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(54) Title: PROCESS FOR PREPARING 3-FLUOROALKYL-5-PYRAZOLECARBOXYLATES AND 3-FLUOROALKYL-5-PYRAZOLECARBOXYLIC ACIDS

(57) Abstract: The present invention relates to a novel process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates from ketimines and oxalic acid derivatives which can be further transformed into 3-fluoroalkyl-5- pyrazolecarboxylic acids.

Process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates and 3-fluoroalkyl-5-pyrazolecarboxylic acids

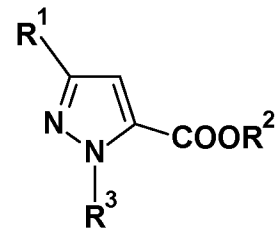
The present invention relates to a novel process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates from ketimines and oxalic acid derivatives which can be further transformed into 3-fluoroalkyl-5-pyrazolecarboxylic acids.

Polyfluoroalkylpyrazolylcarboxylic acid derivatives are valuable precursors of active fungicidal ingredients (WO 2003/070705, WO 2008/013925, WO 2003/000659, 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-difluoroamines in the presence of Lewis acids with acrylic acid derivatives and subsequent reaction thereof with alkylhydrazines. 3-fluoroalkyl-5-pyrazolecarboxylates are hardly accessible.

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-fluoroalkyl-5-pyrazolecarboxylates derivatives in high yields.

The object described above was achieved by a process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates of the formula **(I)**,



(I)

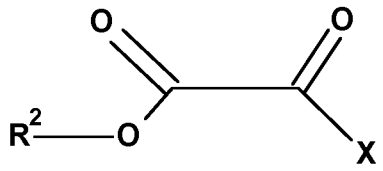
in which

R^1 is selected from C_1-C_6-haloalkyl;

R^2 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl and C_{7-18}-arylalkyl-,

R^3 is selected from H, C_1-C_{12} alkyl, benzyl, phenyl, C_{6-18}-aryl and pyridyl;

characterized in that in step (A), oxalic acid derivatives of the formula **(II)**,



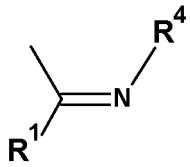
(II)

in which

R^2 is as defined above;

X is F, Cl or Br;

are reacted with compounds of the formula **(III)**,



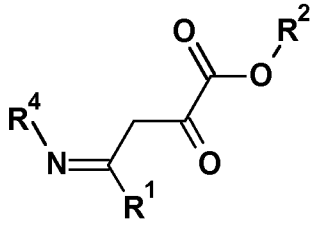
(III)

in which

R^4 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl and C_{7-18}-arylalkyl-;

R^1 is as defined above;

in the presence of a base to form compounds of the formula **(IV)**



(IV)

in which

R^1, R^2, R^4 are as defined above

and that in step (B) in the presence of hydrazine $H_2N\text{-}NHR^3$ **(V)**

in which R^3 is as defined above

and an acid the cyclization of **(IV)** takes place to form **(I)**.

Preferred is a process according to the invention, where the radicals of formula **(I), (II), (III)**, **(IV)** and **(V)** are defined as follows:

R^1 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^2 is selected from methyl, ethyl, propyl and *t*-butyl, benzyl and phenylethyl-;

R^3 is selected from H, C_1-C_8 alkyl, aryl, benzyl and pyridyl;

R^4 is selected from methyl, ethyl, *n*-, *iso*-propyl, *n*-, *iso*-, *sec*- und *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl and phenylethyl-,

X is F or Cl.

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

R^1 is selected from trifluoromethyl, difluoromethyl, difluorochloromethyl and pentafluoroethyl;

R^2 is selected from methyl and ethyl;

R^3 is selected from H, methyl, ethyl, propyl, isopropyl, butyl, pentyl benzyl and phenyl;

R^4 is selected from benzyl and *iso*-propyl;

X is Cl;

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

R^1 is difluoromethyl, difluorochloromethyl or trifluoromethyl;

R^2 is methyl or ethyl;

R^3 is selected from H, methyl, ethyl, benzyl and phenyl;

R^4 is *iso*-propyl or benzyl;

X is Cl.

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

R^1 is difluoromethyl or trifluoromethyl;

R^2 is methyl or ethyl;

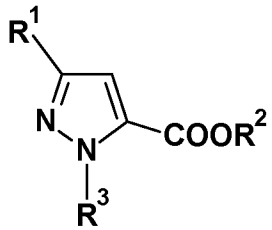
R^3 is selected from H, methyl and phenyl;

R^4 is benzyl;

X is Cl.

Surprisingly, 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 above mentioned disadvantages of the preparation processes previously described in the prior art.

A further aspect of the present invention are compounds of the formula (**I**)



(**I**)

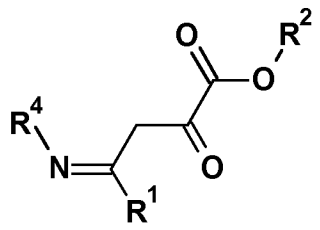
in which

R^1 is CF_2H;

R^2 is methyl or ethyl and

R^3 is methyl or phenyl.

A further aspect of the present invention are compounds of the formula **(IV)**



(IV)

in which

R^1 is difluoromethyl or trifluoromethyl;

R^2 is methyl or ethyl;

R^4 is *iso*-propyl or benzyl.

General definitions

Haloalkyl: straight-chain or branched alkyl groups having 1 to 6 and preferably 1 to 3 carbon atoms, 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.

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.

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.

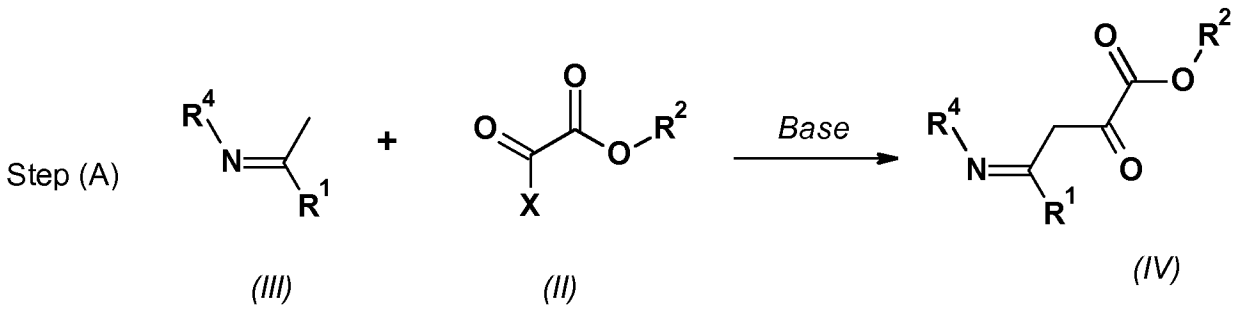
Aryl groups in the context of the present invention are aromatic hydrocarbons. The definition C_{6-18}-aryl encompasses the widest range defined herein for an aryl group having 6 to 18 carbon skeleton atoms. The definition encompasses, for example, phenyl, naphthyl and anthracenyl.

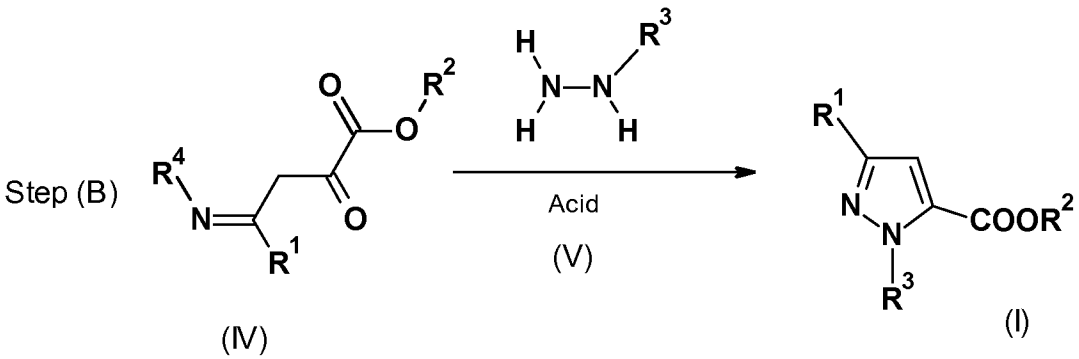
Arylalkyl- groups (aralkyl groups) in the context of the present invention are alkyl groups which are substituted by aryl groups. The definition C_{7-18}aralkyl group encompasses the widest range defined herein for an arylalkyl group having a total of 7 to 18 carbon atoms in the aromatic skeleton and the alkylene chain. This definition encompasses, for example, the meanings of benzyl and phenylethyl.

Process description

The process is illustrated in Scheme 1:

Scheme 1:





Step (A)

In step (A), oxalic acid derivatives of the formula **(II)** are reacted in the presence of a base with ketimines of the formula **(III)**.

Preferred compounds of the formula **(II)** are methyloxalylchloride and ethyloxalylchloride.

Compounds of the formula **(III)** can be prepared from ketones according to literature methods: e.g. Roeschenthaler et al, J.Fluorine.Chem. v. 125, n. 6, 1039-1049; Tetrahedron, 69 (2013), 3878-3884 and WO 2015/144578.

For the process according to the invention 1 to 2 mol, preferably 1 to1,5 mol, more preferably 1 to 1,2 mol of compound of the formula (**II**) is reacted with 1 mol of compound of the formula (**III**). 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.

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. Preference is given to THF, acetonitriles, ethers, toluene, xylene, chlorobenzene, n-hexane, cyclohexane or methylcyclohexane, and particular preference to acetonitrile, THF, ether or dichloromethane.

The reaction of compound **(III)** and **(II)** according to the invention is effected at temperatures of -5 °C to +40 °C, preferably at temperatures of +2 °C to +20 °C, more preferably at 5 °C to +10 °C and under standard pressure.

Reaction is proceeded in the presence of a base. For the process according to the invention 1 to 2 mol, preferred 1,5 to 1,8 mol of the base for 1 mol compound of the formula **(II)** is used.

Suitable bases are trialkylamines (e.g. triethylamines), Hünig base, pyridines, alkylpyridines (e.g. methylpyridines). Preferred are pyridine, 3-methylpyridine, ethyldiisopropylamine.

The intermediates of the formula **(IV)** formed can be used in the cyclization step without prior workup. Alternatively, the intermediates can be isolated by suitable workup steps, characterized and optionally further purified.

Step (B)

According to the invention, 1 mol to 2 mol, preferably 1 to 1.5 mol of the hydrazine of the formula **(V)** NH_2-NHR^3 for 1 mol of the compound of formula **(IV)** is used.

The cyclization in step (B) of the compound of formula **(IV)** is effected at temperatures of -20 °C to +50 °C, preferably at temperatures of +0 °C to +40 °C, more preferably at +20°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.

The cyclization of compound of the formula **(IV)** proceeds under acidic condition.

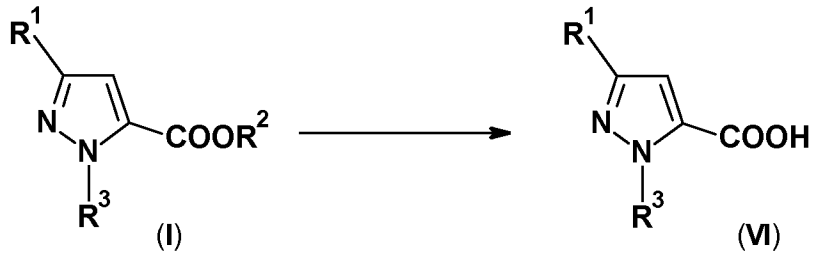
Suitable mineral acids are for example H_2SO_4, HCl, HF, HBr, HI, H_3PO_4 or organic acids, for example CH3COOH, CF_3COOH, p-toluenesulphonic acid, methanesulphonic acid, trifluoromethanesulphonic acid.

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 **(IV)** is used.

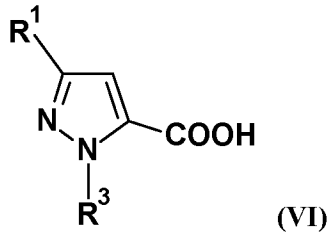
Suitable solvents are, for example, aliphatic, alicyclic or aromatic hydrocarbons, for example petroleum ether, n-hexane, n-heptane, cyclohexane, methylcyclohexane, benzene, toluene, xylene or decalin, and halogenated hydrocarbons, for example chlorobenzene, dichlorobenzene, dichloromethane, chloroform, 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. Preference is given to acetonitrile, ethanol, toluene, xylene, chlorobenzene, n-hexane, cyclohexane or methylcyclohexane, and particular preference to acetonitrile ethanol, 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 **(I)** can be converted into pyrazolecarboxylic acids of the formula **(VI)** by hydrolysis (Scheme 2).

Scheme 2:



A further aspect of the present invention is therefore a process for preparing 3-fluoroalkyl-5-pyrazole acids (**VI**),



in which

R^1 is selected from C_1-C_6-haloalkyl; and

R^3 is selected from H, C_1-C_{12} alkyl, benzyl, phenyl, C_{6-18}-aryl and pyridyl;

comprising

(i) the process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates of the formula **(I)**, in particular 3-fluoroalkyl-5-pyrazolecarboxylates of the formula **(I)** where R^2 equals C_{1-12}-alkyl, and

(ii) hydrolysing the compounds of the formula (**I**) to the compound of the formula (**VI**).

The hydrolysis can be performed under acidic or basic conditions. The reaction can likewise be performed without addition of acid, only in water.

For acidic hydrolysis, preference is given to the following mineral acids: H_2SO_4, HCl, HSO_3Cl, HF, HBr, HI, H_3PO_4 or the following organic acids: CF_3COOH, p-toluenesulphonic acid, methanesulphonic acid, trifluoromethanesulphonic acid. The reaction can be accelerated by the addition of catalysts, for example $FeCl_3$, $AlCl_3$, BF_3, $SbCl_3$, NaH_2PO_4.

Basic hydrolysis is effected in the presence of inorganic bases such as alkali metal hydroxides, for example lithium hydroxide, sodium hydroxide or potassium hydroxide, alkali metal carbonates, for example Na_2CO_3, K_2CO_3 and alkali metal acetates, for example NaOAc, KOAc, LiOAc, and alkali metal alkoxides, for example NaOMe, NaOEt, NaOt-Bu, KOt-Bu of organic bases such as trialkylamines, alkylpyridines, phosphazenes and 1,8-diazabicyclo[5.4.0]undecene (DBU). Preference is given to the inorganic bases, for example NaOH, KOH, Na_2CO_3 or K_2CO_3.

Preference is given to conversion by means of basic hydrolysis.

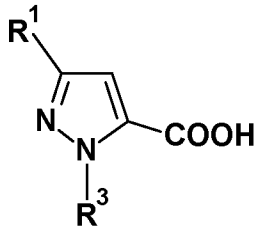
The process step of the invention is performed within a temperature range from 20°C to +150 °C, preferably at temperatures of 30 °C to +110 °C, more preferably at 30 °C to 80 °C.

The process step of the invention is generally performed under standard pressure. Alternatively, however, it is also possible to work under vacuum or under elevated pressure (for example reaction in an autoclave with aqueous HCl).

The reaction time may, according to the batch size and the temperature, be selected within a range between 1 hour and several hours.

The reaction step can be performed in substance or in a solvent. Preference is given to performing the reaction in a solvent. Suitable solvents are, for example, selected from the group comprising water, alcohols such as methanol, ethanol, isopropanol or butanol, aliphatic and aromatic hydrocarbons, for example n-hexane, benzene or toluene, which may be substituted by fluorine and chlorine atoms, such as methylene chloride, dichloroethane, chlorobenzene or dichlorobenzene; ethers, for example diethyl ether, diphenyl ether, methyl tert-butyl ether, isopropyl ethyl ether, dioxane, diglyme, dimethylglycol, dimethoxyethane (DME) or THF; nitriles such as methyl nitrile, butyl nitrile or phenyl nitrile; amides we dimethylformamide (DMF) or N-methylpyrrolidone (NMP) or mixtures of such solvents, particular preference being given to water, acetonitrile, dichloromethane and alcohols (ethanol).

A further aspect of the present invention are compounds of the formula (**VI**)



(**VI**),

in which

R^1 is CF_2H;

R^3 is methyl, ethyl or phenyl.

Experimental Part

Example 1

N-(1,1-difluoropropan-2-ylidene)propan-2-amine, (III-1)

To the mixture of difluoracetone (94 g, 1 mol) in 500 ml methyl*t*-butylether 88 g (1,5 mol) of isopropylamin was added at 10°C. After 1 h 70 g (0,5 mol) BF_3*Et_2O was added and the mixture was stirred additionally for 1 h. The organic solution was separated from bottom syrup and the solvent was distilled off at atmospheric pressure. The remaining liquid was distilled in vacuum yielding 139 g ketimine with a b.p. of 70-72°C/400 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5,9 (t, 1H), 3,7 (m, 1H), 1,8 (s, 3H), 1,1 (d, 6H) ppm.

^{19}F (376 MHz, $CDCl_3$) δ -122 (d, 2F) ppm.

Example 2

N-1,1-difluoropropan-2-ylidene-1-phenylmethanamine, (III-2).

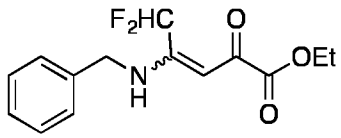
To the mixture of difluoroacetone (94 g, 1 mol) in 500 ml dichloromethane 107 g (1 mol) of benzylamine was slowly added at 10°C. After 6 h at 20°C, CH_2Cl_2 was distilled off at reduced pressure and the remaining liquid was distilled in vacuum, yielding 161 g ketimine with b.p. 80-82°C/1,3 mbar.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7,2-7,4 (m, 5H), 5,9 (t, 1H), 4,5 (s, 2H) , 2,0 (s, 3H) ppm.

^{19}F (376 MHz, $CDCl_3$) δ -1118 (d, 2F) ppm.

Example 3

Ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (IV-1)



A solution of benzyl(1,1-difluoropropan-2-ylidene)amine (1 eq., 250 mg, 1.30 mmol) in dichloromethane (2 mL) was cooled to -20 °C. Pyridine (1.05 eq., 108 mg, 0.11 mL, 1.36 mmol) was added, followed by a solution of ethyl oxalyl monochloride (1.03 eq., 183 mg, 0.15 mL, 1.34 mmol) in dichloromethane (1 mL). The mixture was stirred from -20 °C to room temperature over 18h.

The mixture was taken up in dichloromethane (5 mL) followed by Et_2O (10 mL). The resulting precipitate was filtered off, the filtrate concentrated *in vacuo*. The crude product was purified by flash chromatography (AcOEt in cyclohexane 0 to 15%) to yield 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (224 mg, 0.79 mmol, 61 %) as an orange oil.

NMR ^1H ($CDCl_3$, 400MHz) : 10.91 (s br, N*H*), 7.39 to 7.28 (m, 5*H*, Phenyl), 6.18 (t, C*H*F_2, J = 53 Hz), 6.17 (s, C*H*CO), 4.66 (d, CH_2NH), 4.31 (q, OCH_2), 1.36 (t, OCH$_2$CH_3) ppm.

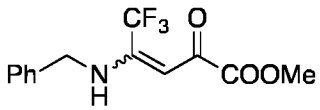
NMR ^{19}F ($CDCl_3$, 376MHz) : -118.9 (d, CHF_2, J = 53 Hz) ppm.

NMR ^{13}C ($CDCl_3$, 100MHz) : 180.2 (*C*(O)COOEt), 162.6 (*C*(O)OEt), 156.8 (t, *C*CHF$_2$, J = 22 Hz), 136.2, 129.2, 128.3, 127.3 (C_{Phenyl}), 111.4 (t, *C*HF$_2$, J = 245 Hz), 91.4 (t, *C*HCO, J = 7 Hz), 62.2 (OCH_2), 48.2 (*C*H$_2$NH), 14.1 (OCH$_2$CH_3) ppm.

Anal. calcd for $C_{14}H_{15}F_2NO_3$: C, 59.36; H, 5.34; F, 13.41; N, 4.94; O, 16.94. Found: C, 59.16; H, 5.36; N, 4.95.

Example 4

Methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (IV-2)



A solution of benzyl(1,1,1-trifluoropropan-2-ylidene)amine (1 eq., 1000 mg, 4.82 mmol) in dichloromethane (10 mL) was cooled to -20 °C. Pyridine (1.03 eq., 391 mg, 0.4 mL, 4.95 mmol) was added, followed by a solution of methyl oxalyl chloride (1.06 eq., 625 mg, 0.47 mL, 5.1 mmol) in dichloromethane (6 mL). The mixture was stirred from -20 °C to room temperature over 18h and was then concentrated and purified by flash chromatography (AcOEt in cyclohexane 0 to 10%), to yield methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (680 mg, 2.37 mmol, 49 %) as a colourless oil.

NMR ^1H ($CDCl_3$, 400MHz) : 11.02 (s br, N*H*), 7.40 to 7.28 (m, 5*H*, Phenyl), 6.40 (s, C*H*CO), 4.64 (d, CH_2NH), 3.87 (s, COOCH_3) ppm.

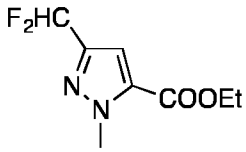
NMR ^{19}F ($CDCl_3$, 376MHz) : -66.6 (s, CF_3) ppm.

NMR ^{13}C ($CDCl_3$, 100MHz) : 180.3 (CHCO), 162.7 (*C*OOMe), 152.6 (q, *C*CF_3, J = 32.5 Hz), 135.8, 129.3, 128.5, 127.4 (C_{Phenyl}), 119.6 (q, *C*F_3, J = 278 Hz), 90.4 (q, *C*HCO, J 5 Hz), 53.1 (COO*C*H_3), 49.0 (*C*H_2NH) ppm.

HRMS (ESI) calcd for $C_{13}H_{12}F_3NNaO_3$ [M+Na]: 310.0661. Found: 310.0635.

Example 5

Ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (I-1)



A solution of ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (1 eq., 520 mg, 1.78 mmol) in MeCN (4 mL) was treated with methyl hydrazine (1.57 eq., 129 mg, 0.15 mL, 2.8 mmol) followed by concentrated H_2SO_4 (0.511 eq., 92 mg, 0.05 mL, 0.91 mmol) under inert atmosphere at room temperature.

The mixture was stirred 1h and then was diluted with dichloromethane, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (Et_2O in pentane 0 to 40%), to yield ethyl 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylate as a colourless oil (230 mg, 63%).

NMR ^1H (CDCl3, 400MHz) : 7.04 (t, 4-C*H*, J = 1 Hz), 6.66 (t, C*H*F_2, J = 55 Hz), 4.36 (q, OCH_2), 4.19 (s, CH_3), 1.38 (t, OCH_2CH_3) ppm.

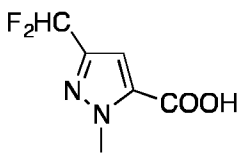
NMR ^{19}F (CDCl3, 376MHz) : -112.1 (d, CHF_2, J = 55 Hz) ppm.

NMR ^{13}C (CDCl3, 100MHz) : 159.4 (*C*=O), 145.1 (t, *C*CHF_2, J = 29.8 Hz), 134.0 (*C*COOEt), 110.8 (t, *C*HF_2, J = 234 Hz), 108.7 (4-*C*H), 61.5 (O*C*H_2), 40.1 (N*C*H_3), 14.3 (OCH_2CH_3) ppm.

HRMS (ESI) calcd for $C_8H_{11}F_2N_2O_2$ [M+H]: 205.0783. Found: 205.0782.

Example 6

3-(difluoromethyl)-1-methyl-1*H*-pyrazole-5-carboxylic acid (VI-1)



A mixture of ethyl 3-(difluoromethyl)-1-methyl-1H-pyrazole-5-carboxylate (1 eq., 185 mg, 0.906 mmol) and 2N NaOH (2.01 eq., 2 M, 0.912 mL, 1.82 mmol) in EtOH (2.61 mL) was stirred at room temperature for 1h. The mixture was treated with HCl 1N until pH 2-3, then was extracted with dichloromethane. The combined organic layer was washed with brine and dried over (Na_2SO_4), filtered and evaporated *in vacuo*, to yield a white solid (160mg, 99%) after trituration in pentane.

M.p.: 179.8 to 180.2°C.

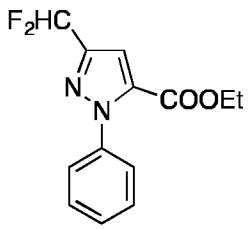
NMR ^{1}H (d^6-DMSO, 400MHz) : 13.7 (s br, COO*H*), 7.02 (s, 4-C*H*), 7.01 (t, C*H*F_2, J = 54.4 Hz), 4.11 (s, NCH_3) ppm.

NMR ^{19}F (d^6-DMSO, 376MHz) : -111.6 (d, CHF_2, J = 54.5 Hz) ppm.

NMR ^{13}C (d^6-DMSO, 100MHz) : 160.1 (*C*=O), 144.0 (t, *C*CHF_2, J = 28.5 Hz), 134.6 (*C*COOH), 110.9 (t, *C*HF_2, J = 232 Hz), 108.4 (4-*C*H), 39.7 (N*C*H_3) ppm.

Example 7

Ethyl 3-(difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylate (I-2)



A solution of ethyl 4-(benzylamino)-5,5-difluoro-2-oxopent-3-enoate (1 eq., 420 mg, 1.44 mmol) in MeCN (4 mL) was treated with phenyl hydrazine (1.47 eq., 228 mg, 0.21 mL, 2.12 mmol) followed by concentrated H_2SO_4 (0.506 eq., 73.6 mg, 0.04 mL, 0.728 mmol) under inert atmosphere. The mixture was refluxed overnight. Dichloromethane (20 mL) was added, the mixture filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (AcOEt in cyclohexane 0 to 2%), to give 310mg of orange oil.

NMR ^{1}H (CDCl3, 400MHz) : 7.50 to 7.41 (m, 5*H*, C_{Phenyl}), 7.24 (s, 4-C*H*), 6.76 (t, C*H*F_2, J = 54.9 Hz), 4.26 (q, OCH_2), 1.26 (t, OCH_2CH_3) ppm.

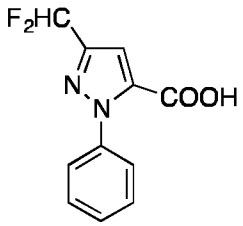
NMR ^{19}F (CDCl3, 376MHz) : -112.2 (d, CHF_2, J = 54.6 Hz) ppm.

NMR ^{13}C (CDCl3, 100MHz) : 158.4 (*C*=O), 146.8 (t, *C*CHF$_2$, J = 30 Hz), 139.8 (NC$_{Phenyl}$), 135.0 (*C*COOEt), 129.2, 128.7, 126.0 (*C*$_{Phenyl}$), 110.7 (t, *C*HF$_2$, J = 234 Hz), 109.6 (4-*C*H), 61.6 (O*C*H$_2$), 13.9 (OCH$_2$*C*H$_3$) ppm.

HRMS (ESI) calcd for $C_{13}H_{13}F_2N_2O_2$ [M+H]: 267.0940. Found: 267.0918.

Example 8

3-(Difluoromethyl)-1-phenyl-1*H*-pyrazole-5-carboxylic acid (VI-2)



A mixture of ethyl 3-(difluoromethyl)-1-phenyl-1H-pyrazole-5-carboxylate (1 eq., 160 mg, 0.601 mmol) and 2N NaOH (1.83 eq., 2 M, 0.55 mL, 1.1 mmol) in EtOH (1 mL) was stirred at room temperature for 1h. The mixture was acidified with HCl 1N to pH 2-3, then was extracted with dichloromethane. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*, to yield a brown solid (160mg) after trituration in pentane. M.p.: 132.7 to 133.5 °C.

NMR ^1H (d^6-DMSO, 400MHz) : 13.6 (*C*OOH), 7.50 (m, 5*H*, C$_{Phenyl}$), 7.25 (s, 4-C*H*), 7.13 (t, C*H*F$_2$, J = 54 Hz) ppm.

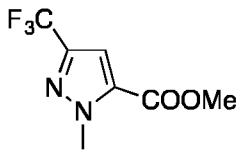
NMR ^{19}F (d^6-DMSO, 376MHz) : -112.2 (d, CH*F*$_2$, J = 53.7 Hz) ppm.

NMR ^{13}C (d^6-DMSO, 100MHz) : 159.3 (*C*OOH), 146.0 (t, *C*CHF$_2$, J = 29 Hz), 139.7 (NC$_{Phenyl}$), 135.9 (*C*COOH), 128.9, 128.7, 125.9 (*C*$_{Phenyl}$), 110.9 (t, *C*HF$_2$, J = 233 Hz), 109.5 (4-*C*H) ppm.

Anal. calcd for $C_{11}H_8F_2N_2O_2$: C, 55.47; H, 3.39; F, 15.95; N, 11.76; O, 13.43. Found: C, 55.97; H, 3.54; N, 11.61.

Example 9

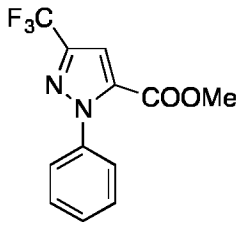
Methyl 1-methyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (I-3)



A solution of methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (1 eq., 150 mg, 0.47 mmol) in MeCN (1 mL) was treated with methyl hydrazine (1.59 eq., 34.4 mg, 40 µL, 0.747 mmol) followed by concentrated H_2SO_4 (0.503 eq., 23.9 mg, 13 µL, 0.237 mmol) under inert atmosphere at room temperature. The mixture was stirred at 90 °C for 1h and removed from oil bath for 5min. Pyridine (8.02 eq., 298 mg, 305 µL, 3.77 mmol) was added, followed by $SOCl_2$ (2.05 eq., 114 mg, 70 µL, 0.965 mmol). The mixture was stirred 30min. Internal standard: fluorobenzene (1.13 eq., 51 mg, 50 µL, 0.531 mmol). ^{19}F NMR yield: >99%.

Example 10

Methyl 1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (I-4)



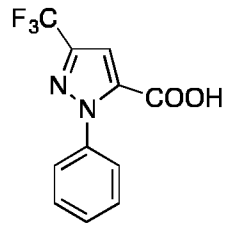
A solution of methyl 4-(benzylamino)-5,5,5-trifluoro-2-oxopent-3-enoate (1 eq., 500 mg, 1.74 mmol) in MeCN (5 mL) was treated with phenylhydrazine (1.51 eq., 283 mg, 0.26 mL, 2.62 mmol) rapidly followed by concentrated H_2SO_4 (0.523 eq., 92 mg, 0.05 mL, 0.91 mmol) under inert atmosphere at room temperature. The mixture was refluxed for 2 days and cooled to room temperature. Pyridine (7.81 eq., 1075 mg, 1.1 mL, 13.6 mmol) was added, followed by a slow addition of $SOCl_2$ (1.98 eq., 410 mg, 0.25 mL, 3.45 mmol) via syringe. The mixture was stirred 30 min.

The mixture was filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (Et_2O in pentane 0 to 5%), to give 370 mg of solid (ca. 80wt.% = 300 mg, 64%).

HRMS (ESI) calcd for $C_{12}H_{10}F_3N_2O_2$ [M+H]: 271.0689. Found: 271.0697.

Example 11

1-phenyl-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid (VI-3)



A mixture of methyl 1-phenyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (1 eq., 170 mg, 0.503 mmol) and 2N NaOH 2N (2.19 eq., 2 M, 0.55 mL, 1.1 mmol) in EtOH (1 mL) was stirred at room temperature for 1h. The mixture was treated with 1N HCl until pH 2-3, then was extracted with dichloromethane. The combined organic layer was washed (brine), dried (Na_2SO_4), filtered and evaporated *in vacuo*, to yield a brown solid. M.p.: 155 - 165 °C (degradation observed).

NMR ^{1}H (d^6-DMSO, 400MHz) : 13.7 (s br, COO*H*), 7.52 (m, 5H, CH_{Phenyl}), 7.50 (4-C*H*) ppm.

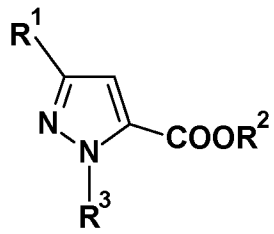
NMR ^{19}F (d^6-DMSO, 376MHz) : -60.9 (s, CF_3) ppm.

NMR ^{13}C (d^6-DMSO, 100MHz) : 158.9 (*C*OOH), 141.0 (q, *C*CF_3, J = 38 Hz), 139.4 (N-1C_{Phenyl}), 136.4 (*C*COOH), 129.3, 128.7, 126.0 (2-6C_{Phenyl}), 120.9 (q, *C*F_3, J = 269 Hz), 110.1 (4-*C*H) ppm.

HRMS (ESI) calcd for $C_{11}H_8F_3N_2O_2$ [M+H]: 257.0532. Found: 257.0536.

Claims:

1. Process for preparing 3-fluoroalkyl-5-pyrazolecarboxylates (**I**),



(I)

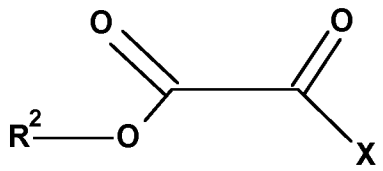
in which

R^1 is selected from C_1-C_6-haloalkyl;

R^2 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{6-18}-aryl and C_{7-18}-arylalkyl-,

R^3 is selected from H, C_1-C_{12} alkyl, benzyl, phenyl, C_{6-18}-aryl and pyridyl;

characterized in that in step (A), oxalic acid derivatives of the formula **(II)**,



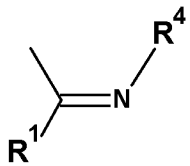
(II)

in which

R^2 is as defined above;

X is F, Cl or Br;

are reacted with compounds of the formula **(III)**,



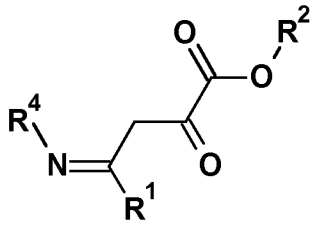
(III)

in which

R^4 is selected from C_{1-12}-alkyl, C_{3-8}-cycloalkyl, benzyl and C_{7-18}-arylalkyl-;

R^1 is as defined above;

in the presence of a base to form compounds of the formula **(IV)**



(IV)

in which

R^1, R^2, R^4 are as defined above

and that in step (B) in the presence of hydrazine H_2N-NHR^3 **(III)**

in which R^3 is as defined above

and an acid the cyclization of **(IV)** takes place to form **(I)**.

2. Process according to claim 1, characterized in that

R^1 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^2 is selected from methyl, ethyl, propyl and *t*-butyl, benzyl and phenylethyl-;

R^3 is selected from H, C_1-C_8 alkyl, aryl, benzyl and pyridyl;

R^4 is selected from methyl, ethyl, *n*-, *iso*-propyl, *n*-, *iso*-, *sec*- und *t*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl and phenylethyl-,

X is F or Cl.

3. Process according to claim 1, characterized in that

R^1 is selected from trifluoromethyl, difluoromethyl, difluorochloromethyl and pentafluoroethyl;

R^2 is selected from methyl and ethyl;

R^3 is selected from H, methyl, ethyl, propyl, isopropyl, butyl, pentyl benzyl and phenyl;

R^4 is selected from benzyl and *iso*-propyl;

X is Cl;

4. Process according to claim 1, characterized in that

R^1 is difluoromethyl, difluorochloromethyl or trifluoromethyl;

R^2 is methyl or ethyl;

R^3 is selected from H, methyl, ethyl, benzyl and phenyl;

R^4 is *iso*-propyl or benzyl;

X is Cl.

5. Process according to claims 1, characterized in that

R^1 is difluoromethyl or trifluoromethyl;

R^2 is methyl or ethyl;

R^3 is selected from H, methyl and phenyl;

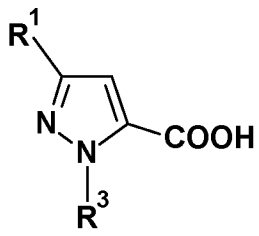
R^4 is benzyl;

X is Cl.

6. Process according to any of claims 1 to 5 wherein the base in step (A) is selected from pyridine, 3-methylpyridine and ethyldiisopropylamine.

7. Process according to any of claims 1 to 6 wherein the acid in step (B) is selected from H_2SO_4, HCl, HF, HBr, HI, H_3PO_4, CH_3COOH, CF_3COOH, p-toluenesulphonic acid, methanesulphonic acid and trifluoromethanesulphonic acid.

8. Process for preparing 3-fluoroalkyl-5-pyrazole acids (**VI**),



(VI)

in which

R^1 is selected from C_1-C_6-haloalkyl;

R^3 is selected from H, C_1-C_{12} alkyl, benzyl, phenyl, C_{6-18}-aryl and pyridyl;

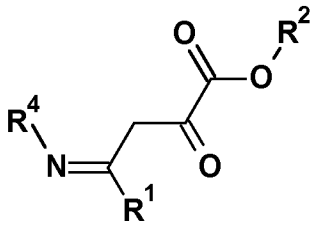
comprising

(i) the process according to any of claims 1 to 7, and

(ii) hydrolysing the compounds of the formula (**I**) to the compound of the formula (**VI**).

9. Process according to claim 8 wherein the reaction is performed under basic conditions, preferably with NaOH, KOH, Na_2CO_3 or K_2CO_3 as base.

10. Compounds of the formula **(IV)**



(IV)

in which

R^1 is difluoromethyl or trifluoromethyl;

R^2 is methyl or ethyl;

R^4 is *iso*-propyl or benzyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/073401

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/14 C07C69/14
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/016282 A2 (DU PONT [US]; ANNIS GARY DAVID [US]; LAHM GEORGE PHILIP [US]; SELBY TH) 27 February 2003 (2003-02-27) Schemes 1-4 on pages 10 and 11; tables 1,3	1-10
A	RIZK E. KHIDRE ET AL: "Synthetic Routes to Pyrazole-3(5)-carboxylates", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 53, no. 1, 11 February 2015 (2015-02-11), pages 13-31, XP055328482, US ISSN: 0022-152X, DOI: 10.1002/jhet.1504 the whole document	1-10

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2017	23/10/2017

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	Guspanová, Jana

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LUCAS MERTENS ET AL: "Fluoroalkyl-Substituted Diazomethanes and Their Application in a General Synthesis of Pyrazoles and Pyrazolines", CHEMISTRY - A EUROPEAN JOURNAL., vol. 22, no. 28, 6 June 2016 (2016-06-06), pages 9542-9545, XP055328440, WEINHEIM, DE ISSN: 0947-6539, DOI: 10.1002/chem.201601707 Scheme 1; tables 1-3 -----	1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/073401

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03016282 A2	27-02-2003	AT 469892 T	15-06-2010
		AU 2002319814 A1	03-03-2003
		CA 2454298 A1	27-02-2003
		EP 1417200 A2	12-05-2004
		JP 4448327 B2	07-04-2010
		JP 2005507873 A	24-03-2005
		US 2004171649 A1	02-09-2004
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