
b1) egy II képletű vegyületet



- a képletben R^1 és R^2 jelentése az I képletű vegyületnél meghatározott -
egy III képletű alkilezőszerrel



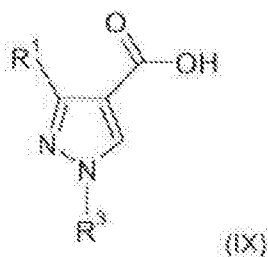
- a képletben R^3 jelentése metil- vagy etilcsoport -
reagáltatunk, amikor egy I képletű vegyületet és egy IV képletű vegyületet



- a képletekben R^1 és R^2 jelentése az I képletű vegyületnél meghatározott -
magában foglaló keveréket kapunk; és

b2) a b1) lépésben kapott keveréket egy III képletű alkilezőszerrel reagáltatjuk egy amid jelenlétében.

10. Eljárás egy IX képletű vegyület



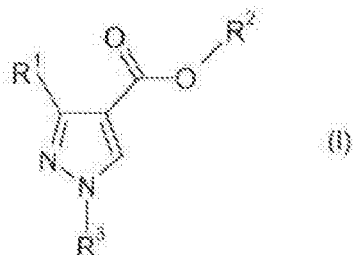
- a képletben

R^1 jelentése C_1 - C_4 halogénalkilcsoport; és

R^3 jelentése metil- vagy etilcsoport -

előállítására, amelynek során

1) előállítunk az 1 - 9. igénypontok bármelyike szerint egy I képletű vegyületet



- a képletben

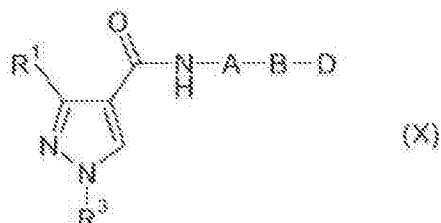
R^1 és R^3 jelentése a IX képletű vegyületnél meghatározott; és

R^2 jelentése adott esetben helyettesített alkil-, adott esetben helyettesített aril- vagy adott esetben helyettesített heteroarilcsoport -;

és

2) az I képletű vegyületet hidrolizáljuk, a IX képletű vegyületet kapva.

11. Eljárás egy X képletű vegyület



- a képletben

R^1 jelentése C_1 - C_4 halogénalkilcsoport;

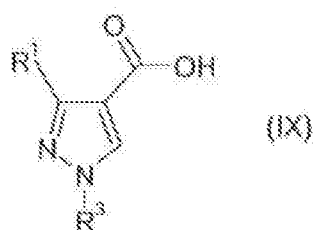
R^3 jelentése metil- vagy etilcsoport;

A jelentése tienil-, fenil- vagy etilcsoport, amelyek mindegyike adott esetben egy, kettő vagy három, halogén, metil és metoxi közül egymástól függetlenül megválasztott helyettesítővel helyettesített lehet;

B jelentése közvetlen kémiai kötés, ciklopropilcsoport vagy egy annelált biciklo[2.2.1]heptán vagy biciklo[2.2.1]heptén gyűrű; és

D jelentése hidrogén, halogén, C_1 - C_6 alkilcsoport, C_1 - C_6 halogénalkilcsoport, C_1 - C_6 alkoxycsoport, C_1 - C_6 halogénalkoxycsoport, C_3 - C_6 cikloalkilcsoport, C_1 - C_6 alkilidén-csoport, C_1 - C_6 halogénalkilidén-csoport, fenilcsoport vagy fenilcsoport, amely adott esetben egy, kettő vagy három, halogén és trihalogénmetillio közül egymástól függetlenül megválasztott helyettesítővel helyettesített lehet –

előállítására, amelynek során biztosítunk a 10. igénypont szerinti eljárással egy IX képletű vegyületet



- a képletben

R^1 jelentése C_1 - C_4 halogénalkilcsoport; és

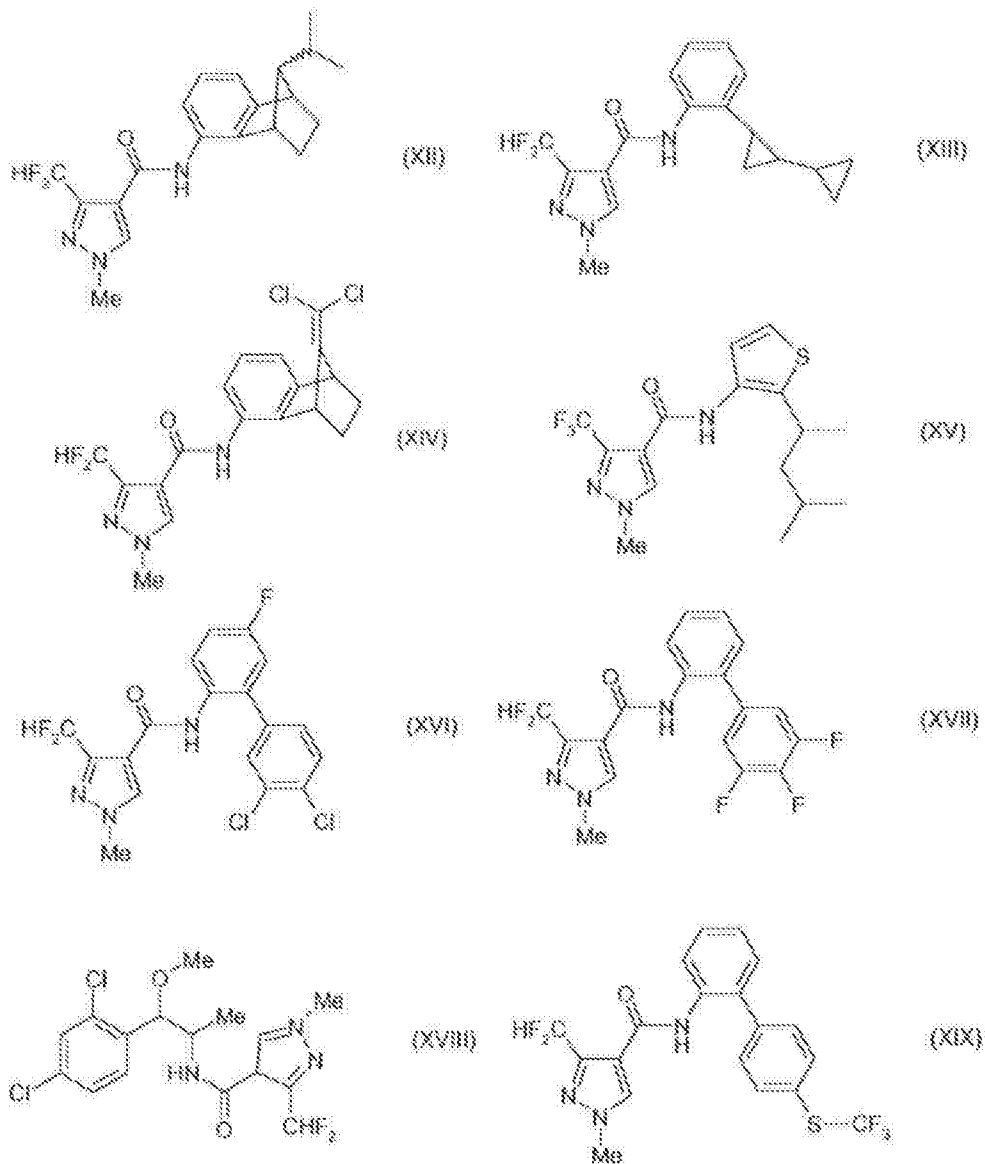
R^3 jelentése metil- vagy etilcsoport -;

és a IX képletű vegyületet vagy a megfelelő savhalogenidet egy XI képletű vegyülettel



- a képletben A, B és D jelentése a X képletű vegyületnél meghatározott –
reagáltatjuk.

12. A 11. igénypont szerinti eljárás, ahol a X képletű vegyület a XII képletű vegyület (izopirazám), a XIII képletű vegyület (szedaxán), a XIV képletű vegyület, a XV képletű vegyület (pentopirád), a XVI képletű vegyület (bixafén), a XVII képletű vegyület (flaxapiraxád), a XVIII képletű vegyület vagy a XIX képletű vegyület:



13. Az 1 – 12. igénypontok bármelyike szerinti eljárás, ahol

R^1 jelentése difluorometil- vagy trifluorometilcsoport;

R^2 jelentése C_1 - C_6 alkilcsoport; és

R^3 jelentése metilcsoport.