



(51) International Patent Classification:

C07C 225/16 (2006.01) C07D 307/46 (2006.01)
C07D 231/14 (2006.01) C07D 405/04 (2006.01)
C07D 231/22 (2006.01)

(21) International Application Number:

PCT/EP2013/052829

(22) International Filing Date:

13 February 2013 (13.02.2013)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

12356003.9 16 February 2012 (16.02.2012) EP

(71) Applicants: **BAYER INTELLECTUAL PROPERTY GMBH** [DE/DE]; Alfred-Nobel-Str. 10, 40789 Monheim (DE). **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE** [FR/FR]; 3, rue Michel Ange, 75794 Paris Cedex 16 (FR).

(72) Inventors: **PAZENOK, Sergii**; Wipperauer Str. 57, 42699 Solingen (DE). **LANGLOIS, Bernard**; 91 rue Duguesclin, F-69006 Lyon (FR). **BILLARD, Thierry**; 11 bis rue Saint Isidore, F-69003 Lyon (FR). **BARBION, Julien**; 3 Square du Village, F-95110 Sannois (FR). **MARREC, Olivier**; 18 Les Hameaux de Langolvas, F-29610 Piouigneu (FR). **VORS, Jean-Pierre**; 6, Allée Adanson, F-69110 Saint Foy les Lyon (FR).

(74) Agent: **BIP PATENTS**; c/o Bayer Intellectual Property GmbH, Creative Campus Monheim, Alfred-Nobel-Str. 10, 40789 Monheim (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

(54) Title: CF₃O-containing enaminoketones and their utilization for the preparation of CF₃O-containing pyrazoles

(57) Abstract: The present invention pertains to novel enaminoketones containing a CF₃O-group, novel pyrazole-derivatives containing a CF₃O group as well as to a novel process for their preparation comprising aminoformylation of CF₃O-ketones and cyclization of the obtained CF₃O-enaminoketones with hydrazines to trifluoromethoxy pyrazoles.



CF₃O-containing enaminoketones and their utilization for the preparation of CF₃O-containing pyrazoles

The present invention pertains to novel enaminoketones containing a CF₃O-group, novel pyrazole-derivatives containing a CF₃O group as well as to a novel process for their preparation comprising
5 aminoformylation of CF₃O-ketones and cyclization of the obtained CF₃O-enaminoketones with hydrazines to trifluoromethoxy pyrazoles.

Fluorine as a substituent in active ingredients plays a significant and increasingly important role. The biggest group of fluorinated pesticides are the compounds containing a trifluoromethyl group (mainly in aromatic rings), followed by aromatic compounds containing at least one isolated fluorine atom. Only
10 five pesticides contain OCF₃-groups are on the market. It was estimated that the number of fluorinated compounds currently under development represent some 35-50% of all the active ingredients under development as described in The pesticide manual, XIII edition; British crop protection council, 2003 .

For the preparation of trifluoromethoxy substituted arenes the chlorination of aromatic methyl groups and exchange with fluorine can be used as disclosed in Yagupol'skii, L. M. Dokl. Akad. Nauk SSSR.

15 When aryl formates are treated with sulfur tetrafluoride, (trifluoromethoxy)arenes are obtained in yields ranging from 9 – 81% as described in Sheppard, W. A. J. Org. Chem. 1964, 29, 1-11.

The oxidative fluorodesulfurization fluorination allows the conversion of dithiocarbonates (xanthogenates) with a huge excess of hydrogen fluoride-pyridine and 1,3-dibromo-5,5-dimethylhydantoin into (trifluoromethoxy)arenes in moderate to excellent yields as disclosed in
20 Kuroboshi, M.; Suzuki, K.; Hiyama, T. Tetrahedron Lett. 1992, 33, 4173-4176; Kanie, K.; Tanaka, Y.; Suzuki, K.; Kuroboshi, M.; Hiyama, T. Bull. Chem. Soc. Japan 2000, 73, 471-484; Kuroboshi, M.; Kanie, K.; Hiyama, T. Adv. Synth. Catal. 2001, 343, 235-250 and Shimizu, M.; Hiyama, T. Angew. Chem. Int. Ed. 2005, 44, 214 – 231.

Obviously, the best synthesis of trifluoromethyl ethers would be the direct introduction of the whole
25 OCF₃ moiety. This was first done by radical condensation of olefins and trifluoromethyl hypofluorite (Rozen, S. Chem. Rev. 1996, 96, 1717-1736) which is highly hazardous and toxic. Then, numerous attempts to carry out nucleophilic trifluoromethoxylation with trifluoromethoxide salts failed since, generally, CF₃O⁻ anion collapses into fluoride and fluorophosgene, even at low temperature.

DE 10 2007 036702 A1 pertains to synergistic herbicidal combinations comprising an herbicide from the
30 group of pyrazolyphenyl derivatives optionally containing a CF₃O-group as a substituent. DE 102006 050516 A1 pertains to Dihydropyrazolon-derivatives optionally containing a CF₃O-group and processes for their synthesis for use as drugs. Both documents do not contain information about the methods of the

preparation of CF₃O-derivatives nor do they disclose references indicating how such a CF₃O-group can be introduced into the pyrazol moiety or its pre-cursors.

There is presently no generally applicable procedure that allows the preparation of trifluoromethoxypyrazoles. Due to the importance of heterocyclic structures in agrochemical ingredients and the use of fluorine atoms and fluorinated groups in general, the possibility to prepare OCF₃-heterocycles will lead to new, so far unknown ingredients.

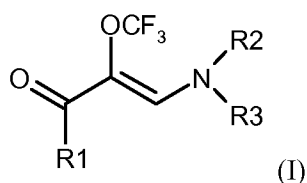
There is thus a strong need for a generally applicable process for the preparation of -OCF₃ pyrazoles.

It was therefore an object of the present invention to provide a generally applicable and economically viable process which can be implemented on the industrial scale for preparing -OCF₃ pyrazoles.

- 10 The problem has been solved according to the present invention by a process for the preparation of trifluoromethoxypyrazoles of formula V-1 or V-2 by first preparing functionalized enaminoketones of formula (I) and then transforming these functionalized enaminoketones into the trifluoromethoxypyrazoles of formula V-1 or V-2.

In one aspect, the present invention thus relates to a process for preparing an enaminoketone of formula

15 I



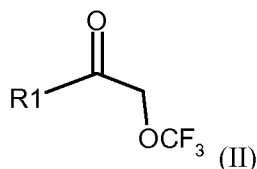
wherein

R¹ is C₅-C₁₀ aryl, optionally substituted by 1 to 5 halogen atoms, or C₅-C₁₀ aryl exhibiting one, two or more heteroatoms selected from oxygen and nitrogen, and

- 20 R² and R³ are independently C₁-C₆ alkyl, C₅-C₁₀ aryl, C₅-C₁₀ aryl exhibiting one, two or more heteroatoms selected from oxygen and nitrogen, or form together a 5 or 7 membered ring

which comprises

(A) reacting a CF₃O-ketone of the formula II



- 25 wherein R¹ is as defined above
with an aminoformylation reagent.

According to a preferred embodiment of the inventive process for preparing an enaminoketone of formula I,

R^1 in formula I or II is 2-furyl, phenyl, or phenyl substituted with one or two chlorine atoms and

R^2 and R^3 in formula I are independently C_1 - C_6 alkyl.

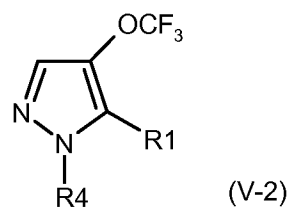
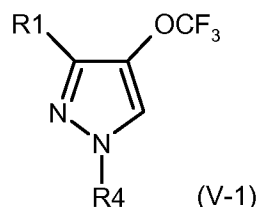
5 According to an even more preferred embodiment of the inventive process for preparing an enaminoketone of formula I,

R^1 in formula I or II is 2-furyl, phenyl, chlorophenyl or dichlorophenyl and

R^2 and R^3 in formula I are C_1 alkyl.

The present invention further relates to a process for preparing trifluoromethoxypyrazoles of formula V-

10 1 or V-2



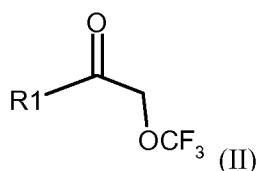
wherein

R^1 is as defined above

R^4 is H, or C_1 - C_6 Alkyl

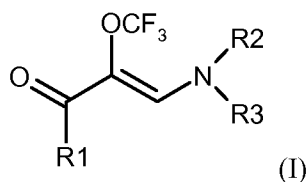
15 which comprises

(A) reacting a CF_3O -ketone of the formula II



wherein R^1 is as defined above

with an aminoformylation reagent to an enaminoketone of formula I



20

wherein

R^1 , R^2 and R^3 are as defined above

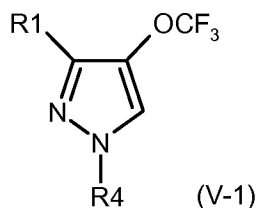
and

(B) reacting the enaminoketone of formula (I) with an hydrazine of formula IV



wherein R^4 is as defined above.

- 5 The present invention further relates to a process for regioselectively preparing trifluoromethoxypyrazoles of formula V-1

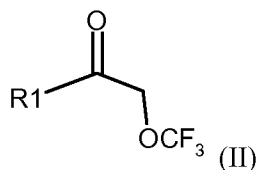


wherein

R^1 and R^4 are as defined above

- 10 which comprises

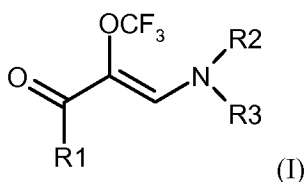
(A) reacting a CF_3O -ketone of the formula II



wherein

R^1 is as defined above

- 15 with an aminoformylation reagent to an enaminoketone of formula I



wherein

R^1 , R^2 and R^3 are as defined above

and

- 20 (B) reacting the enaminoketone of formula (I) with an hydrazine of formula IV



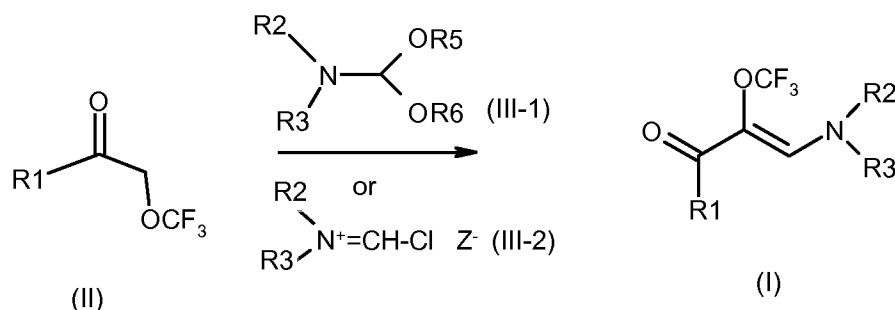
wherein

R^4 is as defined above, with the proviso that R^4 is not hydrogen

wherein (B) is performed in a solvent selected from the group consisting of methanol, ethanol, and trifluoroethanol.

According to a preferred embodiment of the inventive processes for preparing trifluoromethoxypyrazoles of formula V-1 or V-2 or for regioselectively preparing trifluoromethoxypyrazoles of formula V-1, R₄ in formula IV, V-1, or V-2 is H, or C₁-Alkyl.

Step (A) comprises reacting trifluoromethoxyketones according to formula (II) with an aminoformylation reagent according to the subsequent reaction scheme 1:



Scheme 1

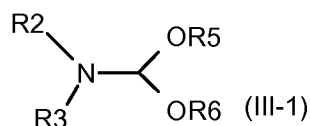
Trifluoromethoxyketones of the formula (II) are commercially available or can be prepared according to the method described in: Marrec, et al. Advanced Synthesis & Catalysis (2010), 352(16), 2831-2837, WO 2009141053 A1 20091126, DE 102008024221, Marrec, et al. Journal of Fluorine Chemistry (2010), 131(2), 200-207.

Trifluoromethoxyketones of the formula (II) can be prepared in two steps starting from the corresponding methylketones. First, methylketones are directly α -iodinated by the following literature processes (Synthesis 2007, 3113-3116; Tetrahedron Lett. 2006, 47, 6883-6886). Then, the resulting α -iodo-methylketones react with trifluoromethyltriflate, in presence of AgF, to perform the substitution of iodine by CF₃O group.

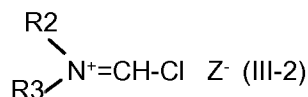
Surprisingly it has been found that 2-(trifluoromethoxy)ketones smoothly react with e.g. Dimethylformamide dimethylacetal to give the novel CF₃O-enaminones.

For the aminoformylation, the following reagents can be used: dimethylformamide dimethylacetal, dimethylformamide diethylacetal, phenylmethylformamidedimethylacetal, or DMF/POCl₃ (which are the precursors of compound III-2 by a Vilsmeier reaction). These reagents are commercially available. According to an especially preferred embodiment of the present invention, Dimethylformamide diethylacetal is used as aminoformylation reagent.

Thus, according to a further embodiment of the present invention, the aminoformylation reagent used for (A) is selected from a compound of the formula III-1



wherein R^2 and R^3 are as defined above and R^5 and R^6 are C_1 - C_6 -Alkyl and a compound of the formula III-2



5 wherein R^2 and R^3 are as defined above.

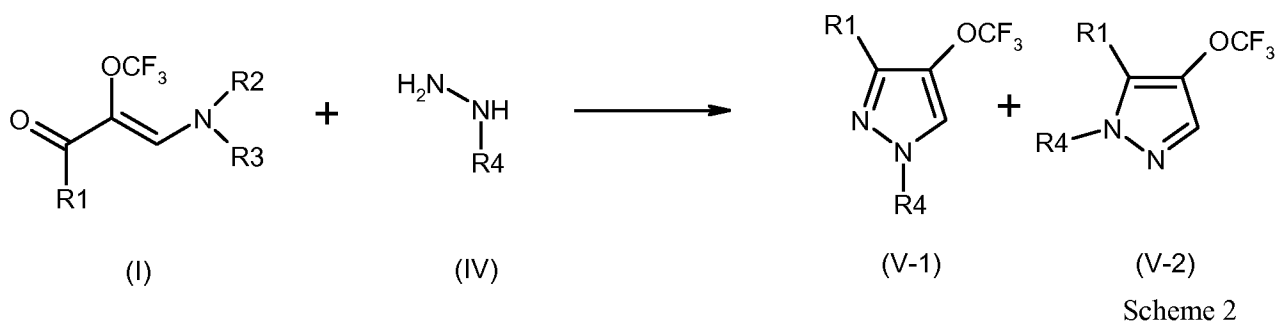
According to a further embodiment of the present invention, (A), as described above, is performed at a temperature of from 50°C to 150°C . More preferably, (A) is performed at a temperature of from 80°C to 120°C .

10 According to a further embodiment of the present invention, (A) is performed in a solvent selected from DMF, toluene, xylenes, chlorobenzenes, and dimethylacetamide.

According to yet another embodiment of the present invention, the reaction time is 3-10 h. More preferably, the reaction time is 4-5 h.

Step (B) Cyclization

15 Step (B) comprises converting enaminoketones of the formula (I) into trifluoromethoxy pyrazoles of the formula (V-1 or V-2) by cyclization with hydrazines of formula (IV) according to the subsequent scheme 2



R^1 , R^2 , R^3 , and R^4 are as defined above.

20 With methylhydrazine, the 2 regioisomeric pyrazoles in a ratio of 60:40 were obtained in acetic acid.

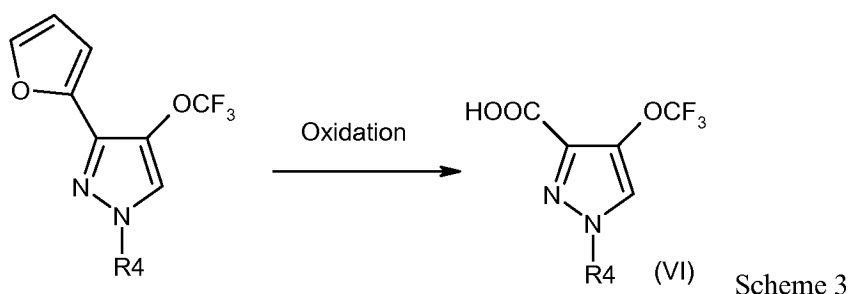
According to a preferred embodiment of the present invention, the process for regioselectively preparing 1-methyl-4-trifluoromethoxy-pyrazoles is performed by using a less acidic solvent, selected from methanol, ethanol, and trifluoroethanol.

25 According to a further embodiment of the present invention, the cyclisation (B) is performed in different solvents selected from alcohols, preferably methanol, ethanol, or isopropanol, nitriles, preferably acetonitrile, or butyronitrile, amides, preferably dimethylformamide, or dimethylacetamide, and organic

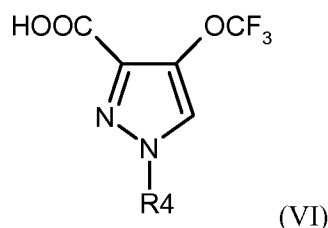
acids, preferably formic acid or acetic acid. Most preferred solvents for the cyclisation (B) are methanol and ethanol.

According to a further embodiment of the present invention, the cyclization (B) is performed at a temperature ranging from 0 °C to 50 °C, more preferably at a temperature ranging from 15°C to 30°C, most preferably at room temperature.

According to a further embodiment of the present invention, pyrazoles of the formula (I) can be further transformed to novel pyrazolic acids bearing a CF₃O-group, if R¹ is 2-Furyl (scheme 3).



The present invention thus further relates to a process for preparing trifluoromethoxypyrazolic acids of formula VI



wherein R⁴ is as defined above, which comprises oxidizing a compound of formula V-1, wherein R¹ is 2-furyl and R⁴ is as defined above.

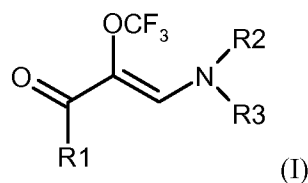
According to a further embodiment of the present invention, the trifluoromethoxypyrazolic acids of formula VI are obtained by oxidizing the compound of formula V-1, wherein R¹ is 2-furyl and R⁴ is as defined above, using an oxidant selected from RuCl₃/NaIO₄, RuO₄, O₃, KMnO₄, and CrO₃.

According to a further preferred embodiment of the present invention, if the system RuCl₂/NaIO is used, 0.05 equivalents of RuCl₃ and 10 equivalents of NaIO₄ are used for 1 equivalent of pyrazole.

The choice of the solvent for the reaction of scheme 3 is very important. It should be inert towards the oxidant. According to a further preferred embodiment of the present invention, the process for preparing trifluoromethoxypyrazolic acids of formula VI is performed in a solvent selected from hexane/AcOEt/H₂O, CCl₄/CH₃CN/H₂O, H₂O/MeCN/AcOEt, and H₂O/CH₂Cl₂/MeCN. Most preferred is the use of hexane/AcOEt/H₂O. Preferred ratios are 1/1/2 for a mixture of hexane/AcOEt/H₂O and 2/2/3 for a mixture of CCl₄/CH₃CN/H₂O.

The oxidation is performed at a temperature ranging from 0°C to 50°C, more preferably at a temperature ranging from 10°C to 30 °C, most preferably at room temperature.

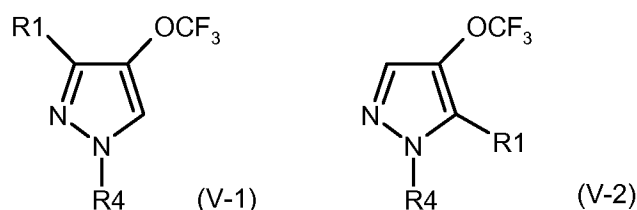
The present invention further relates to a compound of formula I



5 wherein

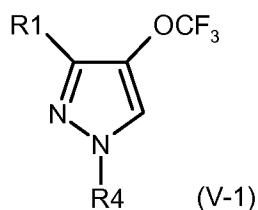
R¹, R² and R³ are as defined above.

The present invention further relates to a compound of formula V-1 or V-2



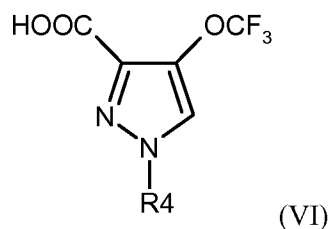
wherein R¹ and R⁴ are as defined above.

10 The present invention further relates to a compound of formula V-1



wherein R¹ and R⁴ are as defined above.

The present invention further relates to a compound of formula VI



15 wherein

R⁴ is as defined above.

General definitions

In connection with the present invention, the term halogen (X) comprises, unless otherwise defined, those elements which are chosen from the group consisting of fluorine, chlorine, bromine and iodine, fluorine, chlorine and bromine being preferably used and fluorine and chlorine being particularly preferably used.

20

Appropriately substituted groups can be mono- or polysubstituted, it being possible for the substituents in polysubstitutions to be identical or different.

Alkyl groups substituted with one or more halogen atoms (-X) are chosen, for example, from trifluoromethyl (CF₃), difluoromethyl (CHF₂), CF₃CH₂, ClCH₂, CF₃CCl₂ and CHF₂CCl₂.

- 5 Alkyl groups in connection with the present invention are, unless otherwise defined, linear, branched or cyclic hydrocarbon groups which can optionally exhibit one, two or more heteroatoms chosen from oxygen, nitrogen, phosphorus and sulphur. In addition, the alkyl groups according to the invention can optionally be substituted by additional groups chosen from -R', halogen (-X), alkoxy (-OR'), thioether or mercapto (-SR'), amino (-NR'²), silyl (-SiR'³), carboxyl (-COOR'), cyano (-CN), acyl (-(C=O)R')
- 10 and amide (-CONR'²) groups, R' being hydrogen or a C₁₋₁₂-alkyl group, preferably a C₂₋₁₀-alkyl group, particularly preferably a C₃₋₈-alkyl group, which can exhibit one or more heteroatoms chosen from nitrogen, oxygen, phosphorus and sulphur.

The definition C₁-C₁₂-alkyl comprises the biggest range defined herein for an alkyl group. Specifically, this definition comprises, for example, the meanings methyl, ethyl, n-propyl, isopropyl, n-butyl,

15 isobutyl, sec-butyl and t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl.

The definition cyclic C₃₋₁₂-alkyl groups comprises the biggest range defined herein for a cyclic alkyl group. Specifically, this definition comprises, for example, the meanings cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

- 20 Alkenyl groups in connection with the present invention are, unless otherwise defined, linear, branched or cyclic hydrocarbon groups which comprise at least one single unsaturation (double bond) and can optionally exhibit one, two or more single or double unsaturations or one, two or more heteroatoms chosen from oxygen, nitrogen, phosphorous and sulphur. In addition, the alkenyl groups according to the invention can optionally be substituted by additional groups chosen from -R', halogen (-X), alkoxy
- 25 (-OR'), thioether or mercapto (-SR'), amino (-NR'²), silyl (-SiR'³), carboxyl (-COOR'), cyano (-CN), acyl (-(C=O)R') and amide (-CONR'²) groups, R' being hydrogen or a C₁₋₁₂-alkyl group, preferably a C₂₋₁₀-alkyl group, particularly preferably a C₃₋₈-alkyl group, which can exhibit one or more heteroatoms chosen from nitrogen, oxygen, phosphorous and sulphur.

The definition C₂-C₁₂-alkenyl comprises the biggest range defined herein for an alkenyl group.

30 Specifically, this definition comprises, for example, the meanings vinyl; allyl (2-propenyl), isopropenyl (1-methylethenyl); but-1-enyl (crotyl), but-2-enyl, but-3-enyl; hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hex-5-enyl; hept-1-enyl, hept-2-enyl, hept-3-enyl, hept-4-enyl, hept-5-enyl, hept-6-enyl; oct-1-enyl, oct-2-enyl, oct-3-enyl, oct-4-enyl, oct-5-enyl, oct-6-enyl, oct-7-enyl; non-1-enyl, non-2-enyl, non-3-enyl, non-4-enyl, non-5-enyl, non-6-enyl, non-7-enyl, non-8-enyl; dec-1-enyl, dec-2-enyl, dec-3-enyl,

dec-4-enyl, dec-5-enyl, dec-6-enyl, dec-7-enyl, dec-8-enyl, dec-9-enyl; undec-1-enyl, undec-2-enyl, undec-3-enyl, undec-4-enyl, undec-5-enyl, undec-6-enyl, undec-7-enyl, undec-8-enyl, undec-9-enyl, undec-10-enyl; dodec-1-enyl, dodec-2-enyl, dodec-3-enyl, dodec-4-enyl, dodec-5-enyl, dodec-6-enyl, dodec-7-enyl, dodec-8-enyl, dodec-9-enyl, dodec-10-enyl, dodec-11-enyl; buta-1,3-dienyl, penta-1,3-dienyl.

Alkynyl groups in connection with the present invention are, unless otherwise defined, linear, branched or cyclic hydrocarbon groups which comprise at least one double unsaturation (triple bond) and can optionally exhibit one, two or more single or double unsaturations or one, two or more heteroatoms chosen from oxygen, nitrogen, phosphorous and sulphur. In addition, the alkynyl groups according to the invention can optionally be substituted by additional groups chosen from -R', halogen (-X), alkoxy (-OR'), thioether or mercapto (-SR'), amino (-NR'2), silyl (-SiR'3), carboxyl (-COOR'), cyano (-CN), acyl (-C(=O)R') and amide (-CONR'2) groups, R' being hydrogen or a linear, branched or cyclic C₁₋₁₂-alkyl group which can exhibit one or more heteroatoms chosen from nitrogen, oxygen, phosphorous and sulphur.

The definition C₂-C₁₂-alkynyl comprises the biggest range defined herein for an alkynyl group. Specifically, this definition comprises, for example, the meanings ethynyl (acetylenyl); prop-1-ynyl and prop-2-ynyl.

Aryl groups in connection with the present invention are, unless otherwise defined, aromatic hydrocarbon groups which can exhibit one, two or more heteroatoms chosen from oxygen, nitrogen, phosphorous and sulphur and can optionally be substituted by additional groups chosen from -R', halogen (-X), alkoxy (-OR'), thioether or mercapto (-SR'), amino (-NR'2), silyl (-SiR'3), carboxyl (-COOR'), cyano (-CN), acyl (-C(=O)R') and amide (-CONR'2) groups, R' being hydrogen or a C₁₋₁₂-alkyl group, preferably a C₂₋₁₀-alkyl group, particularly preferably a C₃₋₈-alkyl group, which can exhibit one or more heteroatoms chosen from nitrogen, oxygen, phosphorous and sulphur.

The definition C₅₋₁₈-aryl comprises the biggest range defined herein for an aryl group having 5 to 18 atoms. Specifically, this definition comprises, for example, the meanings cyclopentadienyl, phenyl, cycloheptatrienyl, cyclooctatetraenyl, naphthyl and anthracenyl.

The definition C₅₋₁₈-aryl groups exhibiting one, two or more heteroatoms chosen from oxygen, nitrogen, phosphorous and sulphur are chosen, for example, from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl and 1,3,4-triazol-2-yl; 1-pyrrolyl, 1-pyrazolyl, 1,2,4-triazol-1-yl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,3,4-

triazol-1-yl; 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 1,3,5-triazin-2-yl and 1,2,4-triazin-3-yl.

Arylalkyl groups (aralkyl groups) in connection with the present invention are, unless otherwise defined, alkyl groups substituted by aryl groups which can exhibit a C₁₋₈-alkylene chain and can be substituted in the aryl backbone or the alkylene chain by one or more heteroatoms chosen from oxygen, nitrogen, phosphorous and sulphur and optionally by additional groups chosen from -R', halogen (-X), alkoxy (-OR'), thioether or mercapto (-SR'), amino (-NR'₂), silyl (-SiR'₃), carboxyl (-COOR'), cyano (-CN), acyl (-(C=O)R') and amide (-CONR'₂) groups, R' being hydrogen or a C₁₋₁₂-alkyl group, preferably a C₂₋₁₀-alkyl group, particularly preferably a C₃₋₈-alkyl group, which can exhibit one or more heteroatoms chosen from nitrogen, oxygen, phosphorous and sulphur.

The definition C₇₋₁₉-aralkyl group comprises the biggest range defined herein for an arylalkyl group with a total of 7 to 19 atoms in the backbone and alkylene chain. Preference is given to those C₇₋₁₉-aralkyl groups comprising 5 or 6 carbon atoms or heteroatoms in the aryl backbone and 1 to 8 carbon atoms in the alkylene chain. Specifically, this definition comprises, for example, the meanings benzyl and phenylethyl.

Alkylaryl groups (alkaryl groups) in connection with the present invention are, unless otherwise defined, aryl groups substituted by alkyl groups which can exhibit a C₁₋₈-alkylene chain and can be substituted in the aryl backbone or the alkylene chain by one or more heteroatoms chosen from oxygen, nitrogen, phosphorous and sulphur and optionally by additional groups chosen from -R', halogen (-X), alkoxy (-OR'), thioether or mercapto (-SR'), amino (-NR'₂), silyl (-SiR'₃), carboxyl (-COOR'), cyano (-CN), acyl (-(C=O)R') and amide (-CONR'₂) groups, R' being hydrogen or a C₁₋₁₂-alkyl group, preferably a C₂₋₁₀-alkyl group, particularly preferably a C₃₋₈-alkyl group, which can exhibit one or more heteroatoms chosen from nitrogen, oxygen, phosphorous and sulphur.

The definition C₇₋₁₉-alkylaryl group comprises the biggest range defined herein for an alkylaryl group with a total of 7 to 19 atoms in the backbone and alkylene chain. Preference is given to those C₇₋₁₉-aralkyl groups comprising 5 or 6 carbon atoms or heteroatoms in the aryl backbone and 1 to 8 carbon atoms in the alkylene chain. Specifically, this definition comprises, for example, the meanings tolyl-, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl.

The alkyl, alkenyl, alkynyl, aryl, alkylaryl and aralkyl groups can furthermore exhibit one or more heteroatoms which, unless otherwise defined, are chosen from nitrogen, oxygen, phosphorous and sulphur. The heteroatoms in this connection replace the carbon atoms indicated.

The compounds according to the invention can exist, if appropriate, as mixtures of different possible isomeric forms, in particular of stereoisomers, such as, e.g., E- and Z-isomers, threo- and erythro-isomers, and optical isomers, but, if appropriate, also tautomers. Both the E- and Z-isomers, as

also the threo- and erythro-isomers, and also the optical isomers, any mixture of these isomers, and the possible tautomeric forms, are disclosed and claimed.

Experimental part

Direct α -Iodination of Aromatic Ketones (Synthesis of educts for synthesis of compounds of formula II):

Finely powdered CuO (1.0 eq.) and I₂ (1.0 eq.) were added to a well-stirred solution of the ketone in anhydrous MeOH (C=0.25M). The mixture was stirred for 5 min and then refluxed. After disappearance of the reactant (monitored by TLC), the mixture was filtered and the solvent was removed under reduced pressure. The residue was poured into 10% Na₂S₂O₃ solution (10 mL/mmol of ketone), the mixture was extracted with AcOEt (3x) and the organic layer was dried (Na₂SO₄). Removal of the solvent and purification of the residue by column chromatography gave the target products (Synthesis 2007, 3113-3116).

Ketone (1.0 eq.) along with I₂ (4.0 eq.) in DME (C=0.2M) was heated in a round-bottomed flask at an oil bath temperature of 90°C for 3 h. Then the contents were cooled and extracted with AcOEt (2x). The combined extract was washed with Na₂S₂O₃ to remove unreacted iodine. Subsequently, the extract was washed with brine (10 mL), dried over MgSO₄ and concentrated. The crude product was purified by silica gel chromatography and the corresponding α -iodo product was isolated (Tetrahedron Lett. 2006, 47, 6883-6886).

2-(Iodoacetyl)furan

Brown oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (dd, J = 1.8/0.9 Hz, 1H), 7.32 (dd, J = 3.6/0.9 Hz, 1H), 6.58 (dd, J = 3.6/1.8 Hz, 1H), 4.24 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 181.9, 149.6, 146.9, 118.8, 112.8, 0.6.

1-(Iodoacetyl)-3,5-dichlorobenzene

Brown oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.82 (d, J = 1.8 Hz, 2H), 7.55 (dd, J = 1.8/1.8 Hz, 1H), 4.34 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 190.2, 139.1, 135.7, 135.6, 133.2, 127.2, 0.9.

1-(Iodoacetyl)-2,3-dichlorobenzene

Brown oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.49 (dd, J = 8.1/1.5 Hz, 1H), 7.35 (dd, J = 7.5/1.5 Hz, 1H), 7.22 (dd, J = 8.1/7.5 Hz, 1H), 4.33 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 194.3, 138.1, 133.7, 132.6, 128.8, 127.7, 127.5, 6.1.

Nucleophilic Trifluoromethoxylation with TFMT and AgF (Synthesis of compounds of formula II):

In a 10 mL round-bottomed flask, equipped with a rubber septum and a magnetic stirrer, AgF (1.1 eq.) was introduced. Under argon atmosphere, anhydrous CH₃CN (C=0.5M) was added and the heterogeneous mixture was cooled to -30°C. TFMT (1.1 eq., 300 µL/mmol of iodoacetyl aromatic compound was then added, the vessel was tightly closed (autogenous pressure of COF₂ is needed to allow the reaction to proceed) and the reaction mixture was stirred for 2 h at -30°C. After addition of the electrophile (1.0 eq., neat when liquid or dissolved in the minimum of CH₃CN when oil or solid) by the mean of a gas-tight syringe, stirring was continued at -30°C for 30 min then at r.t. for 24 h (in the dark). Finally, the vessel was depressurised and the reaction mixture was filtered over Celite®. The filtrate was concentrated in vacuo, the residue was dissolved in DCM, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by chromatography over silica gel finally afforded the pure corresponding trifluoromethyl ether (J. Fluorine Chem. 2010, 131, 200-207).

1-phenyl-2-(trifluoromethoxy)ethanone

Yellow oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.91 (m, 2H) ; 7.65 (m, 1H) ; 7.52 (m, 2H) ; 5.18 (s, 2H). ¹³C NMR : 190.2; 134.4; 133.8; 129.1; 127.9; 121.8 (q, J=256.3) ; 68.4 (q, J=2.9). ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.44 (s, CF₃)

1-(2-Furyl)-2-(trifluoromethoxy)ethanone

Brown oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.63 (dd, J = 1.5/0.6 Hz, 1H), 7.35 (dd, J = 3.6/0.6 Hz, 1H), 6.61 (dd, J = 3.6/1.5 Hz, 1H), 5.01 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 179.4, 150.1, 147.2, 121.6 (q, 1JC-F = 255.0), 118.8, 112.8, 67.6 (q, 3JC-F = 3.0). ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.65 (s).

1-(Trifluoromethoxyacetyl)-3,5-dichlorobenzene

Brown oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.74 (d, J = 1.8 Hz, 2H), 7.59 (dd, J = 1.8/1.8 Hz, 1H), 5.12 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 188.1, 136.1, 135.9, 133.9, 127.3, 126.3, 121.5 (q, 1JC-F = 255.6), 68.1 (q, 3JC-F = 3.0). ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.60 (s).

1-(Trifluoromethoxyacetyl)-2,3-dichlorobenzene

Yellow oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.57 (dd, J = 8.1/1.8 Hz, 1H), 7.33 (dd, J = 7.5/1.8 Hz, 1H), 7.26 (dd, J = 8.1/7.5 Hz, 1H), 5.07 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 192.8, 137.1, 133.9, 133.2, 129.1, 127.7, 127.2, 121.1 (q, 1JC-F = 255.2), 69.7 (q, 3JC-F = 2.9). ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.28 (s).

1-(Trifluoromethoxyacetyl)-3-chlorobenzene

Yellow oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.82 (dd, J = 1.2/0.9 Hz, 1H), 7.73 (ddd, J = 7.8/1.5/1.2 Hz, 1H), 7.54 (ddd, J = 7.8/1.5/0.9 Hz, 1H), 7.40 (dd, J = 7.8/7.8 Hz, 1H), 5.14 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 188.9, 135.2, 135.0, 134.0, 130.2, 127.8, 125.8, 121.4 (q, 1JC-F = 255.1), 68.1 (q, 3JC-F = 2.9). ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.63 (s).

Enaminoketone Synthesis with DMF.DMA (Synthesis of compounds of formula I):

A solution of trifluoromethoxymethyl aryl ketone or trifluoromethoxymethyl heteroaryl ketone (1.0 eq.) and N,N-dimethylformamide dimethyl acetal (DMF.DMA) (10 eq.) was refluxed for 5 hours (monitored by TLC). The reaction mixture was cooled down, concentrated in vacuo and the residue was purified by chromatography over silica gel to yield pure desired trifluoromethoxylated enaminoketone.

(2Z or 2E)-3-(dimethylamino)-1-phenyl-2-(trifluoromethoxy)prop-2-en-1-one

Yellow oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.60 (m, 2H); 7.47-7.33 (massif, 3H); 7.01 (broad s, 1H); 3.12 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ = 188.5; 145.4; 139.4; 130.6; 128.4; 128.2; 122.9 (m); 121.3 (q, 1JC-F=255.0); 42.4 (broad s). ¹⁹F NMR (282 MHz, CDCl₃): δ = -58.96 (s).

15 (2Z or 2E)-3-(Dimethylamino)-1-(2-furyl)-2-(trifluoromethoxy)prop-2-en-1-one

Yellow oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.50 (dd, J = 1.5/0.6 Hz, 1H), 7.46 (bs, 1H), 7.10 (dd, J = 3.6/0.6 Hz, 1H), 6.61 (dd, J = 3.6/1.5 Hz, 1H), 3.12 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ = 173.9, 151.6, 144.8, 143.5, 121.3, 121.1 (q, 1JC-F = 255.0), 116.9, 111.5, 43.3, 42.6. ¹⁹F NMR (282 MHz, CDCl₃): δ = -59.47 (s).

20 (2Z or 2E)-3-(Dimethylamino)-1-(3',5'-dichlorophenyl)-2-(trifluoromethoxy)prop-2-en-1-one

Yellow solid (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.41 (d, J = 1.8 Hz, 2H), 7.36 (dd, J = 1.8/1.8 Hz, 1H), 7.01 (bs, 1H), 3.10 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ = 184.7, 145.3, 141.8, 134.7, 130.1, 126.5, 121.7, 120.9 (q, 1JC-F = 255.5), 30.7, 29.1. ¹⁹F NMR (282 MHz, CDCl₃): δ = -59.02 (s).

(2Z or 2E)-3-(Dimethylamino)-1-(2',3'-dichlorophenyl)-2-(trifluoromethoxy)prop-2-en-1-one

25 Brown solid (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.47 (d, J = 8.1 Hz, 1H), 7.26 (dd, J = 8.1/7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.56 (bs, 1H), 3.13 (bs, 6H). ¹³C NMR (75 MHz, CDCl₃): δ = 183.2, 147.0, 140.2, 132.9, 130.4, 128.7, 126.4, 125.7, 122.3, 120.6 (q, 1JC-F = 255.4), 46.8, 37.8. ¹⁹F NMR (282 MHz, CDCl₃): δ = -58.74 (s).

(2Z or 2E)-3-(Dimethylamino)-1-(3'-chlorophenyl)-2-(trifluoromethoxy)prop-2-en-1-one

Brown oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.52 (bs, 1H), 7.41 (ddd, J = 7.5/1.8/1.2 Hz, 1H), 7.35 (ddd, J = 7.8/1.8/0.9 Hz, 1H), 7.27 (ddd, J = 7.8/7.5/2.4 Hz, 1H), 6.96 (bs, 1H), 3.07 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ = 186.4, 145.3 (bs), 140.8, 134.0, 130.3, 129.3, 128.1, 126.2, 122.1 (bs), 121.0 (q, 1JC-F = 255.1), 30.7. ¹⁹F NMR (282 MHz, CDCl₃): δ = -59.25 (s).

5 **Preparation of Trifluoromethoxylated Pyrazoles (Synthesis of compounds of formula V-1 and V-2):**

To a solution of trifluoromethoxylated enaminoketone (1.0 eq.) in glacial AcOH (C=0.2M) was added hydrazine hydrate (N₂H₄·H₂O) (1.0 eq.) and the resulting mixture was stirred at r.t. overnight. Then, an aqueous solution of AcONa (5%) was added and the mixture was extracted with DCM (3x). The organic
10 layers were combined, washed with saturated aqueous NaHCO₃, brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by chromatography over silica gel finally afforded the pure trifluoromethoxylated pyrazole.

3-Phenyl-4-(trifluoromethoxy)-1H-pyrazole

White solid (at 25°C); Mp = 84-85°C; ¹H NMR (300 MHz, CDCl₃): δ = 9.69 (bs, 1H), 7.73 (m, 2H),
15 7.62 (bs, 1H), 7.47-7.37 (massif, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 138.4 (bs), 131.1 (bs), 129.1, 128.8, 129.6 (bs), 126.7, 120.8 (q, 1JC-F = 256.6); ¹⁹F NMR (282 MHz, CDCl₃): δ = -60.77 (s).

3-(2-Furyl)-4-(trifluoromethoxy)-1H-pyrazole

Orange solid (at 25°C). Mp = 85°C. ¹H NMR (300 MHz, CDCl₃): δ = 11.45 (bs, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.51 (dd, J = 1.8/0.9 Hz, 1H), 6.80 (dd, J = 3.3/0.9 Hz, 1H), 6.56 (dd, J = 3.3/1.8 Hz, 1H). ¹³C
20 NMR (75 MHz, CDCl₃): δ = 144.1, 142.2, 132.2 (bs), 129.3 (bs), 124.9 (bs), 120.8 (q, 1JC-F = 252.2), 111.8, 108.8. ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.00 (s).

3-(3',5'-dichlorophenyl)-4-(trifluoromethoxy)-1H-pyrazole

White solid (at 25°C). Mp = 89°C. ¹H NMR (300 MHz, CDCl₃): δ = 11.56 (bs, 1H), 7.68 (bs, 1H), 7.61 (d, J = 1.8 Hz, 2H), 7.36 (dd, J = 1.8/1.8 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 137.8 (bs), 135.6,
25 132.0, 131.9 (bs), 128.7, 125.0, 124.9 (bs), 120.5 (q, 1JC-F = 257.6). ¹⁹F NMR (282 MHz, CDCl₃): δ = -60.92 (s).

3-(2',3'-dichlorophenyl)-4-(trifluoromethoxy)-1H-pyrazole

Yellow oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 11.13 (bs, 1H), 7.59 (bs, 1H), 7.51 (dd, J = 7.5/1.8 Hz, 1H), 7.28 (dd, J = 7.8/1.8 Hz, 1H), 7.22 (dd, J = 7.8/7.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 137.1 (bs), 133.9, 132.0, 131.3, 129.8 (bs), 129.7, 127.2, 125.0 (bs), 120.4 (q, 1JC-F =
30 256.7). ¹⁹F NMR (282 MHz, CDCl₃): δ = -60.97 (s).

3-(3'-Chlorophenyl)-4-(trifluoromethoxy)-1H-pyrazole

Yellow solid (at 25°C). Mp = 44°C. ¹H NMR (300 MHz, CDCl₃): δ = 12.20 (bs, 1H), 7.63 (bs, 1H), 7.54 (bs, 1H), 7.51 (dd, J = 7.8/1.8 Hz, 1H), 7.26 (dd, J = 7.8/1.8 Hz, 1H), 7.24 (dd, J = 7.8/7.8 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 137.8, 134.8, 130.9 (bs), 130.5, 130.1, 128.9, 126.5, 125.7 (bs), 124.7, 120.6 (q, 1JC-F = 257.0). ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.10 (s).

Regioselective preparation of Trifluoromethoxylated Methylpyrazoles (Synthesis of compounds of formula V-1):

To a solution of trifluoromethoxylated enaminoketone (1.0 eq.) in absolute EtOH (C=0.2M) was added methyl hydrazine (MeNHNH₂) (5.0 eq.) and the resulting mixture was stirred at r.t. for 5 hours (monitored by TLC). Then, the reaction mixture was concentrated in vacuo, the residue was dissolved in AcOEt, washed with water and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by chromatography over silica gel finally afforded the pure trifluoromethoxylated methylpyrazole.

3-(2-Furyl)-1-methyl-4-(trifluoromethoxy)pyrazole

Colourless oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.48 (dd, J = 1.8/0.9 Hz, 1H), 7.40 (d, J = 0.9 Hz, 1H), 6.70 (dd, J = 3.3/0.9 Hz, 1H), 6.47 (dd, J = 3.3/1.8 Hz, 1H), 3.90 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 145.2, 142.2, 135.0, 129.1 (bs), 122.6, 120.6 (q, 1JC-F = 256.0), 111.1, 108.1, 40.0. ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.08 (s).

3-(3',5'-dichlorophenyl)-4-(trifluoromethoxy)-1-methylpyrazole

Yellow oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.72 (d, J = 1.8 Hz, 2H), 7.43 (d, J = 1.2 Hz, 1H), 7.30 (dd, J = 1.8/1.8 Hz, 1H), 3.88 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 138.8, 135.1, 133.7, 130.7 (q, 3JC-F = 2.4), 127.8, 124.6, 123.0, 120.5 (q, 1JC-F = 257.0), 40.0. ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.20 (s).

3-(2',3'-dichlorobenzyl)-4-(trifluoromethoxy)-1-methylpyrazole

White solid (at 25°C). Mp = 62°C. ¹H NMR (300 MHz, CDCl₃): δ = 7.51 (dd, J = 7.8/1.5 Hz, 1H), 7.47 (bs, 1H), 7.33 (dd, J = 7.8/1.8 Hz, 1H), 7.24 (dd, J = 7.8/7.8 Hz, 1H), 3.93 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 140.8 (bs), 133.5, 132.3, 132.0, 131.1 (bs), 130.7, 130.0, 127.0, 122.1, 120.4 (q, 1JC-F = 254.8), 40.0. ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.12 (s).

3-(3'-Chlorophenyl)-4-(trifluoromethoxy)-1-methylpyrazole

Yellow oil (at 25°C). ¹H NMR (300 MHz, CDCl₃): δ = 7.83 (bs, 1H), 7.69 (ddd, J = 6.9/1.8/1.2 Hz, 1H), 7.36 (d, J = 1.2 Hz, 1H), 7.29 (dd, J = 7.5/6.9 Hz, 1H), 7.27 (dd, J = 7.5/1.8 Hz, 1H), 3.80. ¹³C NMR (75 MHz, CDCl₃): δ = 140.0, 134.4, 132.6, 130.5 (q, 3JC-F = 2.4), 129.7, 127.9, 126.3, 124.4, 122.9 (bs), 120.5 (q, 1JC-F = 256.4), 39.7. ¹⁹F NMR (282 MHz, CDCl₃): δ = -61.25 (s).

5 Oxidation of heterocycles bearing a 2-furyl moiety (Synthesis of compounds of formula VI):

To a solution of (2-furyl)-pyrazole (1.0 eq.) in a mixture of n-Hexane/AcOEt/H₂O (1:1:2, C=0.1M) was added NaIO₄ (10 eq.) (can be previously dissolved in H₂O before addition), followed by RuCl₃ (0.05M aqueous solution) (0.05 eq.). The heterogeneous reaction mixture was vigorously stirred at r.t. overnight. Then, the mixture was poured into solid NaCl (4g/mmol of heterocycle) and a minimum of water. After 10 min of vigorous agitation, the reaction mixture was extracted with AcOEt (x3) (pH=3-4 for the combined aqueous layers). The organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo to give the crude desired carboxylic acid. The reaction may also be performed with (2-furyl)-pyridine or (2-furyl)-pyrimidine.

4-(Trifluoromethoxy)-3-carboxy-1H-pyrazole

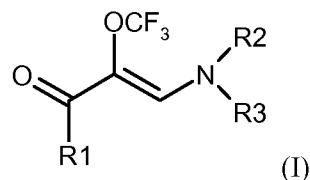
15 White solid (at 25°C). ¹H NMR (300 MHz, (CD₃)₂CO): δ = 10.66 (bs, 1H), 7.94 (d, J = 0.9 Hz, 1H). ¹³C NMR (75 MHz, (CD₃)₂CO): δ = 160.4, 134.6 (bs), 131.2, 128.0, 121.4 (q, 1JC-F = 254.6). ¹⁹F NMR (282 MHz, (CD₃)₂CO): δ = -61.70 (s).

4-(Trifluoromethoxy)-3-carboxy-1-methylpyrazole

20 White solid (at 25°C). ¹H NMR (300 MHz, (CD₃)₂CO): δ = 10.76 (bs, 1H), 7.98 (s, 1H), 3.98 (s, 3H). ¹³C NMR (75 MHz, (CD₃)₂CO): δ = 161.3, 134.7, 134.1 (q, 3JC-F = 2.7), 125.6, 121.3 (q, 1JC-F = 254.5), 40.7. ¹⁹F NMR (282 MHz, (CD₃)₂CO): δ = -61.86 (s).

CLAIMS:

1. Process for preparing an enaminoketone of formula I



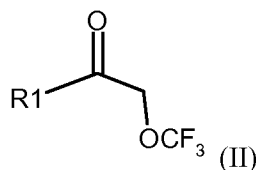
wherein

- 5 R^1 is C_5 - C_{10} aryl, optionally substituted by 1 to 5 halogen atoms, or C_5 - C_{10} aryl exhibiting one, two or more heteroatoms selected from oxygen and nitrogen, and

R^2 and R^3 are independently C_1 - C_6 alkyl, C_5 - C_{10} aryl, C_5 - C_{10} aryl exhibiting one, two or more heteroatoms selected from oxygen and nitrogen, or form together a 5 or 7 membered ring

which comprises

- 10 (A) reacting a CF_3O -ketone of the formula II



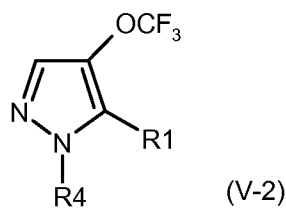
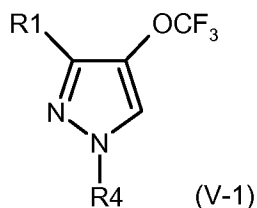
wherein R^1 is as defined above with an aminoformylation reagent.

2. Process according to Claim 1, wherein

R^1 is 2-furyl, phenyl, or phenyl substituted with one or two chlorine atoms and

- 15 R^2 and R^3 are independently C_1 - C_6 alkyl.

3. Process for preparing trifluoromethoxypyrazoles of formula V-1 or V-2



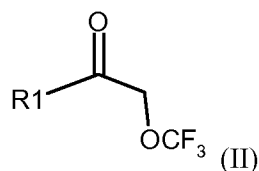
wherein

R^1 is as defined in Claim 1 or 2, and

- 20 R^4 is H, or C_1 - C_6 Alkyl

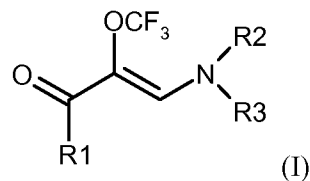
which comprises

- (A) reacting a CF_3O -ketone of the formula II



wherein R^1 is as defined in Claim 1 or 2

with an aminoformylation reagent to an enaminoketone of formula I



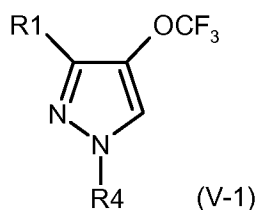
5 wherein R^1 , R^2 and R^3 are as defined in Claim 1 or 2 and

(B) reacting the enaminoketone of formula (I) with an hydrazine of formula IV



wherein R^4 is as defined above.

4. Process for regioselectively preparing trifluoromethoxypyrazoles of formula V-1



10

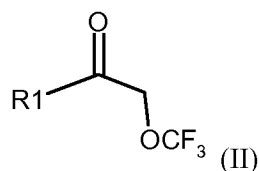
wherein

R^1 is as defined in Claim 1 or 2 and

R^4 is as defined in Claim 3, with the proviso that R^4 is not hydrogen,

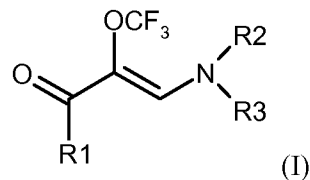
which comprises

15 (A) reacting a CF_3O -ketone of the formula II



wherein R^1 is as defined in Claim 1 or 2

with an aminoformylation reagent to an enaminoketone of formula I



20

wherein R^1 , R^2 and R^3 are as defined in Claim 1 or 2 and

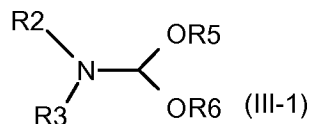
(B) reacting the enaminoketone of formula (I) with an hydrazine of formula IV



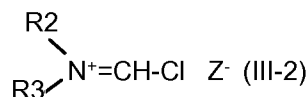
wherein R^4 is as defined in Claim 3,

wherein (B) is performed in a solvent selected from the group consisting of methanol, ethanol, and trifluoroethanol.

5. Process according to any of Claims 1 to 4, wherein the aminoformylation reagent used for (A) is selected from a compound of the formula III-1

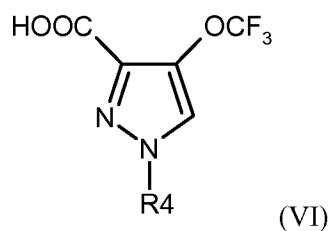


wherein R^2 and R^3 are as defined in Claim 1 or 2 and R^5 and R^6 are C_1 - C_6 -Alkyl and a compound of the formula III-2



wherein R^2 and R^3 are as defined in Claim 1 or 2.

6. Process according to any of Claims 1 to 5, wherein (A) is performed at a temperature of from 50°C to 150°C .
7. Process according to any of Claims 1 to 6, wherein the (A) is performed in a solvent selected from DMF, toluene, xylenes, chlorobenzenes, and dimethylacetamide.
8. Process according to any of Claims 2 to 7, wherein (B) is performed at a temperature of from 0°C to 50°C .
9. Process for preparing trifluoromethoxypyrazolic acids of formula VI



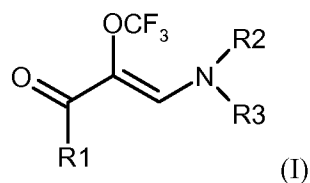
wherein R^4 is as defined in Claim 3,

which comprises oxidizing a compound of formula V-1, wherein R^1 is 2-Furyl and R^4 is as defined in Claim 3.

10. Process according to Claim 9, wherein the compound of formula V-1 is oxidized using an oxidant selected from $\text{RuCl}_3/\text{NaIO}_4$, RuO_4 , O_3 , KMnO_4 , and CrO_3 .

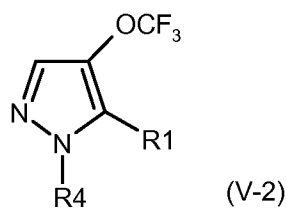
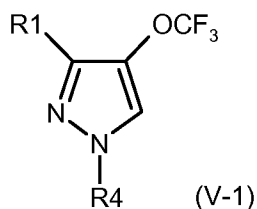
11. Process according to Claim 9 or 10, wherein the process is performed in a solvent selected from hexane/AcOEt/H₂O, CCl₄/CH₃CN/H₂O, H₂O/MeCN/AcOEt, and H₂O/CH₂Cl₂/MeCN.

12. Compound of formula I



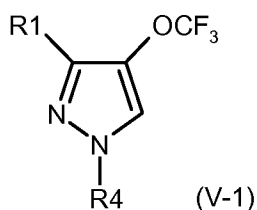
5 wherein R¹, R² and R³ are as defined in Claim 1 or 2.

13. Compound of formula V-1 or V-2



wherein R¹ is as defined in claim 1 or 2 and R⁴ is as defined in Claim 3.

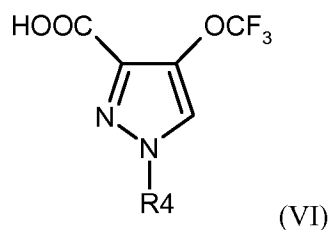
14. Compound of formula V-1



10

wherein R¹ is as defined in Claim 1 or 2 and R⁴ is as defined in Claim 3.

15. Compound of formula VI



wherein R⁴ is as defined in Claim 3.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/052829

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C225/16 C07D231/14 C07D231/22 C07D307/46 C07D405/04
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)
C07C C07D

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

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

EPO-Internal, WPI Data, BEILSTEIN 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 2009/141053 A1 (MERCK PATENT GMBH [DE]; IGNATYEV NIKOLAI MYKOLA [DE]; HIERSE WOLFGANG) 26 November 2009 (2009-11-26) cited in the application claims; examples	1-15
A	MARREC O ET AL: "A deeper insight into direct trifluoromethoxylation with trifluoromethyl triflate", JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER, NL, vol. 131, no. 2, 1 February 2010 (2010-02-01), pages 200-207, XP026871303, ISSN: 0022-1139 [retrieved on 2009-11-17] cited in the application the whole document	1-15
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"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

26 April 2013

Date of mailing of the international search report

07/05/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Zervas, Brigitte

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/052829

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUODONG YIN ET AL: "Highly Efficient and Clean Method for Direct [alpha]-Iodination of Aromatic Ketones", SYNTHESIS, vol. 2007, no. 20, 1 October 2007 (2007-10-01), pages 3113-3116, XP055031150, ISSN: 0039-7881, DOI: 10.1055/s-2007-983880 cited in the application the whole document	1-15
A	----- DE 10 2006 050516 A1 (BAYER HEALTHCARE AG [DE]) 30 April 2008 (2008-04-30) claims 1,5; examples	1-15
A	----- DE 10 2007 036702 A1 (BAYER CROPSCIENCE AG [DE]) 5 February 2009 (2009-02-05) claim 1 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/052829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009141053 A1	26-11-2009	CN 102036943 A	27-04-2011
		DE 102008024221 A1	26-11-2009
		EP 2280918 A1	09-02-2011
		JP 2011522798 A	04-08-2011
		KR 20110009716 A	28-01-2011
		RU 2010152006 A	27-06-2012
		US 2011082312 A1	07-04-2011
		WO 2009141053 A1	26-11-2009

DE 102006050516 A1	30-04-2008	AR 063392 A1	28-01-2009
		AU 2007328052 A1	12-06-2008
		CA 2667382 A1	12-06-2008
		CN 101631785 A	20-01-2010
		CO 6170359 A2	18-06-2010
		CR 10750 A	16-09-2009
		CU 200900066 A7	21-09-2011
		CU 20110119 A7	31-01-2012
		DE 102006050516 A1	30-04-2008
		EP 2084151 A1	05-08-2009
		EP 2383269 A2	02-11-2011
		EP 2546253 A1	16-01-2013
		GT 200900095 A	12-10-2011
		HN 2009000784 A	27-02-2012
		JP 2010507602 A	11-03-2010
		JP 2011006486 A	13-01-2011
		KR 20090074811 A	07-07-2009
		MA 30914 B1	02-11-2009
		NZ 576458 A	22-12-2011
		PE 06202012 A1	27-05-2012
		PE 06352012 A1	20-05-2012
		PE 08952008 A1	05-09-2008
		RU 2009119431 A	10-12-2010
		SG 176421 A1	29-12-2011
		SV 2009003236 A	19-01-2010
		TW 200833330 A	16-08-2008
		US 2010305085 A1	02-12-2010
		US 2012121727 A1	17-05-2012
		UY 30663 A1	31-05-2008
		WO 2008067871 A1	12-06-2008
		ZA 200902705 A	30-06-2010

DE 102007036702 A1	05-02-2009	NONE	
