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(54) Title: NOVEL PROCESS FOR THE PREPARATION OF 5-(4-CHLOROPHENYL)-1-(2,4-DICHLOROPHENYL)-4-METHYL-N-(PIPERIDIN-1-YL)PYRAZOLE-3-CARBOXAMIDE

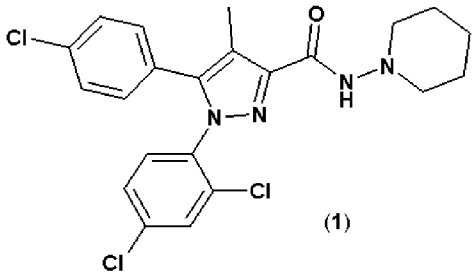
(57) Abstract: The present invention relates to a novel process for the preparation of certain pyrazole derivatives, in particular for the preparation of Rimonabant. The process employs carbon-nitrogen-coupling of a pyrazole-derivative in the presence of a transition metal catalyst.

Novel Process for the preparation of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)pyrazole-3-carboxamide

The present invention relates to a process for the synthesis of Rimonabant, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)pyrazole-3-carboxamide.

Background of the invention

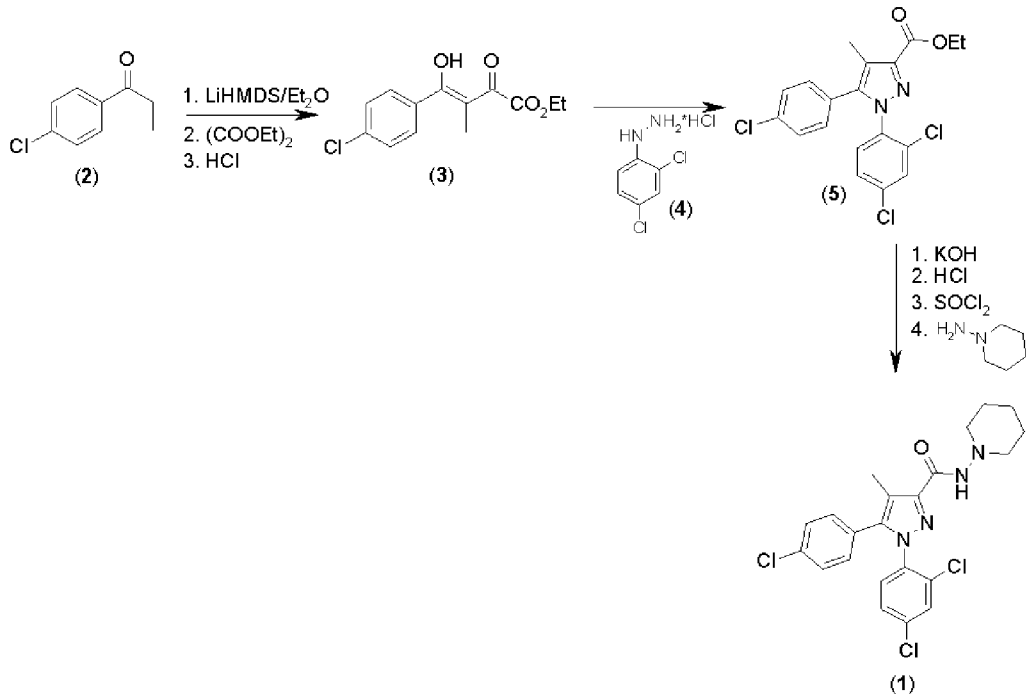
Rimonabant is a drug with the CAS name 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)pyrazole-3-carboxamide, having structural formula 1



(1)

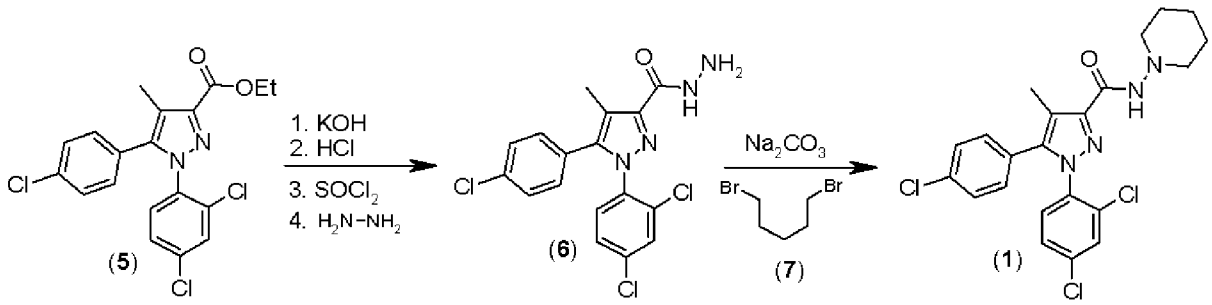
Rimonabant as a free base is presently being used for the treatment of obesity and its mode of function is presumed to be via inhibition of the CB_1-receptor. The compound was first disclosed in EP 656354 and also in US 5624941. Rimonabant may be prepared according to the process disclosed in EP 656354, by a general condensation reaction to produce the pyrazole-ring system 5 (according to Murray et al., J. Heterocycl. Chem. 1989, 26, 1389ff.) which is further modified by a coupling reaction to obtain Rimonabant, as described in Scheme 1.

Scheme 1



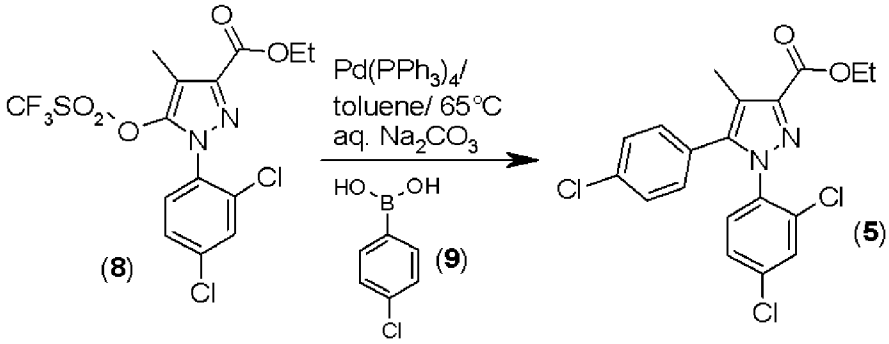
A further process is disclosed in WO2006021652 in which Rimonabant is formed via an alkylation reaction of the hydrazide 6 with dibromopentane (7) in the presence of base as outlined in Scheme 2.

Scheme 2



A further process to a key intermediate of Rimonabant is disclosed in WO2005115989 in which the heterocyclic carboxylic ester is formed via a Suzuki-coupling reaction of the pyrazoletrifluoromethansulfonate 8 with 4-chlorophenylboronic acid 9 as outlined in Scheme 3.

Scheme 3

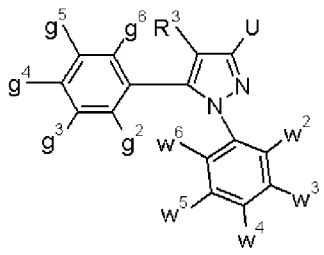


All three processes have in common that the synthesis to the major intermediate 5 has disadvantages with regard to regioselectivity during the formation of the pyrazole-ring. Therefore, there is a need in the art for a process that overcomes the problems of the prior art.

The present invention relates to a novel process for the preparation of pyrazole derivatives of formula (10), in particular for the preparation of Rimonabant. The process employs carbon-nitrogen-coupling of a pyrazole-derivative in the presence of a transition metal catalyst and optionally a suitable phosphine-derived ligand. The process of the present invention is applicable to pilot plant and even industrial scale synthesis. It has been found that no regioselectivity problems occur during the synthesis of the pyrazole-derivative by the inventive process.

Detailed description of the invention

The present invention provides a process for the preparation of pyrazole-derivatives of structural formula 10:



(10)

wherein U is –CN or a group of formula , wherein the carbon atom of the carbonyl group is bonded to pyrazol heterocycle, g^2, g^3, g^4, g^5 and g^6, and w^2, w^3, w^4, w^5 and w^6 are identical or different from another and may independently be hydrogen, chlorine, bromine , $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, trifluoromethyl or a nitro group;

R^3 may be hydrogen or $(C_1$-$C_3)$alkyl, in particular methyl;

R may be a group NR^1R^2 in which R^1 and R^2 are independently selected from the group of
$(C_1$-$C_6)$alkyl;
non-aromatic $(C_3$-$C_{15})$ carbocyclic radical, optionally substituted;
amino-$(C_1$-$C_4)$alkyl wherein the amino group is optionally disubstituted by a $(C_1$-$C_3)$alkyl;
cycloalkyl-$(C_1$-$C_3)$ alkyl wherein the cycloalkyl is C_3-C_{12};
phenyl which may be unsubstituted, monosubstituted or polysubstituted by halogen, by a $(C_1$-$C_5)$alkyl or by a $(C_1$-$C_5)$alkoxy;
phenyl $(C_1$-$C_3)$alkyl;
diphenyl-$(C_1$-$C_3)$alkyl;
naphthyl;
anthracenyl;
saturated 5- to 8-membered heterocyclic radical which is unsubstituted or substituted $(C_1$-$C_3)$alkyl, by a hydroxyl or by a benzyl group;
1-adamantylmethyl;
and aromatic heterocycle, which may be unsusbtituted, mono- or polysubstituted by a halogen, a $(C_1$-$C_5)$alkyl, a $(C_1$-$C_5)$alkoxy;

a $(C_1$-$C_3)$alkyl substituted by an aromatic heterocycle unsubstituted or mono- or polysubstituted by a halogen, a $(C_1$-$C_5)$alkyl, a $(C_1$-$C_5)$alkoxy,
or wherein R^1 and R^2 are both hydrogen or else R^1 is hydrogen and R^2 is as defined above, or else R^1 and R^2 together with the nitrogen atom to which they are bonded, form a saturated 5- to 8-membered heterocyclic radical;

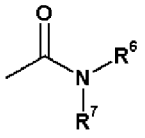
or wherein R may be a group OH;

or wherein R may be a group OR^4, with R^4 being an optionally substituted $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl or an optionally substituted aryl group,;

or wherein R may be a group R^5, R^5 being $(C_1$-$C_3)$alkyl; $(C_3$-$C_{12})$cycloalkyl which is unsubstituted or substituted by a halogen or by a $(C_1$-$C_5)$alkyl; $(C_1$-$C_3)$alkyl- cycloalkyl in which the cycloalkyl is C_3-C_{12} and is unsubstituted or substituted by a $(C_1$-$C_5)$alkyl; or a 2-norbornylmethyl;
or of a salt of compound of formula 10.

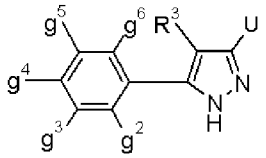
In a preferred embodiment of the present invention g^2, g^3, g^4, g^5, g^6 are all independently selected from hydrogen, halogen, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$alkoxy and w^2, w^3, w^4, w^5 and w^6 are all independently selected from hydrogen, halogen, $(C_1$-$C_3)$alkyl or $(C_1$-$C_3)$alkoxy.

In a more preferred embodiment of the present invention g^2, g^3,g^5, g^6 are all hydrogen and g4 is chlorine, bromine, $(C_1$-$C_3)$alkyl, or $(C_1$-$C_3)$alkoxy and
w^3, w^5, w^6 are all hydrogen and w^2, w^4 are chlorine or bromine. Even more preferably g^2, g^3,g^5, g^6 are all hydrogen and g^4 is chlorine and w^3, w^5, w^6 are all hydrogen and w^2, w^4 are chlorine.



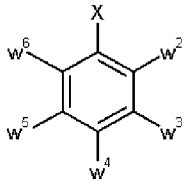
In a further preferred embodiment U is a group of formula wherein R^6 is hydrogen and R^7 is a non-aromatic C_3-C_{15} carbocyclic radical or a saturated 5- to 8-membered heterocyclic radical selected from 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl.

The process of the present invention comprises carbon-nitrogen-bond formation, in particular a step wherein a compound of formula 11:



(11)

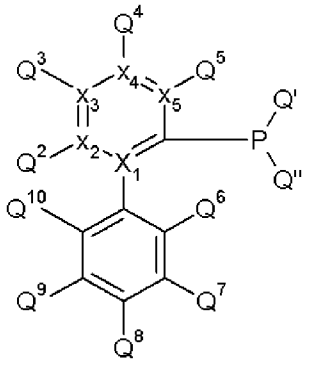
in which U, R^3 , g^2, g^3, g^4, g^5 and g^6 are defined as above for (10), is reacted in a suitable organic solvent with a compound of formula 12:



(12)

in which w^2, w^3, w^4, w^5 and w^6 are defined as above for (10) and X is a suitable leaving group, in particular a leaving group selected from
a halogen , for example chloro, bromo and iodo,
a sulfonate-type leaving-group, for example trifluoromethansulfonate (triflate), nonafluorotrimethylmethanesulfonate (nonaflate), methanesulfonate, Benzenesulfonate, para-toluenesulfonate,
and $-B(OH)_2$;
in the presence of a base and a transition metal catalyst, in particular a transition metal catalyst selected from group 5-12 metals, preferably the group VIIIA metals.

In a preferred embodiment, X is a halogen atom or a sulfonate-type leaving-group, the transition metal catalyst is selected from the group consisting of V, Mn, Fe, Co, Ni, Rh, Pd, Ir and Pt, with Pd and Ni being particularly preferred, and the reaction is carried out in the presence of a trisubstituted phosphine. Advantageously the trisubstituted phosphine is a ligand of formula 13:



(13)

wherein X_1 is a carbon- or nitrogen atom, X_{2-5} are independently from each other either carbon or nitrogen, wherein X_{1-5} combine with the carbon atom bonded to X_1 and X_5 to form an aromatic-type heterocycle;

Q^{2-10} is independently selected from the group of
hydrogen, methyl, branched or unbranched C_{2-20} alkyl, wherein optionally one or more hydrogen atoms are replaced by fluoro, chloro or bromo,
cycloalkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, arylmino, diarylamino, alkylarylamino, pentafluorsulfuranyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, thio, alkylthio, arylthio, diarylphosphino, alkylarylphosphino, if necessary substituted aminocarbonyl, CO_2-, alkyl or alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, nitro, cyano, aryl- or alkylsulfone, arylsulfonyl and alkylsulfonyl,
or two neighbouring groups Q^{1-5} may form an aromatic, heteroaromatic or aliphatic condensed ring.

Q' and Q'' independently from each other may be identical or different residues selected from the group of
hydrogen, methyl, branched or unbranched C_{2-20}alkyl, optionally substituted, C_{5-8} cycloalkyl, and phenyl, optionally substituted,
or Q' and Q'' may together constitute a ring, wherein the bridging element may be selected from substituted alkyliden, branched alkyliden and cyclid alkyliden or Q' and Q'' are independently from each other one or two polycyclic residues for example norbornyl or adamantyl.

Preferred trisubstituted phosphines are described in WO 00/02887 on page 328, claim 1. Particularly preferred are those trisubstituted phosphines decribed on page 330 in claim 7 and page 332-333 in claim 13. Even more preferred are those trisubstituted phosphines listed in figures 2, 18 and 19 of WO 00/02887.

In a alternative preferred embodiment of the present invention X is $-B(OH)_2$ and the transition metal is selected from groups 5-12 metals, preferably from group IXA metals, in particular wherein the transition metal catalyst is copper or silver.

In general, it is preferred to add a base in order to achieve fast reaction rates. Suitable bases are hydroxides, alcoholates and fluorides of alkaline and alkaline earth metal, carbonates, hydrogencarbonates, tertiary amines, pyridine and its substituted derivatives, alkali phosphates and mixtures thereof. In a preferred embodiment of the invention bases are selected from the group of potassium tert-butoxide, sodium tert-butoxide, cesium tert-butoxide, lithium tert-butoxide as well as the corresponding isopropylates, triethylamine and pyridine. Usually the amount of base used in the reaction corresponds to the amount of formula (11), mostly 0.6 to 6.0 equivalents, preferentially 1.2 to 3.0 equivalents of base referring to compound (11) are used.

The reaction is performed in a suitable solvent or in a one phase or multiphasic solvent mixture, which can dissolve all reactands whereas heterogenic performance is also possible (example via use of nearly unsoluble bases). Preferentially the reaction is done in polar, aprotic or protic solvents. Very well suited are open-chained and cyclic ether or diether, oligo- and polyether as well as substituted simple alcohols or polyalcohols and if necessary substituted aromatic ring systems. In a preferred embodiment of the

present invention one or more solvents are selected from diglyme, substituted glymes, 1,4-dioxane, isopropanol, tert-butanol, 2,2-dimethyl-1-propanol, toluene, xylene.

The reaction is preferably performed at temperatures between room temperature and the boiling point of the used solvent. More preferably the reaction takes place at elevated temperatures, for example in the preferred range from 0 to 240°C, to achieve a faster reaction. In a preferred embodiment of the present invention the temperature range is being selected from 20 to 200°C, particularly from 50 to 150°C.

Pyrazole of formula (11) and the aromatic reaction partner (12) can be used in molar ratios of 10:1 to 1:10, preferred are ratios from 3:1 to 1:3, particularly preferred are ratios from 1,2:1 to 1:1,2.

The compound of formula (11) may be prepared, for example, according to the process disclosed in J. Med. Chem 2003, 46, 3945 or with herein found compounds to further transformation to compounds of formula (11) following known methods, eg. amide bond formation.

In a preferred embodiement of the present invention all substances are charged to a suitable vessel and the resulting mixture is heated under stirring to its reaction temperature. In a further preferred embodiment, which is particularly suitable for large-scale synthesis, substance of formula (11) and if necessary further substances, for example base, transition metal catalyst or pre-catalyst are added during the reaction to the reaction mixture via dosage. Alternatively the base can be added slowly via controlled dosage which leads to controlled reaction.

In a preferred embodiment the invention relates to a process for the preparation of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid comprising the step of reacting

a) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate with 2,4-dichlorophenylboronic acid in the presence of copper catalyst and a base; or

b) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate with 2,4-dichloro-1-bromobenzene in the presence of a palladium catalyst, a trisubstituted phosphine and a base.

In a further preferred embodiment the invention relates to a process according to the present invention for the preparation of Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylate comprising the step of reacting Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate with 2,4-dichlorophenylboronic acid in the presence of a copper catalyst and a base.

In a further preferred embodiment the invention relates to a process according to the present invention for the preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide comprising the step of reacting

a) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide with 2,4-dichlorophenylboronic acid in the presence of a copper catalyst and base; or

b) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide with 2,4-dichloro-1-bromobenzene in the presence of a palladium catalyst, a trisubstituted phosphine and a base.

Examples

Having described the invention with reference to certain preferred embodiments, other embodimetns will become apparent to one skilled in the art from consideration of the specification. The invention is further described in detail in the following examples describing in detail the preparation of the composition and methods of use of the present invention. However, the examples are not to be construed to be in any way limiting to the scope of protection of the present invention.

It will become apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

Example 1: Preparation, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid

Method 1:

529 mg (2 mmol) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate, 452 mg (2 mmol) 2,4-dichloro-1-bromobenzene, 384 mg (4 mmol) NaOt-Bu, 23.0 mg Bis(dibenzylideneacetone)palladium(0) (2 mol%) and 31.5 mg 2-(N,N-dimethylamino)-2'-(dicyclohexylphosphino)biphenyl (4 mol%) are heated in 12 ml degassed toluene, free of water for 15 h to 120 C until the starting aryl bromide has been completely comsumed as judged by GC analysis. The reaction mixture is then cooled to room temperature, diluted with ether and filtered through celite. Water is added to the filtrate and the phases are separated. The aqueous phase is acidified by addition of HCl until pH = 1.5. The resulting mixture is stirred, the precipitate formed is filtered off and dried under vacuum.

Method 2:

529 mg (2 mmol) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate, 452 mg (2 mmol) 2,4-dichloro-1-bromobenzene, 384 mg (4 mmol) NaOt-Bu, 23.0 mg Bis(dibenzylideneacetone)palladium(0) (2 mol%) and 30.4 mg 2-Dicyclohexylphosphino-2'-methoxy-1,1'-biphenyl (4 mol%) are heated in 12 ml degassed toluene, free of water for 15 h to 120 C until the starting aryl bromide has been completely comsumed as judged by GC analysis. The reaction mixture is then cooled to room temperature, diluted with ether and filtered through celite. Water is added to the filtrate and the phases are separated. The aqueous phase is acidified by addition of HCl until pH = 1.5. The resulting mixture is stirred, the precipitate formed is filtered off and dried under vacuum.

Method 3:

264 mg (1 mmol) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate, 381.6 mg (2 mmol) 2,4-dichlorophenylboronic acid, 81 µl (2 mmol) pyridine, 18.1 mg cupric acetate (0.1 mol) and 375 mg 4 Å molecular sieves are stirred at room temperature in 8 ml dry dichloromethane under air for 48 h. The progress of the reaction is being monitored by by GC analysis. The reaction is quenched with a 3 ml of 4M NH_3 in MeOH and filtered through celite. The solvent is evaported and a solution of 5 ml of 10 M NaOH is added to the residue. The resulting mixture is heated for 4 hours at 70±3°C with vigorous stirring. The mixture is then neutrailzed and further acidified to pH=1.5 by addition of HCl. The resulting mixture is stirred, the precipitate formed is filtered off and dried under vacuum.

Example 2: Preparation, Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylate

264 mg (1 mmol) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate, 381.6 mg (2 mmol) 2,4-dichlorophenylboronic acid, 81 µl (2 mmol) pyridine, 18.1 mg cupric acetate (0.1 mol) and 375 mg 4 Å molecular sieves are stirred at room temperature in 8 ml dry dichloromethane under air for 48 h. The progress of the reaction is being monitored by by GC analysis. The reaction is quenched with a 3 ml of 4M NH_3 in MeOH and filtered through celite. After separation of the phases the solvent of the organic alyer is evaported and the resutling residue is purified by chromatography on 230-400 mesh silica gel using cyclohexane/ethyl acetate (85/15; v/v).

Example 3: Preparation, N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide

A) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide

2.64 g (10 mmol) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate, 1.00 (10 mmol) 1-piperidinamine are heated in 60 ml Ethanol to reflux for three days. The reaction mixture is then cooled to room temperature and diluted with ethyl acetate. Water is added and the phases are separated. The solvent of the organic layer is evaporated and the resulting residue is purified by chromatography silica gel using toluene/ethyl acetate (80/20; v/v).

B) N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide

Method 1:

637 mg (2 mmol) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide, 452 mg (2 mmol) 2,4-dichloro-1-bromobenzene, 384 mg (4 mmol) NaOt-Bu, 23.0 mg Bis(dibenzylideneacetone)palladium(0) (2 mol%) and 31.5 mg 2-(N,N-dimethylamino)-2'-(dicyclohexylphosphino)biphenyl (4 mol%) are heated in 12 ml degassed toluene, free of water for 15 h to 120 C until the starting aryl bromide has been completely comsumed as judged by GC analysis. The reaction mixture is then cooled to room temperature, diluted with ether and filtered through celite. Water is added to the filtrate and the phases are separated. The solvent of the organic layer is evaporated and the resulting residue is purified by chromatography silica gel using toluene/ethyl acetate (90/10; v/v).

Method 2:

637 mg (2 mmol) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide, 452 mg (2 mmol) 2,4-dichloro-1-bromobenzene, 384 mg (4 mmol) NaOt-Bu, 23.0 mg Bis(dibenzylideneacetone)palladium(0) (2 mol%) and 30.4 mg 2-Dicyclohexylphosphino-2'-methoxy-1,1'-biphenyl (4 mol%) are heated in 12 ml degassed toluene, free of water for 15 h to 120 C until the starting aryl bromide has been completely comsumed as judged by GC analysis. The reaction mixture is then cooled to room temperature, diluted with ether and filtered through celite. Water is added to the filtrate and the phases are separated. The solvent of the organic layer is evaporated and the resulting residue is purified by chromatography silica gel using toluene/ethyl acetate (90/10; v/v). Crystallization from isopropylether give desired pure compund 1.

Method 3:

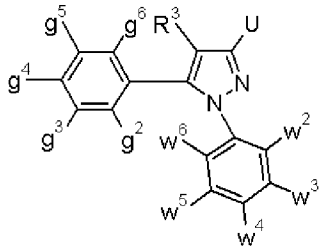
637 mg (2 mmol) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide, 452 mg (2 mmol) 2,4-dichloro-1-bromobenzene, 384 mg (4 mmol) NaOt-Bu, 23.0 mg Bis(dibenzylideneacetone)palladium(0) (2 mol%) and 24.9 mg 2,2'-bis(diphenylphosphino)-1,1'-biphenyl (4 mol%) are heated in 15 ml degassed toluene, free of water for 15 h to 80 C until the starting aryl bromide has been completely comsumed as judged by GC analysis. The reaction mixture is then cooled to room temperature, diluted with ether and filtered through celite. Water is added to the filtrate and the phases are separated. The solvent of the organic layer is evaporated and the resulting residue is purified by chromatography silica gel using toluene/ethyl acetate (90/10; v/v). Crystallization from isopropylether give desired pure compund 1.

Method 4:

318 mg (1 mmol) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide, 381.6 mg (2 mmol) 2,4-dichlorophenylboronic acid, 81 µl (2 mmol) pyridine, 18.1 mg cupric acetate (0.1 mol) and 375 mg 4 Å molecular sieves are stirred at room temperature in 8 ml dry dichloromethane under air for 48 h. The progress of the reaction is being monitored by by GC analysis. The reaction is quenched with a 3 ml of 4M NH_3 in MeOH and filtered through celite. The solvent of the organic layer is evaporated and the resulting residue is purified by chromatography silica gel using toluene/ethyl acetate (90/10; v/v). Crystallization from isopropylether give desired pure compund 1.

Claims

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



(10)

wherein U is –CN or a group of formula , g^2, g^3, g^4, g^5 and g^6, and w^2, w^3, w^4, w^5 and w^6 are identical or different from another and may independently be hydrogen, chlorine, bromine , $(C_1$-$C_3)$alkyl, $(C_1$-$C_3)$alkoxy, trifluoromethyl or a nitro group;

R^3 may be hydrogen or $(C_1$-$C_3)$alkyl, in particular methyl;

R may be a group NR^1R^2 in which R^1 and R^2 are independently selected from the group of
$(C_1$-$C_6)$alkyl;
non-aromatic $(C_3$-$C_{15})$ carbocyclic radical, optionally substituted;
amino-$(C_1$-$C_4)$alkyl wherein the amino group is optionally disubstituted by a $(C_1$-$C_3)$alkyl;
cycloalkyl-$(C_1$-$C_3)$ alkyl wherein the cycloalkyl is C_3-C_{12};
phenyl which may be unsubstituted, monosubstituted or polysubstituted by halogen, by a $(C_1$-$C_5)$alkyl or by a $(C_1$-$C_5)$alkoxy;
phenyl $(C_1$-$C_3)$alkyl;
diphenyl-$(C_1$-$C_3)$alkyl;
naphthyl;
anthracenyl;
saturated 5- to 8-membered heterocyclic radical which is unsubstituted or substituted $(C_1$-$C_3)$alkyl, by a hydroxyl or by a benzyl group;
1-adamantylmethyl;
and aromatic heterocycle, which may be unsusbtituted, mono- or polysubstituted by a halogen, a $(C_1$-$C_5)$alkyl, a $(C_1$-$C_5)$alkoxy;
a $(C_1$-$C_3)$alkyl substituted by an aromatic heterocycle unsubstituted or mono- or polysubstituted by a halogen, a $(C_1$-$C_5)$alkyl, a $(C_1$-$C_5)$alkoxy,
or wherein R^1 and R^2 are both hydrogen or else R^1 is hydrogen and R^2 is as defined above, or else R^1 and R^2 together with the nitrogen atom to which they are bonded, form a saturated 5- to 8-membered heterocyclic radical;

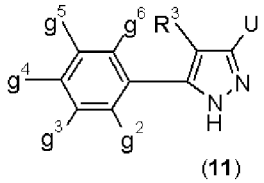
or wherein R may be a group OH;

or wherein R may be a group OR^4, with R^4 being an optionally substituted $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl or an optionally substituted aryl group;

or wherein R may be a group R^5, R^5 being $(C_1$-$C_3)$alkyl; $(C_3$-$C_{12})$cycloalkyl which is unsubstituted or substituted by a halogen or by a $(C_1$-$C_5)$alkyl; $(C_1$-$C_3)$alkyl- cycloalkyl in which the cycloalkyl is C_3-C_{12}

and is unsubstituted or substituted by a (C_1-C_5)alkyl; or a 2-norbornylmethyl;
or of a salt of a compound of formula 10;

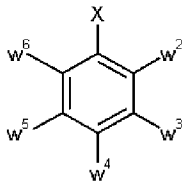
comprising the step of reacting a compound of formula 11:



(11)

in which U, R^3 , g^2, g^3, g^4, g^5 and g^6 are defined as above for (10),

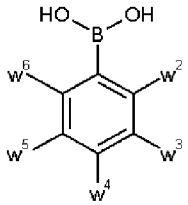
with a compound of formula 12:



(12)

in which w^2, w^3, w^4, w^5 and w^6 are defined as above for (10) and X is a leaving group,
in a suitable organic solvent in the presence of a base and a transition metal catalyst.

2. The process according to claim 1, wherein the compound of formula 12 is a compound of formula 14:



(14)

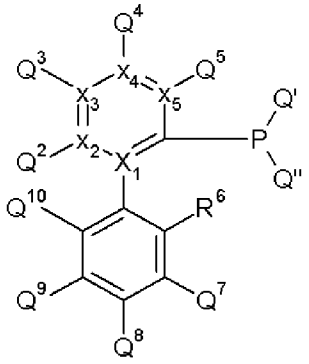
and wherein the transition metal catalyst is selected from group 5-12 metals, preferably from the group IXA metals.

3. The process of claim 2 wherein the transition metal is copper or silver.

4. The process according to claim 1, wherein the leaving group X is a halogen atom or a sulfonate-type leaving-group, and the reaction is carried out in the presence of a trisubstituted phosphine.

5. The process according to claim 4, wherein the transition metal catalyst is selected from the group consisting of V, Mn, Fe, Co, Ni, Rh, Pd, Ir and Pt, in particular wherein the transition metal catalyst is Pd or Ni.

6. The process according to claims 4 or 5, wherein the trisubstituted phosphine is a compound of formula 13:



(13)

wherein X_1 is a carbon- or nitrogen atom, X_{2-5} are independently from each other either carbon or nitrogen, wherein X_{1-5} combine with the carbon atom bonded to X_1 and X_5 to form an aromatic-type heterocycle;

Q_{2-10} is independently selected from the group of
hydrogen, methyl, branched or unbranched C_{2-20} alkyl, wherein optionally one or more hydrogen atoms are replaced by fluoro, chloro or bromo,
cycloalkyl, hydroxyl, alkoxy, amino, alkylamino, dialkylamino, arylmino, diarylamino, alkylarylamino, pentafluorsulfuranyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, thio, alkylthio, arylthio, diarylphosphino, alkylarylphosphino, if necessary substituted aminocarbonyl, CO_2^-, alkyl or alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, nitro, cyano, aryl- or alkylsulfone, arylsulfonyl and alkylsulfonyl,
or two neighbouring groups Q_{1-5} may form an aromatic, heteroaromatic or aliphatic condensed ring,

Q' and Q'' independently from each other may be identical or different residues selected from the group of
hydrogen, methyl, branched or unbranched C_{2-20}alkyl, optionally substituted, C_{5-8} cycloalkyl, and phenyl, optionally substituted,
or Q' and Q'' may together constitute a ring, wherein the bridging element may be selected from substituted alkyliden, branched alkyliden and cyclid alkyliden or Q' and Q'' are independently from each other one or two polycyclic residues for example norbornyl or adamantyl.

7. The process according to any one of the preceeding claims wherein the base is a hydroxide, alcoholate, amide of alkali- or earth alkali, or alkalicarbonate, alkaliphosphate tertiary amines, pyridine ad its substituted mixtures thereof or mixtures thereof.

8. The process according claim 7 wherein the base is selected from potassium tert-butoxide, sodium tert-butoxide, cesium tert-butoxide, lithium tert-butoxide as well as the corresponding isopropylates, triethylamine and pyridine.

9. The process according to any one of the preceeding claims wherein 1,0 to 3,0 equivalents of base are present in relation to the amount of the compound of formula 12 or 14.

10. The process according to any of the preceeding claims wherein the solvent is selected from hydrocarbons, halogenated hydrocarbons, open-chained and cycled ether and diether, oligo- and polyether, tertiary amines, DMSO, NMP, DMF, DMAc, substituted alcohols, polyols and suitable substituted aromatic hydrocarbons or a mixture of these solvents.

11. The process according to any of the preceeding claims wherein the process is carried out at a temperatur from 0°C to 240°C.

12. The process according to any of the preceeding claims wherein the catalyst is present in an amount of 0.001 mol% to 100 mol% relative to compound of formula 11.

13. The process according to any one of the preceeding claims for the preparation of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylic acid comprising the step of reacting

a) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate with 2,4-dichlorophenylboronic acid in the presence of copper catalyst and a base; or

b) Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate with 2,4-dichloro-1-bromobenzene in the presence of a palladium catalyst, a trisubstituted phosphine and a base.

14. The process according to any one of the preceeding claims for the preparation of Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxylate comprising the step of reacting Ethyl 5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxylate with 2,4-dichlorophenylboronic acid in the presence of a copper catalyst and a base.

15. The process according to any one of the preceeding claims for the preparation of N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide comprising the step of reacting

a) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide with 2,4-dichlorophenylboronic acid in the presence of a copper catalyst and base; or

b) N-piperidino-5-(4-chlorophenyl)-4-methyl-pyrazole-3-carboxamide with 2,4-dichloro-1-bromobenzene in the presence of a palladium catalyst, a trisubstituted phosphine and a base.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/051802

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D231/14

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2005/115989 A (SANOFI AVENTIS [FR]; DAUMAS MARC [FR]; VAYRON PHILIPPE [FR]) 8 December 2005 (2005-12-08) cited in the application page 9, line 25 - page 11, line 7	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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

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Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2008	02/06/2008

Name and mailing address of the ISA/	Authorized officer
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