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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF SUBSTITUEREDE PHENOXYPHENYLKETONER**

(56) Fremdragne publikationer:
EP-A2- 0 735 142
WO-A1-2013/007767
WO-A1-2013/024076
CN-A- 102 951 996
PAUL TARRANT ET AL: "The Formation and Deamination of Brominated m-Aminobenzotrifluorides 1", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 75, no. 12, 1 June 1953 (1953-06-01), pages 3034-3035, XP055114801, ISSN: 0002-7863, DOI: 10.1021/ja01108a519
JUN-SIK LEE ET AL: "Low-Temperature Formation of Functionalized Grignard Reagents from Direct Oxidative Addition of Active Magnesium to Aryl Bromides", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 65, no. 17, 26 July 2000 (2000-07-26) , pages 5428-5430, XP055114795, ISSN: 0022-3263, DOI: 10.1021/jo000413i

DESCRIPTION

[0001] The present invention relates to a process for providing substituted phenoxyphenyl ketones.

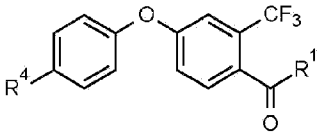
[0002] Furthermore, the invention relates to a process for the preparation of triazoles.

[0003] The substituted phenoxyphenyl ketones provided by the process according to the present invention are valuable intermediate compounds for the synthesis of triazole compounds having pesticidal, in particular fungicidal activity. WO 2013/007767 is directed to fungicidal substituted 1-[4-phenoxy-2-(halogenalkyl)phenyl]-2-(1,2,4-triazol-1-yl)ethanol compounds, that can be synthesized via a respective phenoxyphenyl ketones intermediate compound. WO 2014/108286 (EP 13150663.6; PCT/EP2013/077083) describes an improved process for the synthesis of certain fungicidally active triazole compounds.

[0004] The methods known from the literature are sometimes not suitable for the efficient synthesis of substituted phenoxyphenyl ketones because the yield is not sufficient and/or the reaction conditions and parameters such as solvents and/or catalysts and/or the proportion of the reactants and ingredients to each other are not optimal or suitable for an upscale to industrially relevant amounts. Inter alia because said substituted phenoxyphenyl ketones are valuable intermediates for the synthesis of triazole compounds with promising fungicidally activity, there is an ongoing need for improved processes that easily make such intermediates and compounds available.

[0005] An object of the present invention was to provide an improved process for the synthesis of substituted phenoxyphenyl ketones (IA) that are valuable intermediates for the preparation of fungicidally active triazole compounds.

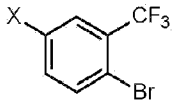
[0006] It has now surprisingly been found a highly efficient synthesis for the synthesis of substituted phenoxyphenyl ketone compounds of formula (IA), and thus, an efficient synthesis to triazole compounds as active ingredients. The present invention relates thus to a process for the preparation of the ketone compounds (IA)



(IA)

comprising the following steps:

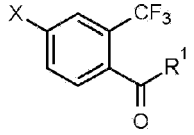
1. (i) reacting a compound of the formula (III)



(III)

with R'-Mg-Hal (IV) or Mg and $R^1C(=O)Cl$ (V) in the presence of a Cu(I)-catalyst in an amount of 0.005 to 0.065 mole equivalents per 1 mole of compound (III), to result in

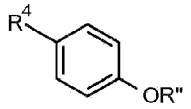
compounds II



(II)

and

2. (ii) reacting compound (II) as defined in step (i) with a phenol derivative of formula (VI)



(VI)

in the presence of a base if R" is hydrogen;
wherein the variables are defined as follows:

X
: is F or Cl;

R^1
: is C_1-C_6-alkyl or C_3-C_8-cycloalkyl; and

R^4
: is F or Cl;

R'
: is C_1-C_4-alkyl or C_3-C_6-cycloalkyl;

Hal
: is halogen; and

R"
: is hydrogen or an alkali metal kation.

[0007] In the process step (i) according to the present invention, substituted phenyl compounds of formula (III) are used, wherein X is F or Cl.

[0008] The 2-bromo-5-fluoro/chloro-benzotrifluoride of the formula (III) is reacted with the Grignard reagent R'-Mg-Hal (IV) or magnesium (Mg) and the acyl chloride $R^1C(=O)Cl$ (V) in the presence of a Cu(I)catalyst in an amount of 0.005 to 0.065 mol equivalents per 1 mol of compound (III).

[0009] According to a preferred embodiment, the Grignard reagent R'-Mg-Hal (IV) is used in the process. R' in the Grignard reagent is C_1-C_4-alkyl or C_3-C_6-cycloalkyl, in particular is selected from methyl, ethyl, isopropyl, tert-butyl, sec-butyl and cyclopropyl. Specifically, R' in the Grignard reagent is selected from isopropyl, tert-butyl, sec-butyl and cyclopropyl. In one specific embodiment, R' is isopropyl. In one further embodiment, R' is sec-butyl. Hal stands for halogen, in particular Cl or Br. Also more than one Grignard reagent can be used in the same reaction, such as, for example reagent (IV), wherein Hal is Br together with the respective reagent (having the same R'), wherein Hal is Cl. According to one embodiment, Hal is Cl and R' in the Grignard reagent is selected from isopropyl, tert-butyl, sec-butyl and cyclopropyl.

According to a further embodiment, Hal is Br and R' in the Grignard reagent is selected from isopropyl, tert-butyl, sec-butyl and cyclopropyl. In one preferred embodiment, in the inventive process, the Grignard reagent is (iso-propyl)-Mg-Cl or (iso-propyl)-Mg-Br. In one further preferred embodiment, in the inventive process, the Grignard reagent is (sec-butyl)-Mg-Cl or (sec-butyl)-Mg-Br.

[0010] Preferably, the Grignard reagent is used in an amount of 1 eq to 2 eq, in particular 1.1 to 1.8 eq, more specifically 1.2 to 1.6 eq, in relation to one equivalent of compound (III). In particular the amounts of 1.3 to 1.5, more particularly 1.2 to 1.4 per mole of compound (III) may be favorable according to the present invention. Usually, the Grignard reagent is used in excess, preferably in slight excess.

[0011] One further embodiment relates to the inventive process, wherein Mg is used then forming a Grignard reagent with compound (III) and reacting with compound (V). It can be preferred if Mg is used in an amount slightly less than compound (III). Here, the same details regarding solvents apply.

[0012] As generally known to the skilled person, the structure of a Grignard reagent can be described by the so-called Schlenck equilibrium. A Grignard reagent undergoes a solvent-dependent equilibrium between different magnesium compounds. The Schlenck equilibrium for the Grignard reagent used according to the present invention can be schematically illustrated as follows:

$$2\ R'\text{-Mg-Hal} \rightleftarrows (R')_2Mg + Mg(Hal)_2 \rightleftarrows (R')_2Mg \bullet Mg(Hal)_2$$

[0013] Furthermore, it is known, that solvent molecules, in particular ethers such as diethylether or THF, which are commonly used for reactions with Grignard reagents, can add to the magnesium of the Grignard reagent thereby forming etherates.

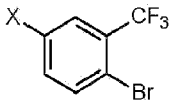
[0014] Depending on the solvent used in the inventive reaction, solvent molecules may add to the Mg-reagents, thereby forming - in case of the use of ethers - the respective etherates.

[0015] For general information regarding structures of Grignard reagents, see also Milton Orchin, Journal of Chemical Education, Volume 66, Number 7, 1999, pp 586 to 588.

[0016] According to an embodiment of the inventive process, LiCl is added to the reaction mixture of step (i). According to an alternative, before contacting the Grignard reagent (IV) with the reagents of the inventive process, it is brought together with LiCl, thereby forming an addition product R'MgHal • LiCl ((IV)•LiCl). According to this alternative, ((IV)•LiCl) is then used in step (i). The use of LiCl together with Grignard reagents is generally known in the art, see for example Angew. Chem. Int. Ed. 2004, 43, 3333 and Angew. Chem. Int. Ed. 2006, 45, 159.

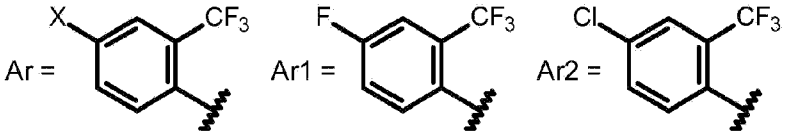
[0017] The Grignard reagents (IV) or their addition products with LiCl ((IV)•LiCl) are commercially available or can be made according to processes well-known to the skilled person (see Angew. Chem. Int. Ed. 2004, 43, 3333).

[0018] The reaction of the educt (III)



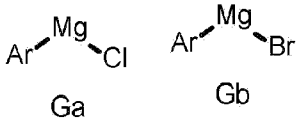
(III)

with a suitable Grignard reagent (IV) or mixture of suitable Grignard reagents may lead to the following specific compounds, wherein "Ar" stands for the respective substituted phenyl unit resulting from compound (III) that has been reacted with the Grignard reagent, as defined herein, in particular, wherein X is F or Cl, namely "Ar1" and "Ar2", respectively. During the reaction different of said Grignard species may occur and also multiple may be formed in parallel:



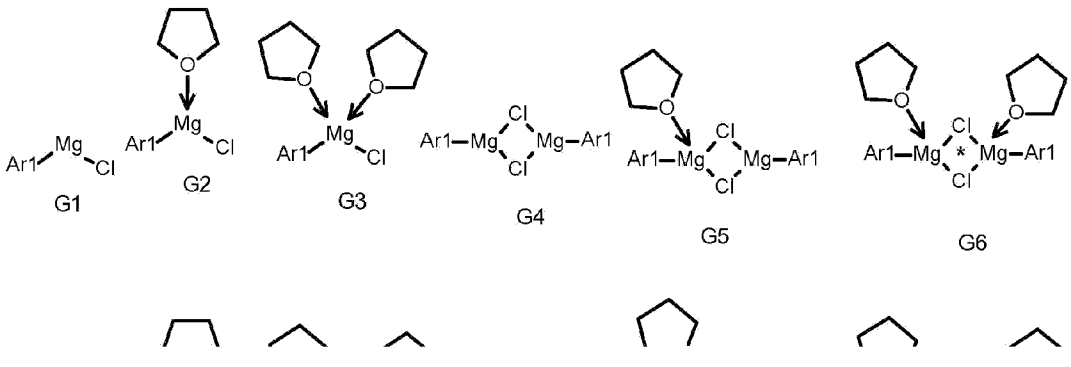
[0019] Some of the compounds include solvent molecules such as THF (tetrahydrofurane) as illustrated in the following. It is apparent fo the skilled person that also other solvent molecules may be present, depending on the solvent used in the reaction. Also these addition products with solvent molecules are encompassed by the present invention.

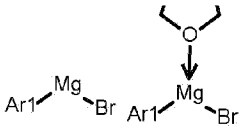
[0020] Generally, the Grignard species formed during the reaction of (III) with the Grignard reagent (IV) can be depicted as the species "Ga" and "Gb":



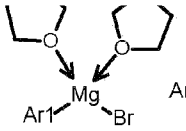
[0021] Depending on the Grignard reagent (IV) used, Ga or Gb may occur alone or Ga and Gb may be formed both. As outlined above, other Grignard species from the ones detailled below can be formed during the reaction and the different species can convert into one another.

[0022] Note 1: "Ar1" or "Ar2", or Cl or Br, having two bonds stands for a three-center-two-electron-bond





G7 G8



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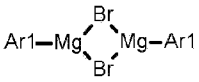

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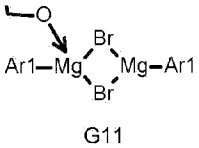

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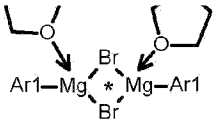

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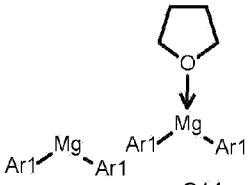
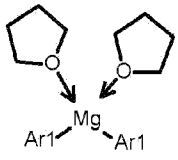


G13 G14



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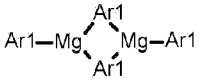

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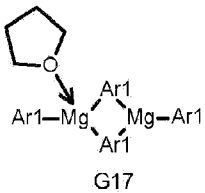

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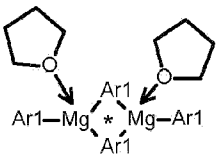

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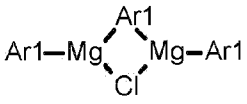

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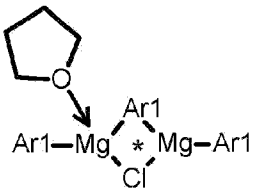

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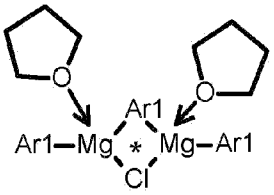

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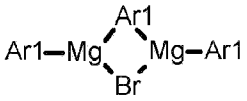

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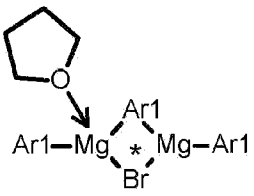

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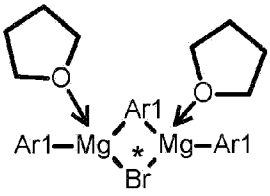

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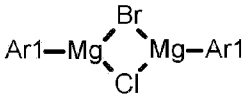

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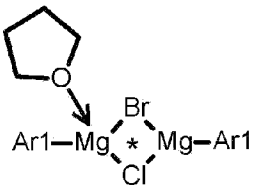

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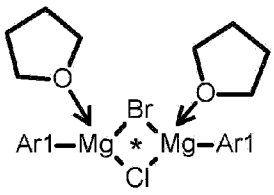

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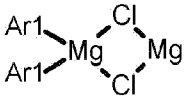

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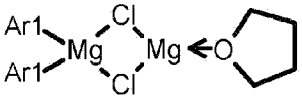

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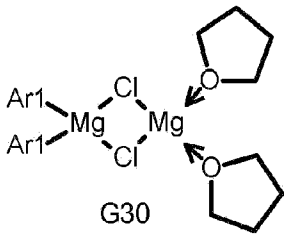

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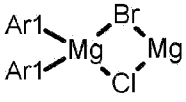

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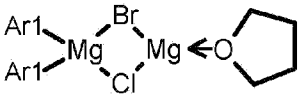

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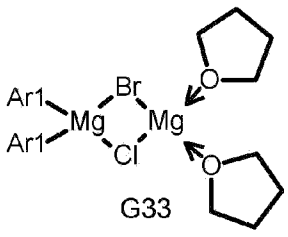

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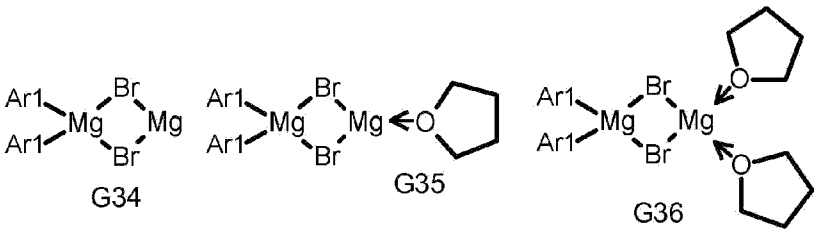

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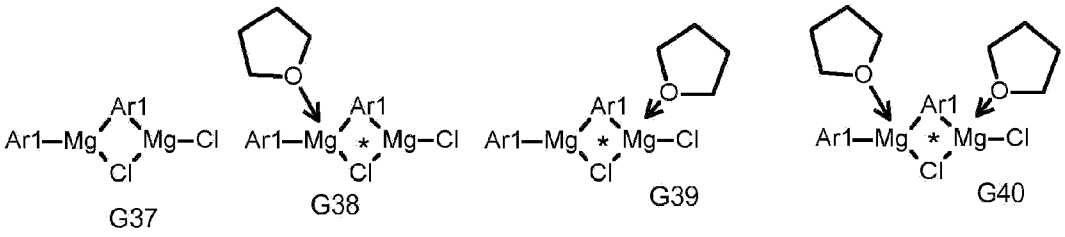
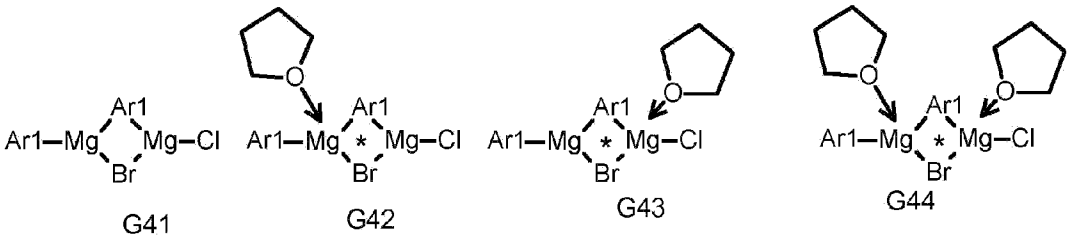
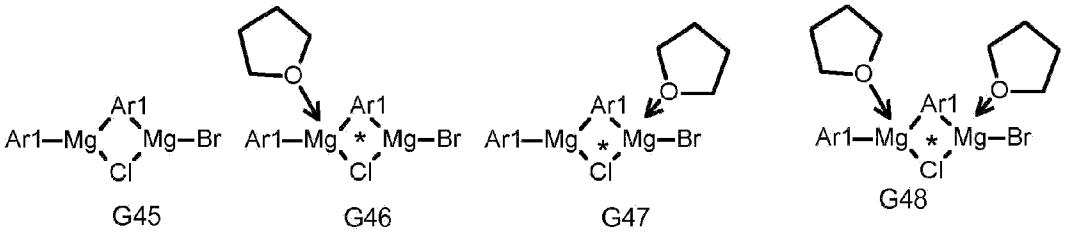


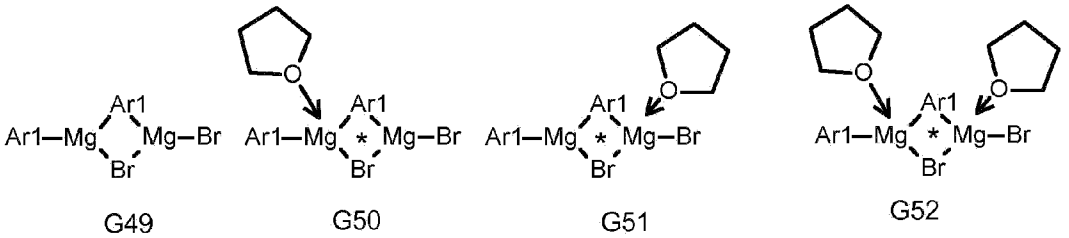
G37 G38 G39 G40



G41 G42 G43 G44



G45 G46 G47 G48



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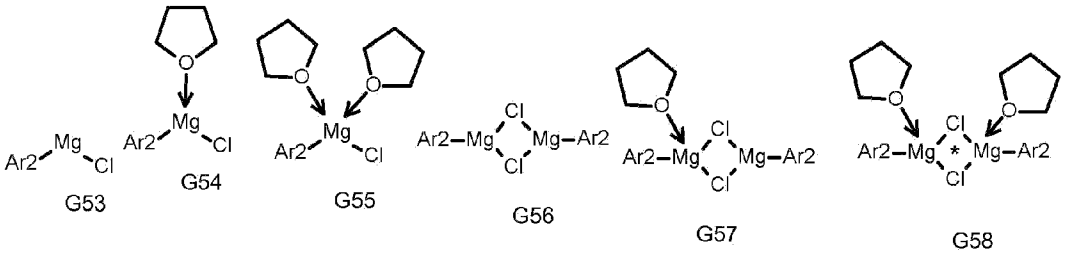

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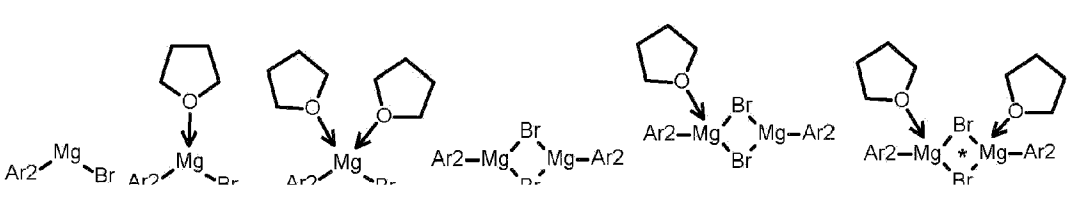

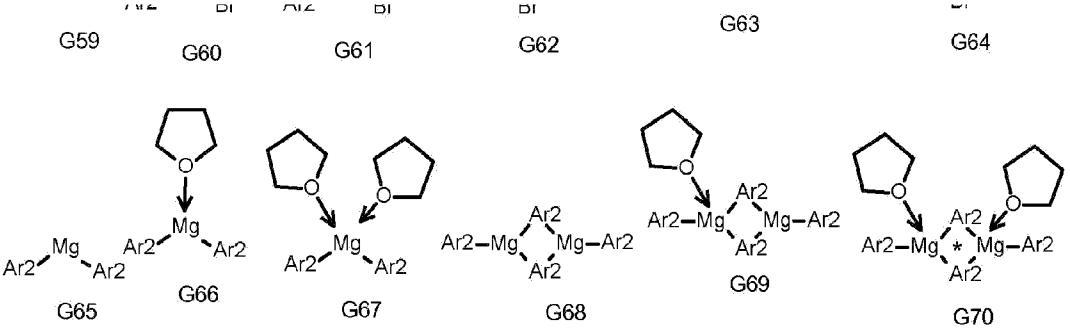
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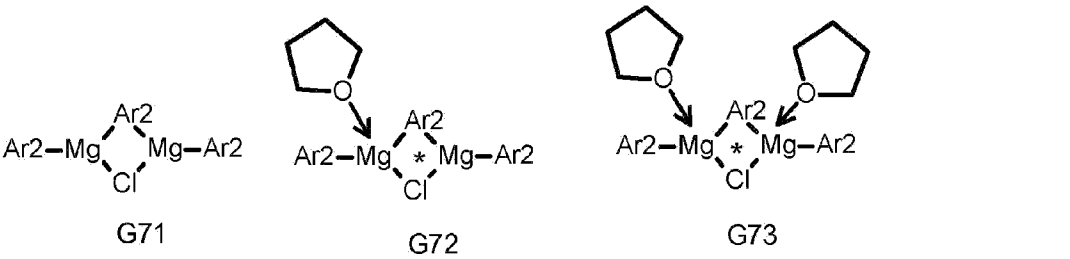
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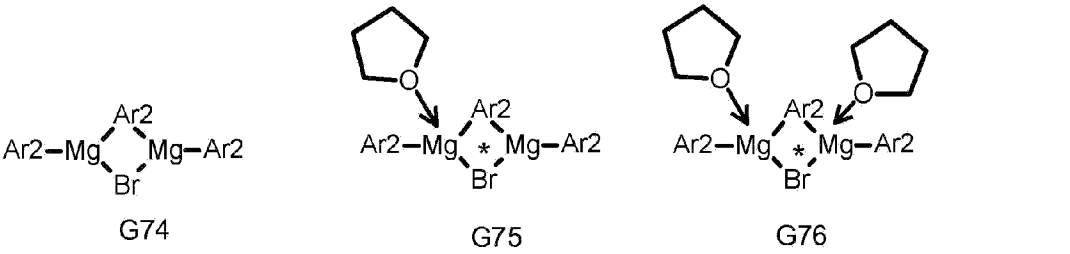
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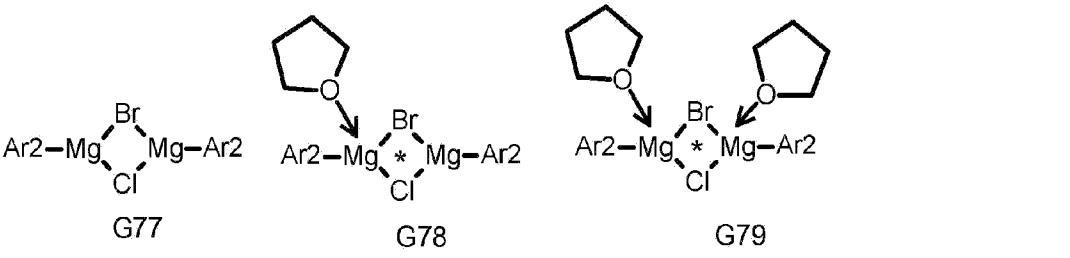
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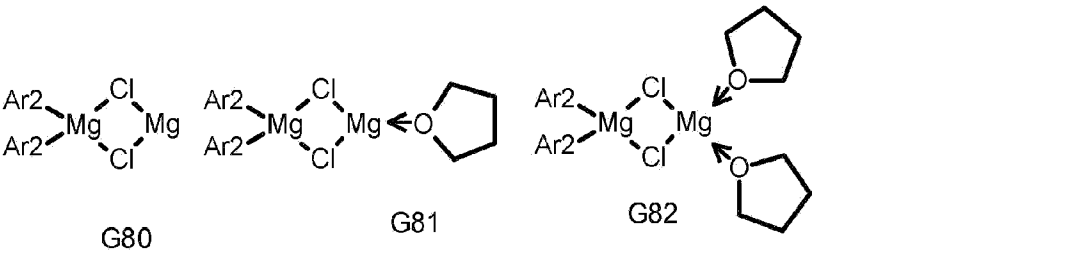
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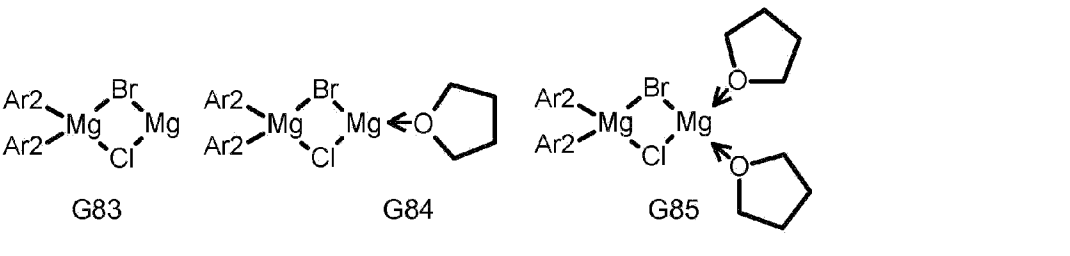
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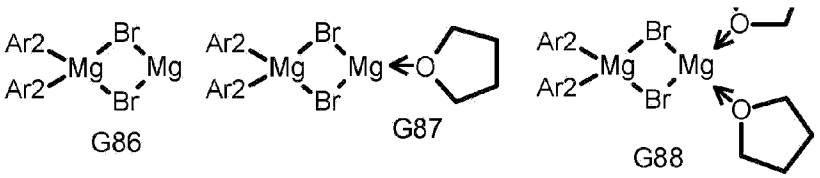

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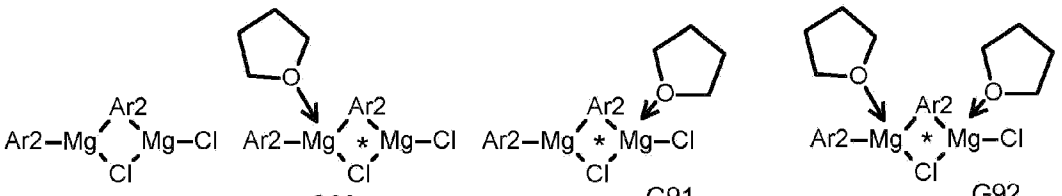
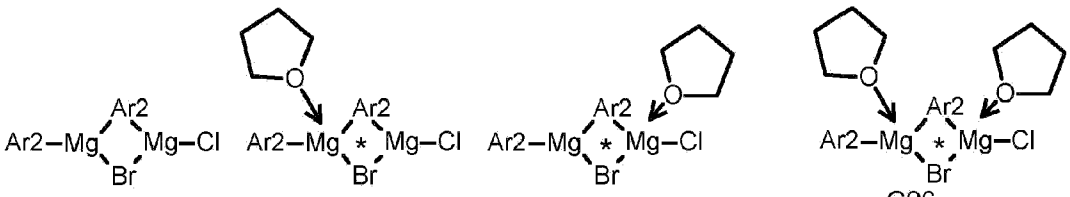


G89 G90 G91 G92



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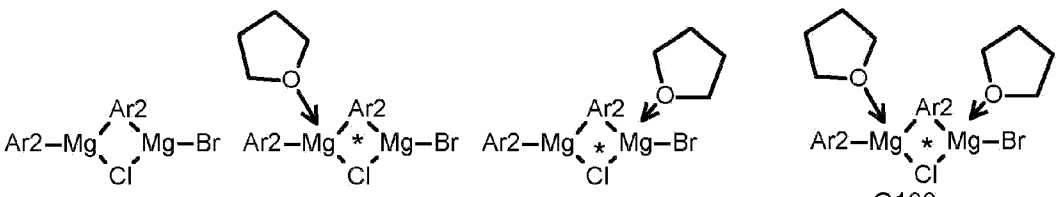
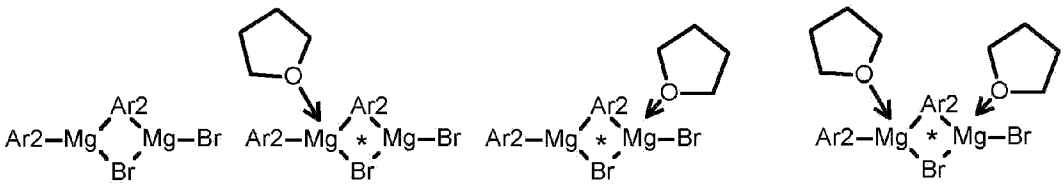
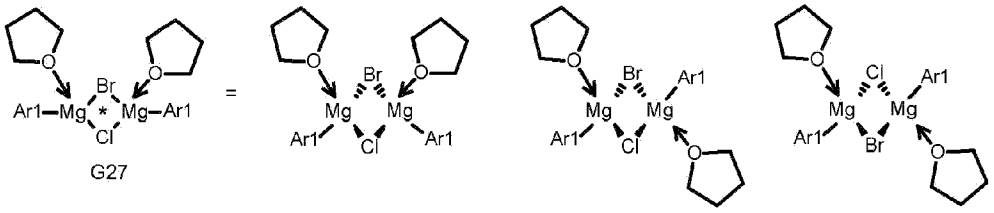


G97 G98 G99 G100



G101 G102 G103 G104

*Note 2: If Mg carries four substituents, it is coordinated tetrahedrally. Thereby, depending on the specific structure, stereoisomers (diastereomers and/or enantiomers) may occur (marked with *). This is demonstrated on a specific example as follows:



G27

[0023] Different magnesium compounds, in particular of the kind as shown above, and possible adducts with solvent molecules occur in the inventive process.

[0024] In the carbonyl chloride $R^1C(=O)Cl$ (V), and in the compounds (II), (IA), (IB) and (IC),

respectively, R^1 is C_1-C_6-alkyl or C_3-C_8-cycloalkyl, in particular selected from CH_3, $CH(CH_3)_2$ and cyclopropyl.

[0025] According to one embodiment, R^1 is C_1-C_6-alkyl, more specifically C_1-C_4-alkyl, in particular selected from CH_3, C_2H_5, n-C_3H_7, $CH(CH_3)_2$, n-butyl, iso-butyl and tert-butyl, more particularly selected from CH_3, C_2H_5, $CH(CH_3)_2$ and $C(CH_3)_3$. According to a further embodiment, R^1 is C_3-C_8-cycloalkyl, in particular C_3-C_6-cycloalkyl, such as C_3H_5 (cyclopropyl), C_4H_7 (cyclobutyl), cyclopentyl or cyclohexyl. A further embodiment relates to compounds, wherein R^1 is C_3H_5 (cyclopropyl) or C_4H_7 (cyclobutyl), more specifically cyclopropyl.

[0026] The carbonyl chloride $R^1C(=O)Cl$ (V) is preferably used in an equimolar amount or in excess compared to the reagent of formula (III). Specifically, the carbonyl chloride is used in an amount of 1 eq to 3 eq, in particular 1.1 to 2.5 eq, more specifically 1.2 to 2 eq, in relation to one equivalent of compound (III). In particular the amounts of 1.3 to 1.8 eq, more specifically 1.4 to 1.6 eq per mole of compound (III) may be favorable according to the present invention. Usually, the carbonyl chloride is used in excess, preferably in slight excess.

[0027] The Grignard reagent is added in the manner as is common to the skilled person. In particular, it can be added as solution in an appropriate solvent such as tetrahydrofurane (THF), 1,4-dioxane, diethylether and 2-methyl-tetrahydrofurane.

[0028] Examples for appropriate solvents for step (i) of the inventive process are aprotic organic solvents such as for example diethylether, tetrahydrofurane (THF), methyl-tert-butylether (MTBE), toluene, ortho-xylene, meta-xylene, para-xylene and mixtures thereof. Typically, the Grignard reagent is added as solution in THF, 1,4-dioxane, diethylether or 2-methyl-tetrahydrofurane (2-Me-THF), in particular in THF or diethylether, to the reaction vessel or flask containing the reagent (III) and a solvent such as, for example, toluene, MTBE, ortho-xylene, meta-xylene, para-xylene, mesitylene and/or diisopropylether, in particular toluene, MTBE and/or ortho-xylene. The reaction temperature when adding the Grignard reagent in step (i) is preferably held at a maximum of 50°C, in particular at a maximum of 40 °C, more preferably at a maximum of 35°C.

[0029] Generally, it is preferred to have a reaction temperature of 20°C to 45 °C, in particular room temperature to 45°C, in particular 25°C to 40 °C. In a further embodiment, the temperature is 20°C to 35°C, specifically 25°C to 30°C.

[0030] In the further course of reaction step (i), the temperature is preferably held at a maximum of 60°C, in particular at a maximum of 50°C, more preferably at a maximum of 45°C. Generally, it is preferred to have a reaction temperature of 30°C to 50°C, in particular 35°C to 45°C. In a further embodiment, the temperature is 20°C to 35°C, specifically 25°C to 30°C.

[0031] An appropriate Cu(I)-catalyst for the inventive process is a Cu(I) salt or Cu(I) oxide, in

particular a Cu(I) salt such as Cu(I)Cl or Cu(I)Br or any mixture thereof. According to one specific embodiment, Cu(I)Cl is used. According to the present invention, the Cu(I)-catalyst is present in an amount of 0.005 to 0.065 mol equivalents per 1 mole of compound (III). It is critical to the present invention, that the Cu(I)-catalyst is used in the range of 0.005 to 0.065 mole equivalents per 1 mole of compound (III) defined by the present invention. It has been surprisingly found that lower or higher amounts of the Cu(I)-catalyst are unfavourable due to significantly lower yields. Furthermore, high amounts of the Cu(I)-catalyst lead to increasing problems with phase separations, high costs for the Cu(I)-catalyst and high amounts of undesired toxic Cu(I) and/or Cu(II) in the wastewater, leading in turn to higher process costs for its removal. The present invents avoids these disadvantages and provides a process suitable for industrial upscale.

[0032] It may be preferred if 0.005 to 0.055 mol equivalents per 1 mole of compound (III) are used. Also, it may be preferred if 0.055 to 0.045 mol equivalents per 1 mole of compound (III), more specifically 0.005 to 0.04 mol equivalents per 1 mole of compound (III) are used. In particular, the amount of Cu(I)-catalyst is 0.01 to 0.03 mole equivalents per 1 mole of compound III, more particularly 0.015 to 0.025 mole equivalents, even more particularly 0.015 to 0.02, per 1 mole of compound III, specifically 0.018 to 0.023 mole equivalents per 1 mole of compound (III). According to one embodiment, the Cu(I)-catalyst is added in several portions to the reaction mixture, for example in two portions a half of the total amount.

[0033] An appropriate course of reaction is such that the Grignard reagent is first reacted with the compound of formula (III) and then, this reaction mixture is added to the carbonyl chloride and a portion of the Cu(I)-catalyst, in particular half of the total amount of the Cu(I) catalyst. After about half of the Grignard mixture has been added to the carbonyl chloride reaction mixture, the remaining amount of Cu(I) is added. According to a further embodiment, the whole amount of Cu(I)-catalyst is added in one portion.

[0034] By means of the inventive process step (i), the compounds of formula (II) can be prepared in surprisingly high yields. Preferably, the yields are at least 60%, more preferably 70 %, even more preferred at least 75%, even more preferred at least 80%.

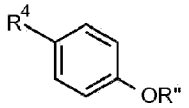
[0035] After step (i), a work-up of the reaction mixture can be carried out by procedures known in a general manner to the person skilled in the art. Usually, after completion of the reaction, water is added and the organic phase is washed with water, then the solvent is removed from the separated organic phases. Favorably, the so-obtained raw product is directly used in step (ii) of the inventive process. However, the raw product can also be further worked up and/or purified as generally known to the skilled person. If thisis deemed appropriate, the reaction mixture is extracted with a suitable organic solvent (for example aromatic hydrocarbons such as toluene and xylenes) and the residue is, if appropriate, purified by recrystallization and/or chromatography.

[0036] By means of the inventive process, the compounds of formula (II) can be prepared in surprisingly high yields. Preferably, the yields are at least 60%, more preferably at least 70 %,

even more preferred at least 75%, even more preferred at least 80%.

[0037] According to one embodiment of the invention, in step (i) no $AlCl_3$ is added to the reaction. Consequently, the reaction is carried out in the absence of or at least essentially without $AlCl_3$. In particular at most traces of $AlCl_3$ are present, such as at most 0.0065 mol% $AlCl_3$, for example traces due to impurities of other reagents. It has surprisingly been found that, contrary to what is taught in the prior art, the addition of $AlCl_3$ is unfavourable. It has been found that no addition of $AlCl_3$ according to this embodiment of the invention leads to higher yields.

[0038] According to step (ii) of the inventive process, compounds (II) are reacted with a phenol of formula (VI)



(VI)

in the presence of a base.

[0039] R" in fomula (VI) is hydrogen ((IV) is a substituted phenol) or a alkali metal kation ((VI) is a substituted phenolate). R^4 in formula (VI) and formulae (IA), (IB) and (IC), respectively, is F or Cl, in particular Cl.

[0040] As described above, compound (II) can be used directly from step (i) without further purification or can be used in purified form.

[0041] Examples for appropriate solvents for step (ii) of the inventive process are aprotic organic solvents such as for example dimethyl formamide (DMF), N-methyl pyrrolidone (NMP), Dimethyl imidazolidinone (DMI), toluene, o-xylene, dimethylactamide (DMA) and any mixtures thereof. In particular DMF, NMP, toluene and DMA or any mixtures, more specifically DMF, are particularly suitable.

[0042] It may be preferred, if the solvent used in step (ii) contains not more than 3 eq DMF in relation to 1 eq of the phenol of formula (VI), in particular not more than 2.8 eq to 1 eq of the phenol of formula (VI), more specifically not more than 2.6 eq to 1 eq of the phenol of formula (VI). It may be preferred if not more than 2.4, specifically not more than 2.2 eq DMF are used in the process of the invention.

[0043] The base used in step (ii) is preferably an inorganic base, according to one embodiment selected from NaOH, KOH, Na_2CO_3 and K_2CO_3, more specifically from Na_2CO_3 and K_2CO_3. According to one particular embodiment, Na_2CO_3 is used. According to a further particular embodiment, K_2CO_3 is used.

[0044] The base can be used in solid form or as a solution, e.g. as aqueous solution.

[0045] The reagents for step (ii) are preferably added at ambient temperature and the reaction temperature is then elevated, wherein the reaction temperature after the reagents have been added is preferably held at a maximum of 150°C, in particular at a maximum of 140°C, more preferably at a maximum of 130°C. Generally, it is preferred to have a reaction temperature of 20°C to 135°C, in particular 50°C to 135°C, more particularly 100°C to 130°C.

[0046] After step (ii), a work-up of the reaction mixture can be carried out by procedures known in a general manner to the person skilled in the art. Generally, water is added and the aqueous phase is extracted with a suitable solvent, e.g. tolene or o-xylene. The raw product obtained after evaporation of the solvent(s) can directly be used in a further step, if desired. However, the raw product can also be further worked up and/or purified as generally known to the skilled person.

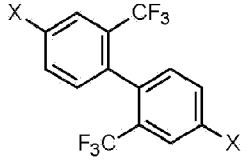
[0047] According to one embodiment of the invention, after completion of the reaction, most of the solvent (e.g. DMF or toluene) is removed from the reaction mixture, preferably under reduced pressure. Then, a suitable organic solvent, such as, for example, toluene or o-xylene, is added together with water. According to the inventive process, it may be favorable to carry out one to three, preferably two extractions of the aqueous phase.

[0048] By means of the inventive process, the compounds of formula (IA) can be prepared in surprisingly high yields. Preferably, the yields of step (ii) are at least 60%, more preferably at least 70 %, even more preferred at least 75%, even more preferred at least 80%.

[0049] By means of the inventive process, the compounds of formula (IA) can be prepared in surprisingly high yields. Preferably, the yields of steps (i) and (ii) are at least 60%, more preferably at least 70 %, even more preferred at least 75%, even more preferred at least 80%.

[0050] The starting compounds (III) for the inventive processes can be synthesized as known to the skilled person or are also partly commercially available.

[0051] Generally, one undesired side product in the synthesis of compounds (IA), in particular during step (i), that may occur in undesired amounts is the biphenyl compound (Y1)



(Y1)

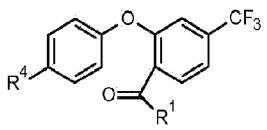
,

wherein X is F or Cl.

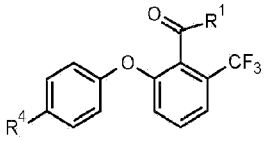
[0052] According the reaction conditions of the invention, it is possible to reduce the amount of (Y1). Consequently, according to the inventive process, it is possible to improve the yield of the desired compounds.

[0053] Furthermore, the reagents in the inventive process may contain impurities of isomers of compound (III), wherein the Br is attached to another position in the phenol. Accordingly, side

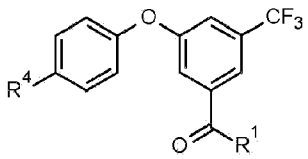
products (Y2), (Y3) and/or (Y4) may occur:



(Y2)



(Y3)



(Y4)

[0054] In particular possible side-products (Y2), (Y3) and (Y4), depending on the meaning of variables R^1 and R^4, are described in Table Y. Therein, every line corresponds to one compound of formula (Y2), (Y3) or (Y4):

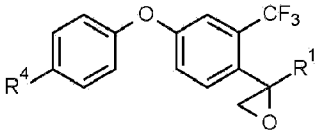
Table Y:

line	R^1	R^4	Formula
Y-1	CH_3	Cl	(Y2)
Y-2	CH_2CH_3	Cl	(Y2)
Y-3	$CH_2CH_2CH_3$	Cl	(Y2)
Y-4	$CH(CH_3)_2$	Cl	(Y2)
Y-5	$CH_2CH_2CH_2CH_3$	Cl	(Y2)
Y-6	$C(CH_3)_3$	Cl	(Y2)
Y-7	C_3H_5(cyclopropyl)	Cl	(Y2)
Y-8	CH_3	Cl	(Y3)
Y-9	CH_2CH_3	Cl	(Y3)
Y-10	$CH_2CH_2CH_3$	Cl	(Y3)
Y-11	$CH(CH_3)_2$	Cl	(Y3)
Y-12	$CH_2CH_2CH_2CH_3$	Cl	(Y3)
Y-13	$C(CH_3)_3$	Cl	(Y3)
Y-14	C_3H_5 (cyclopropyl)	Cl	(Y3)
Y-15	CH_3	Cl	(Y4)
Y-16	CH_2CH_3	Cl	(Y4)
Y-17	$CH_2CH_2CH_3$	Cl	(Y4)
Y-18	$CH(CH_3)_2$	Cl	(Y4)
Y-19	$CH_2CH_2CH_2CH_3$	Cl	(Y4)
Y-20	$C(CH_3)_3$	Cl	(Y4)

line	R^1	R^4	Formula
Y-21	C_3H_5 (cyclopropyl)	Cl	(Y4)

[0055] The ketone (IA) obtained according to the inventive process can be used as reagent for the synthesis of an oxirane of the formula (IB) that are useful intermediates for the synthesis of triazole active ingredients of formula (IC), that are effective against phytopathogenic fungi. See in particular WO 2013/007767. In EP 13150663.6 favorable process details are outlined. See also JACS 1965, 87, p 1353ff, Heterocycles 8, 1977, p. 397 ff, Synth. Communications, 15, 1985, p 753, J. Agric. Food Chem. 2009, 57, 4854-4860 and DE3733755.

[0056] Accordingly, according to a further embodiment of the present invention, following step (ii), the process further comprises the step:
(iii) reacting a ketone of the formula (IA) as defined in step (ii) to result in oxiranes (IB)



(IB)

wherein R^1 and R^4 are defined as described and preferably described herein, in particular in the context of formula (IA), (II) and (III).

[0057] In this process step, for obtaining an oxirane from the keto group, compound (IA) is preferably reacted with a trimethylsulf(ox)onium halide ($(CH_3)_3S^+$ $(O)Hal^-$) (VII) or trimethylsulfonium methylsulfate of the formula (VIII) $(CH_3)_3S^+$ $CH_3SO_4^-$.

[0058] Acording to one embodiment, in the process step (iii), the ketone (IA) is reacted with trimethylsulfonium methylsulfate of the formula VIII $(CH_3)_3S^+$ $CH_3SO_4^-$, preferably in aqueous solution in the presence of a base.

[0059] Step (iii) for the preparation of oxiranes (IB) particularly is as follows:
(iii) reacting an oxo compound of the formula (IA) with trimethylsulfonium methylsulfate of the formula VII

VIII $(CH_3)_3S^+$ $CH_3SO_4^-$

in aqueous solution in the presence of a base, wherein the variables R^1, R^4 are defined as given and preferably described herein for compounds (IA).

[0060] In this process step (iii) using trimethylsulfonium methylsulfate of the formula VIII, preferably, 1 to 4 equivalents, in particular 1.2 to 3.5 eq, more specifically 1.5 to 3.3 eq, of water in relation to one equivalent of compound (IA) are used. It may be favorable, if more than 1.5 eq of water, in particular more than 1.5 eq of water to 4 eq of water, more specifically

more than 1.5 eq to 3.5 eq of water, even more particularly more than 1.5 eq water to 2.5 eq water per mole of compound (IA) are used. In particular the ratios of 1.6 to 3.8, more specifically 1.7 to 3.3 eq, more specifically 1.8 to 2.8 eq or 1.9 to 2.5 of water per mole of compound (IA) may be favorable according to the present invention.

[0061] The reagent VIII is preferably used in an amount of 1.1 to 2.5, in particular 1.2 to 2, more specifically 1.3 to 1.6 equivalents of VIII per 1 equivalent (mole) of compound (IA).

[0062] In general, the reagent of formula VIII can be prepared from dimethylsulfide and dimethylsulfate. According to one embodiment, reagent VIII is prepared in-situ by adding dimethylsulfate to the reaction mixture containing dimethylsulfide. The dimethylsulfide is usually used in excess.

[0063] It is preferred to use as reagent VIII an aqueous solution of trimethylsulfonium methylsulfate containing 33 to 37 wt%, preferably 34 to 36 wt%, more specifically 34 to 35.3 wt%, also more specifically 34.3 to 35.9 wt%, of trimethylsulfonium kation.

[0064] In particular, the reagent VIII solution contains 33 to 37 wt%, preferably 34 to 36 wt%, more specifically 34 to 35.3 wt%, also more specifically 34.3 to 35.9 wt%, of trimethylsulfonium kation. Accordingly, the amount of trimethylsulfonium-methylsulfate in the reagent, measured as summation of trimethsulfonium-cation and methylsulfate-anion, is about 80 to 90 wt%, preferably about 83 to 88 wt-%, more specifically about 83 to 86 wt-%. The quantification can be, for example, accomplished by means of quantitative NMR-spectroscopie.

[0065] The viscosity of the aqueous reagent VIII solution is comparatively low. The solutions are stable at room temparture, in particular at 25°C, and can be stored over a longer time. In particular, the reagent solution does not crystallize out during storage over a longer time, such as several weeks, e.g. up to 12 weeks, at temperatures of 10 to 25°C.

[0066] The reagent can be prepared by adding dimethylsulfate to water and dimethylsulfide. Dimethylsulfide is normally used in excess, generally 2 to 8, more preferably 4 to 6, more specifically 4.5 to 5.5, equivalents.

[0067] In the preparation of the aqueous solution of reagent VIII, preferably 1.3 to 2.2 eq, more preferably 1.45 to 2.0 eq, water in relation to the dimethylsulfate are used.

[0068] Preferably, the temperature of the reaction mixture when adding the dimethylsulfate is room temperature, in particular 25°C to 40°C.

[0069] The aqueous reagent separates as the lower phase and can be further used as such.

[0070] The use of the aqueous solution of the reagent VIII has been proven very efficient also for up-scaled reaction conditions, since it is stable and since it contains a defined amount of reagent, so that reagent VIII can be easily and precisely dosed to the reaction mixture.

[0071] Thus it is a preferred embodiment, if the reagent VIII is added as an aqueous solution of trimethylsulfonium methylsulfate containing 33 to 37 wt%, preferably 34 to 36 wt%, more specifically 34 to 35.3 wt%, also more specifically 34.3 to 35.9 wt% of trimethylsulfonium kation.

[0072] The base used in step (iii) is preferably selected from KOH and NaOH. In a preferred embodiment, KOH is used, preferably as solid pellets or flakes. It is preferred if at least 3 equivalents of base, preferably at least 3.2 eq, more specifically at least 3.4 eq per 1 equivalent of compound (IA) are used. It may be preferred if the amount of base is 3 to 6 eq, more specifically 3 to 5 eq per mole of compound (IA).

[0073] According to one embodiment of the inventive process, dimethylsulfide is also used as solvent in step (iii). According to a further embodiment, an additional solvent is used. In particular, an aprotic organic solvent is suitable, such as for example diethylether, methyl-tert-butylether, chlorobenzene, xylene or toluene.

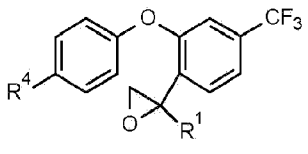
[0074] The reaction temperature in step (iii) is preferably held at a maximum of 50°C, in particular at a maximum of 45, more preferably at a maximum of 40°C. Generally, it is also preferred to have a reaction temperature of at least 20 °C, in particular at least room temperature, in particular at least 25°C. In a further embodiment, the temperature is at least 30°C. It may be preferred if the temperature is at least 35 °C.

[0075] The oxiranes of formula (IB) can be prepared in high yields. Preferably, the yields are at least 60%, more preferably 70 %, even more preferred at least 75%, even more preferred at least 80%.

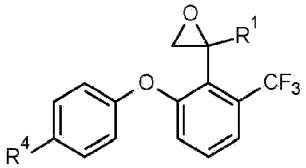
[0076] The order of adding the reactants to the reaction mixture is variable. In one embodiment, the base is added to the solution of compound (IA) and solvent first and then reagent VIII is added.

[0077] According to another embodiment, the reagent VIII is added first to the solution of compound (IA) and then the base is added. According to a further embodiment, a solution of compound (IA) and the reagent VIII are added simultaneously to the base. In the latter embodiment, the base is preferably suspended in sufficient solvent and is stirred during the addition of the reagents.

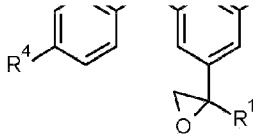
[0078] For example if side products are contained in the starting material, also the respective undesired side-oxirane products of this process step for obtaining the oxirane (IB) may occur in the reaction. Accordingly, side products (Z2), (Z3) and/or (Z4) may occur:



(Z2)



(Z3)



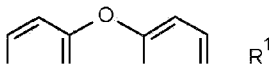
(Z4)

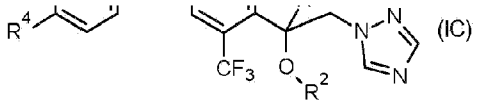
[0079] In particular possible side-products (Z2), (Z3) and (Z4), depending on the meaning of variables R^1 and R^4, are described in Table Z. Therein, every line corresponds to one compound of formula (Z2), (Z3) or (Z4):

Table Z:

line	R^1	R^4	Formula
Z-1	CH_3	Cl	(Z2)
Z-2	CH_2CH_3	Cl	(Z2)
Z-3	$CH_2CH_2CH_3$	Cl	(Z2)
Z-4	$CH(CH_3)_2$	Cl	(Z2)
Z-5	$CH_2CH_2CH_2CH_3$	Cl	(Z2)
Z-6	$C(CH_3)_3$	Cl	(Z2)
Z-7	C_3H_5 (cyclopropyl)	Cl	(Z2)
Z-8	CH_3	Cl	(Z3)
Z-9	CH_2CH_3	Cl	(Z3)
Z-10	$CH_2CH_2CH_3$	Cl	(Z3)
Z-11	$CH(CH_3)_2$	Cl	(Z3)
Z-12	$CH_2CH_2CH_2CH_3$	Cl	(Z3)
Z-13	$C(CH_3)_3$	Cl	(Z3)
Z-14	C_3H_5 (cyclopropyl)	Cl	(Z3)
Z-15	CH_3	Cl	(Z4)
Z-16	CH_2CH_3	Cl	(Z4)
Z-17	$CH_2CH_2CH_3$	Cl	(Z4)
Z-18	$CH(CH_3)_2$	Cl	(Z4)
Z-19	$CH_2CH_2CH_2CH_3$	Cl	(Z4)
Z-20	$C(CH_3)_3$	Cl	(Z4)
Z-21	C_3H_5 (cyclopropyl)	Cl	(Z4)

[0080] The oxiranes (IB) can be further reacted to a triazole of formula (IC)





(IC)

wherein the variables R^1 and R^4 are defined and preferably defined herein, and wherein specific combinations for R^1 and R^4 are given in Table Y above, and

R^2 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl, phenyl-C_1-C_4-alkyl, phenyl-C_2-C_4-alkenyl or phenyl-C_2-C_4-alkynyl; wherein the aliphatic moieties of R^2 are not further substituted or do carry one, two, three or up to the maximum possible number of identical or different groups R^{12a} which independently are selected from:

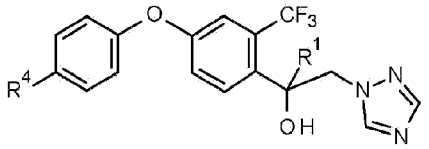
R^{12a} halogen, OH, CN, nitro, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl, C_3-C_8-halocycloalkyl and C_1-C_4-halogenalkoxy;

wherein the cycloalkyl and/or phenyl moieties of R^2 are not further substituted or do carry one, two, three, four, five or up to the maximum number of identical or different groups R^{12b} which independently are selected from:

R^{12b} halogen, OH, CN, nitro, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenalkyl, C_3-C_8-cycloalkyl, C_3-C_8-halocycloalkyl and C_1-C_4-halogenalkoxy.

[0081] Consequently, according to a further embodiment of the present invention, following step (iii), the process further comprises the step:

(iv) reacting the oxirane of the formula (IB) as defined in step (iii) with 1H-1,2,4-triazole and a base, resulting in compounds of formula (IC), wherein R^2 is hydrogen (compounds (IC-1)

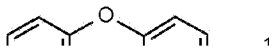


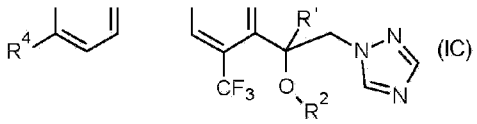
(IC-1)

and, for obtaining compounds (IC), wherein R^2 is different from hydrogen (compounds IC-2);

(v) derivatizing the compound of formula (IC-1) as defined in step (iv) under basic conditions with R^2-LG, wherein LG is a nucleophilically replaceable leaving group; to result in compounds (IC-2).

[0082] Accordingly, a further aspect of the invention relates to a process for the preparation of triazole compounds of the formula (IC)





comprising the following steps:

1. (i) as described herein;
2. (ii) as described herein;
3. (iii) reacting a ketone of the formula (IA) as defined in step (ii), in particular with a trimethyl-sulf(ox)onium halide ($(CH_3)_3S^+$ $(O)Hal^-$) (VII) or trimethylsulfonium methylsulfate of the formula (VIII) $(CH_3)_3S^+$ $CH_3SO_4^-$, to result in oxiranes (IB); and
4. (iv) reacting the oxirane (IB) as defined in step (iii) with 1H-1,2,4-triazole in the presence of a base to obtain compounds (IC), wherein R^2 is hydrogen (compounds IC-1); and, for obtaining compounds wherein R^2 is different from hydrogen:
5. (v) derivatizing the compound of formula (IC-1) as defined in step (iv) under basic conditions with R^2-LG, wherein LG is a nucleophilically replaceable leaving group; to result in compounds (IC-2).

[0083] According to one embodiment, the oxirane (IB) is prepared by reaction of the respective oxo-group-containing compound (IA) with trimethylsulf(ox)onium halides ($(CH_3)_3S^+$ $(O)Hal^-$), preferably trimethylsulfoniumiodide, preferably in the presence of a base such as sodium hydroxide (see also JACS 1965 87 p. 1353).

[0084] According to one embodiment, the oxirane (IB) is prepared by reaction of the respective oxo-group-containing compound (IA) with trimethylsulfonium methylsulfate of the formula (VIII) $(CH_3)_3S^+$ $CH_3SO_4^-$ as detailled above.

[0085] LG represents a nucleophilically replaceable leaving group such as halogen, alkylsulfonyl, alkylsulfonyloxy and arylsulfonyloxy, preferably chloro, bromo or iodo, particularly preferably bromo.

[0086] According to one embodiment, R^2 is selected from C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, phenyl, phenyl-C_1-C_4-alkyl, phenyl-C_2-C_4-alkenyl and phenyl-C_2-C_4-alkynyl, wherein the R^2 are in each case unsubstituted or are substituted by R^{12a} and/or R^{12b} as defined and preferably defined herein.

[0087] According to a further embodiment, R^2 is C_1-C_6-alkyl, in particular C_1-C_4-alkyl, such as CH_3, C_2H_5, $CH(CH_3)_2$, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$. A further embodiment relates to compounds, wherein R^2 is C_1-C_6-alkyl, in particular C_1-C_4-alkyl, that is substituted by

one, two or three or up to the maximum possible number of identical or different groups R^{12a}, as defined and preferably defined herein. According to a specific embodiment thereof, R^2 is C_1-C_6-haloalkyl, in particular C_1-C_4-haloalkyl, more particularly C_1-C_2-haloalkyl. According to a further specific embodiment thereof, R^2 is C_1-C_4-alkoxy-C_1-C_6-alkyl, in particular C_1-C_4-alkoxy-C_1-C_4-alkyl, such as CH_2OCH_3 or $CH_2CH_2OCH_3$. According to still a further specific embodiment thereof, R^2 is hydroxy-C_1-C_6-alkyl, in particular hydroxyl-C_1-C_4-alkyl, such as CH_2CH_2OH.

[0088] According to still another embodiment, R^2 is C_3-C_8-cycloalkyl-C_1-C_6-alkyl, in particular C_3-C_6-cycloalkyl-C_1-C_4-alkyl. A further embodiment relates to compounds, wherein R^2 is C_3-C_8-cycloalkyl-C_1-C_6-alkyl, in particular C_3-C_6-cycloalkyl-C_1-C_4-alkyl, more particularly C_3-C_6-cycloalkyl-C_1-C_2-alkyl, that is substituted by one, two or three or up to the maximum possible number of identical or different groups R^{12a} in the alkyl moiety and/or substituted by one, two, three four or five or up to the maximum possible number of identical or different groups R^{12b} in the cycloalkyl moiety. R^{12a} and R^{12b} are in each case as defined and preferably defined herein.

[0089] According to another embodiment, R^2 is C_2-C_6-alkenyl, in particular C_2-C_4-alkenyl, such as $CH_2CH=CH_2$, $CH_2C(CH_3)=CH_2$ or $CH_2CH=CHCH_3$. A further embodiment relates to compounds, wherein R^2 is C_2-C_6-alkenyl, in particular C_2-C_4-alkenyl, that is substituted by one, two or three or up to the maximum possible number of identical or different groups R^{12a} as defined and preferably defined herein. According to a specific embodiment thereof, R^2 is C_2-C_6-haloalkenyl, in particular C_2-C_4-haloalkenyl, such as $CH_2C(Cl)=CH_2$ and $CH_2C(H)=CHCl$. According to a further specific embodiment thereof, R^2 is C_3-C_8-cycloalkyl-C_2-C_6-alkenyl or C_3-C_8-halocycloalkyl-C_2-C_6-alkenyl, in particular C_3-C_6-cycloalkyl-C_2-C_4-alkenyl or C_3-C_6-halocycloalkyl-C_2-C_4-alkenyl.

[0090] According to still another embodiment, R^2 is C_2-C_6-alkynyl, in particular C_2-C_4-alkynyl, such as $CH_2C\equiv CH$ or $CH_2C\equiv CCH_3$. A further embodiment relates to compounds, wherein R^2 is C_2-C_6-alkynyl, in particular C_2-C_4-alkynyl, that is substituted by one, two or three or up to the maximum possible number of identical or different groups R^{12a}, as defined and preferably defined herein. According to a specific embodiment thereof, R^2 is C_2-C_6-haloalkynyl, in particular C_2-C_4-haloalkynyl. According to a further specific embodiment thereof, R^2 is C_3-C_8-cycloalkyl-C_2-C_6-alkynyl or C_3-C_8-halocycloalkyl-C_2-C_6-alkynyl, in particular C_3-C_6-cycloalkyl-C_2-C_4-alkynyl or C_3-C_6-halocycloalkyl-C_2-C_4-alkynyl.

[0091] According to still another embodiment, R^2 is phenyl-C_1-C_4-alkyl, in particular phenyl-C_1-

C_2-alkyl, such as benzyl, wherein the alkyl moiety in each case is unsubstituted or carries one, two or three R^{12a} as defined and preferably defined herein, in particular selected from halogen, in particular F and Cl, C_1-C_4-alkoxy, in particular OCH_3, and CN, and wherein the phenyl in each case is unsubstituted or carries one, two or three R^{12b} as as defined and preferably defined herein, in particular selected from halogen, in particular Cl and F, C_1-C_4-alkoxy, in particular OCH_3, C_1-C_4-alkyl, in particular CH_3 or C_2H_5, and CN.

[0092] According to still another embodiment, R^2 is phenyl-C_2-C_4-alkenyl, in particular phenyl-C_2-C_3-alkenyl, such as phenylethenyl, wherein the alkenyl moiety in each case is unsubstituted or carries one, two or three R^{12a} as defined and preferably defined herein, in particular selected from halogen, in particular F and Cl, C_1-C_4-alkoxy, in particular OCH_3, and CN, and wherein the phenyl in each case is unsubstituted or carries one, two or three R^{12b} as defined and preferably defined herein, in particular selected from halogen, in particular Cl and F, C_1-C_4-alkoxy, in particular OCH_3, C_1-C_4-alkyl, in particular CH_3 or C_2H_5, and CN.

[0093] According to still another embodiment, R^2 is phenyl-C_2-C_4-alkynyl, in particular phenyl-C_2-C_3-alkynyl, such as phenylethinyl, wherein the alkynyl moiety in each case is unsubstituted or carries one, two or three R^{12a}, as defined and preferably defined herein, in particular selected from halogen, in particular F and Cl, C_1-C_4-alkoxy, in particular OCH_3, and CN, and wherein the phenyl in each case is unsubstituted or carries one, two or three R^{12b} as defined and preferably defined herein, in particular selected from halogen, in particular Cl and F, C_1-C_4-alkoxy, in particular OCH_3, C_1-C_4-alkyl, in particular CH_3 or C_2H_5, and CN.

[0094] According to still another embodiment, R^2 is C_3-C_8-cycloalkyl, in particular C_3-C_6-cycloalkyl, such as C_3H_5 (cyclopropyl), C_4H_7 (cyclobutyl), cyclopentyl or cyclohexyl. A further embodiment relates to compounds, wherein R^2 is C_3-C_8-cycloalkyl, in particular C_3-C_6-cycloalkyl, such as C_3H_5 (cyclopropyl) or C_4H_7 (cyclobutyl), that is substituted by one, two, three four or five or up to the maximum possible number of identical or different groups R^{12b} as defined and preferably defined herein. According to a specific embodiment thereof, R^2 is C_3-C_8-halocycloalkyl, in particular C_3-C_6-halocycloalkyl, such as halocyclopropyl, in particular 1-F-cyclopropyl or 1-Cl-cyclopropyl. According to a further specific embodiment thereof, R^2 is C_3-C_8-cycloalkyl-C_3-C_8-cycloalkyl, in particular C_3-C_6-cycloalkyl-C_3-C_6-cycloalkyl, wherein each of said cycloalkyl-cycloalkyl moieties is unsubstituted or carries one, two or three R^{12b} as defined and preferably defined herein.

[0095] According to still another embodiment, R^2 is phenyl, wherein the phenyl is unsubstituted or carries one, two, three, four or five independently selected R^{12b} as defined and preferably

defined herein, in particular selected from halogen, in particular Cl and F, C_1-C_4-alkoxy, in particular OCH_3, C_1-C_4-alkyl, in particular CH_3 or C_2H_5, and CN.

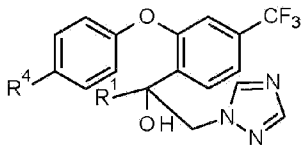
[0096] In a further embodiment of the invention, R^2 is selected from C_1-C_6-alkyl, C_2-C_6-alkenyl and C_2-C_6-alkynyl, wherein the R^2 are in each case unsubstituted or are substituted by R^{12a} and/or R^{12b} as defined and preferably defined herein. In each case, the substituents may also have the preferred meanings for the respective substituent as defined above.

[0097] R^{12a} according to the invention is independently selected from halogen, OH, CN, nitro, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl, C_3-C_8-halocycloalkyl and C_1-C_4-halogenalkoxy. According to one embodiment R^{12a} is independently selected from halogen, OH, CN, C_1-C_2-alkoxy, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl and C_1-C_2-halogenalkoxy. Specifically, R^{12a} is independently selected from F, Cl, OH, CN, C_1-C_2-alkoxy, cyclopropyl, 1-F-cyclopropyl, 1-Cl-cyclopropyl and C_1-C_2-halogenalkoxy.

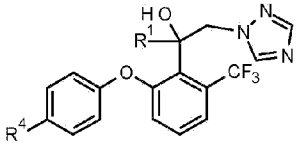
[0098] R^{12b} according to the invention is is independently selected from halogen, OH, CN, nitro, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenalkyl, C_3-C_8-cycloalkyl, C_3-C_8-halocycloalkyl and C_1-C_4-halogenalkoxy. According to one embodiment R^{12b} is independently selected from halogen, CN, nitro, C_1-C_2-alkyl, C_1-C_2-alkoxy, C_1-C_2-halogenalkyl, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl and C_1-C_2-halogenalkoxy. Specifically, R^{12b} is independently selected from F, Cl, OH, CN, nitro, CH_3, OCH_3, cyclopropyl, 1-F-cyclopropyl, 1-Cl-cyclopropyl and halogenmethoxy.

[0099] For example if side products are contained in the starting material, also the respective undesired triazole side-products may occur in the reaction:

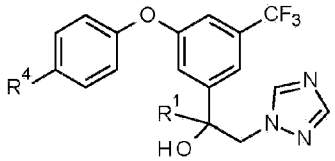
[0100] Accordingly, side products (T2), (T3) and/or (T4) may occur:



(T2)



(T3)



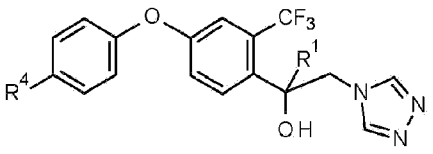
(T4)

In particular possible side-products (T2), (T3) and (T4), depending on the meaning of variables R^1 and R^4, are described in Table T. Therein, every line corresponds to one compound of formula (T2), (T3) or (T4):

Table T:

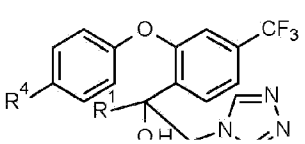
line	R^1	R^4	Formula
T-1	CH_3	Cl	(T2)
T-2	CH_2CH_3	Cl	(T2)
T-3	$CH_2CH_2CH_3$	Cl	(T2)
T-4	$CH(CH_3)_2$	Cl	(T2)
T-5	$CH_2CH_2CH_2CH_3$	Cl	(T2)
T-6	$C(CH_3)_3$	Cl	(T2)
T-7	C_3H_5 (cyclopropyl)	Cl	(T2)
T-8	CH_3	Cl	(T3)
T-9	CH_2CH_3	Cl	(T3)
T-10	$CH_2CH_2CH_3$	Cl	(T3)
T-11	$CH(CH_3)_2$	Cl	(T3)
T-12	$CH_2CH_2CH_2CH_3$	Cl	(T3)
T-13	$C(CH_3)_3$	Cl	(T3)
T-14	C_3H_5 (cyclopropyl)	Cl	(T3)
T-15	CH_3	Cl	(T4)
T-16	CH_2CH_3	Cl	(T4)
T-17	$CH_2CH_2CH_3$	Cl	(T4)
T-18	$CH(CH_3)_2$	Cl	(T4)
T-19	$CH_2CH_2CH_2CH_3$	Cl	(T4)
T-20	$C(CH_3)_3$	Cl	(T4)
T-21	C_3H_5 (cyclopropyl)	Cl	(T4)

[0101] An undesired side-product of the triazole reaction is also the symmetric triazole

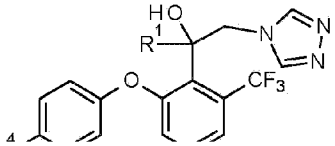


(ICs-1)

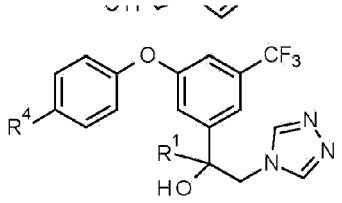
[0102] Accordingly, the respective symmetric side products of (T2), (T3) and/or (T4) may occur, named (Ts2), (Ts3) and (Ts4), respectively:



(Ts2)



(Ts3)



(Ts4)

[0103] In particular possible side-products (Ts2), (Ts3) and (Ts4), depending on the meaning of variables R^1 and R^4, are described in Table Ts. Therein, every line corresponds to one compound of formula (Ts2), (Ts3) or (Ts4):

Table Ts:

line	R^1	R^4	Formula
Ts-1	CH_3	Cl	(Ts2)
Ts-2	CH_2CH_3	Cl	(Ts2)
Ts-3	$CH_2CH_2CH_3$	Cl	(Ts2)
Ts-4	$CH(CH_3)_2$	Cl	(Ts2)
Ts-5	$CH_2CH_2CH_2CH_3$	Cl	(Ts2)
Ts-6	$C(CH_3)_3$	Cl	(Ts2)
Ts-7	C_3H_5 (cyclopropyl)	Cl	(Ts2)
Ts-8	CH_3	Cl	(Ts3)
Ts-9	CH_2CH_3	Cl	(Ts3)
Ts-10	$CH_2CH_2CH_3$	Cl	(Ts3)
Ts-11	$CH(CH_3)_2$	Cl	(Ts3)
Ts-12	$CH_2CH_2CH_2CH_3$	Cl	(Ts3)
Ts-13	$C(CH_3)_3$	Cl	(Ts3)
Ts-14	C_3H_5 (cyclopropyl)	Cl	(Ts3)
Ts-15	CH_3	Cl	(Ts4)
Ts-16	CH_2CH_3	Cl	(Ts4)
Ts-17	$CH_2CH_2CH_3$	Cl	(Ts4)
Ts-18	$CH(CH_3)_2$	Cl	(Ts4)
Ts-19	$CH_2CH_2CH_2CH_3$	Cl	(Ts4)
Ts-20	$C(CH_3)_3$	Cl	(Ts4)
Ts-21	C_3H_5 (cyclopropyl)	Cl	(Ts4)

[0104] In one embodiment of the invention, the process (iv) is as follows:

(iv) reacting the oxirane (IB) as defined in step (iii) with 1H-1,2,4-triazole and an inorganic base to obtain compounds (IC), wherein R^2 is hydrogen (compounds IC-1).

[0105] The inorganic base used in step (iv) is preferably selected from NaOH, KOH, Na_2CO_3 and K_2CO_3, more specifically from NaOH and KOH. According to one embodiment, NaOH is used. According to a further embodiment, KOH is used.

[0106] According to a specific embodiment, the sodium salt of 1H-1,2,4-triazole as a base is used, wherein said sodium salt is prepared using triazole and a base preferably selected from NaOH, NaH and Na-alcoholates. See also DE 3042302.

[0107] The amount of base used in step (iv) is preferably equal to or less than 1 eq, in particular less than 1 eq, more preferably equal to or less than 0.8 eq, even more preferably equal to or less than 0.6 equivalents per 1 equivalent of compound (IB). Also preferred are amounts of base being equal to or less than 0.4 equivalents, in particular equal to or less than 0.2 equivalents, specifically equal to or less than 0.1 eq per 1 equivalent of compound (IB). Preferably, at least 0.1 eq, more preferably at least 0.2 equivalents, in particular at least 0.3, more specifically at least 0.4 eq base per 1 equivalent of compound (IB) are used.

[0108] Higher yields of compounds (IC-1) can be acchieved, if less than 1 eq of base is used in relation to the compound (IB). In specific embodiments thereof, NaOH is used in as base, preferably in an amount as given above, in particular in an amount of 0.1 to 0.55 eq in relation to the oxirane of formula (IB).

[0109] In order to have preferably low reaction times, temperatures of at least 100 °C, more preferably at least 110 °C, in particular at least 120 °C are favorable. It is also an embodiment to reflux the reaction mixture. Preferably, the reaction temperature is not higher than 150°C, in particular not higher than 140°C. Specifically, a reaction temperature of 120°C to 140°C is used.

[0110] The amount of 1H-1,2,4-triazole used in step (iv) generally is at least 1 eq per mole of oxirane (IB). According to one embodiment, the 1H-1,2,4-triazole is used in excess in relation to the oxirane (IB). Preferred are more than 1 eq to 2 eq, more preferably more than 1 eq to 1.8 eq, even more preferred more than 1 eq to 1.6 eq. Mostly for economic reason, it can be preferred to use at least 1.1 eq, specifically 1.15 eq, to 1.5 eq of triazole in relation to oxirane (IB).

[0111] The solvent used in step (iv) is preferably selected from dimethylformamide, dimethylacetamide, N-metylpyrrolidone. Most preferred is dimethylformamide.

[0112] According to one preferred embodiment, the compounds (IC-1) resulting from step (iv) are crystallized from a suitable solvent such as, for example toluene, an aliphatic alcohol, acetonitrile, ethyl acetate and/or cyclohexane, in particular toluene and/or an aliphatic alcohol.

[0113] In particular, the aliphatic alcohol is selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, isobutanol or any mixture thereof. In particular, the aliphatic alcohol is selected from methanol and ethanol.

[0114] Generally, for the crystallizing step, the solvent, in particular dimethylformide as described above, is firstly evaporated in large part, preferably under reduced pressure. Preferably, at least 55% of the solvent, more preferably at least 60 % of the sovent, more specifically at least 70% of the solvent are removed. Specifically, it may be preferred, if at least 80%, more specifically at least 90 % of the solvent, such as DMF, are removed The solvent can then be recycled to be used again in the process step (iv), if necessary after it has been further rectificated before.

[0115] Then, water and the respective suitable solvent such as an ether, for example diethylether, diisopropylether, methyl-tert-butylether (MTBE), methylenechlorid and /or tolulene, in particular toluene, are added. Also ethyl acetate can be appropriate as solvent. The product (IC-1) is then preferably obtained by crystallization directly from the concentrated, e.g. toluene-reaction mixture. Also preferred and suitable according to the invention is the change of solvent to e.g. methanole or ethanole (see above) for the crystallization of the products.

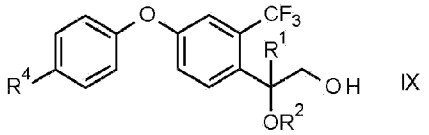
[0116] According to one embodiment, seed crystals are added for the crystallization step.

[0117] By using the crystallizing step, in particular when carrying out the process steps (iv) the formation of the undesired symmetric triazole (ICs-1) as described above can be reduced to equal or less than 10%, more preferably equal or less than 8%, even more preferably equal or less than 5%, even more preferably equal or less than 2%.

[0118] Preferably, the ratio of isolated compound (IC-1) to the symmetric triazole (ICs-1) is at least 20:1, more preferably at least 30:1, even more preferably 50:1, more specifically 70:1. In particular, the ratio of compound (IC-1) to (ICs-1) is at least 30:1.

[0119] Also other methods of further reacting the oxiranes (IB) to end products (IC) can be carried out.

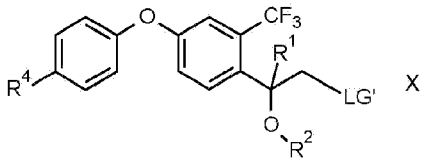
[0120] For example, the epoxide ring of compounds (IB) may be cleaved by reaction with alcohols R^2OH preferably under acidic conditions to result in compounds IX:



IX

[0121] Thereafter, the resulting compounds IX are reacted with halogenating agents or sulfonating agents such as PBr_3, PCl_3 mesyl chloride, tosyl chloride or thionyl chloride, to obtain compounds X wherein LG' is a nucleophilically replaceable leaving group such as

halogen, alkylsulfonyl, alkylsulfonyloxy and arylsulfonyloxy, preferably chloro, bromo or iodo, particularly preferably bromo or alkylsulfonyl. Then compounds X are reacted with 1H-1,2,4-triazole to obtain compounds IC as known in the art and/or described above:



X

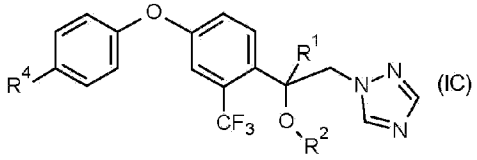
[0122] For obtaining compounds of formula IC, wherein the alcohol group is derivatized into an ether group to result in compounds of formula IC-2, wherein the variables are defined above, the following step can be carried out:
(v) derivatizing the compound of formula (IC-1) as defined in step (iv) under basic conditions with R^2-LG, wherein LG is a nucleophilically replaceable leaving group; to result in compounds (IC-2).

[0123] LG represents a nucleophilically replaceable leaving group such as halogen, alkylsulfonyl, alkylsulfonyloxy and arylsulfonyloxy, preferably chloro, bromo or iodo, particularly preferably bromo. Preferably a base is ues in step (iii) such as for example, NaH.

[0124] Suitable solvents are for example ethers, in particular cyclic ethers. Possible solvents are for example tetrahydrofuran (THF), 2-methyl-tetrahydrofuran (2-Me-THF), diethyl ether, TBME (tert-butyl methyl ether), CPME (cyclopentyl methyl ether), DME (1,2-dimethoxyethane) and 1,4-dioxane. Further solvents that may be suitable are, for example, diisopropyl ether, di-n-butyl ether and/or diglyme. Often, the use of THF or 2-methyl-THF is particularly suitable. Furthermore, it may also be suitable to use combinations of two or more different solvents, such as for example any combination of the solvents listed above or any one of the listed ethers with aliphatic hydrocarbons like n-hexane, heptane or aromatic hydrocarbons like toluene or xylenes.

[0125] The skilled person is familiar with the reaction in step (v) and may vary the reaction conditions analogously to known syntheses.

[0126] In one embodiment, a triazole compound of the formula IC is obtained by



(IC)

(iv-a)reacting an oxirane of the formula (IB) as defined herein; with 1H-1,2,4-triazole and an inorganic base, wherein less than 1 equivalent of said base is used per 1 equivalent of compound (IB), resulting in compounds of formula (IC).

[0127] For obtaining compounds of formula (IC-2), wherein the alcohol group is derivatized (resulting in "OR^2", see above), the above derivatizing step can be carried out.

[0128] In the definitions of the variables given herein, collective terms are used which are generally representative for the substituents in question. The term "C_n-C_m" indicates the number of carbon atoms possible in each case in the substituent or substituent moiety in question.

[0129] The term "halogen" refers to fluorine, chlorine, bromine and iodine.

[0130] The term "C_1-C_6-alkyl" refers to a straight-chained or branched saturated hydrocarbon group having 1 to 6 carbon atoms, e.g. methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl. Likewise, the term "C_2-C_4-alkyl" refers to a straight-chained or branched alkyl group having 2 to 4 carbon atoms, such as ethyl, propyl (n-propyl), 1-methylethyl (iso-propoyl), butyl, 1-methylpropyl (sec.-butyl), 2-methylpropyl (iso-butyl), 1,1-dimethylethyl (tert.-butyl).

[0131] The term "C_3-C_8-cycloalkyl" refers to monocyclic saturated hydrocarbon radicals having 3 to 8 carbon ring members, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

[0132] The meanings and preferred meanings described herein for the variables R^1, R^2, R^4, X, R' and R" apply to all compounds and the precursors of the compounds and side products in any of the process steps detailed herein.

[0133] R^4 according to the present invention is independently selected from F and Cl.Specifically, the following compounds IC.1 to IC.7 can advantageously be prepared using the process according to the present invention:

compound IC.1 2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-(1,2,4-triazol-1-yl)propan-2-ol;

compound IC.2 1-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-cyclopropyl-2-(1,2,4-triazol-1-yl)ethanol;

compound IC.3 2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-3-methyl-1-(1,2,4-triazol-1-yl)butan-2-ol;

compound IC.4 2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-(1,2,4-triazol-1-yl)butan-2-ol;

compound IC.5 1-[2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-methoxy-propyl]-1,2,4-

triazole;

compound IC.6 1-[2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-cyclopropyl-2-methoxyethyl]-1,2,4-triazole;

compound IC.7 1-[2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-methoxy-butyl]1,2,4-triazole;

[0134] Compounds (IC) comprise chiral centers and they are generally obtained in the form of racemates. The R- and S-enantiomers of the compounds can be separated and isolated in pure form with methods known by the skilled person, e.g. by using chiral HPLC. Furthermore, components I can be present in different crystal modifications, which may differ in biological activity. The compounds may be present in various crystal modifications.

Examples

[0135] The following examples further illustrate the present invention and do not restrict the invention in any manner.

Example 1-1: Synthesis of [4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-cyclopropyl-methanone

Steps 1-1a and 1-1b:

[0136] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 94.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 0.38mol) and 150g toluene. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 60 min this solution was added to a mixture of 150g toluene, 61.0g cyclopropanecarbonyl chloride (0.57mol), and 1.1g copper(I)chloride (0.01 mol) in a 1000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After half of the Grignard solution was dosed another 1.1g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 2h at 40°C. 300g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with a mixture of 250g water and 60g 25%-ammonia solution. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave a dark brown product. This was dissolved in 220g DMF, and transferred to a 11-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel. 68g potassium

carbonate (0.49mol) and a mixture of 54g 4-chlorophenol (0.42mol) and 20g DMF was added at ambient temperature, the vessel was heated to 130°C and kept at this temperature for 2h. The mixture was cooled to 120°C and the pressure was slowly reduced to 100mbar. Distillation of the solvent was continued under these conditions until no more condensate was formed. The vessel was cooled to 25°C, 200ml of toluene followed by 500g of water were added under stirring. The phases were separated and the aqueous phase was extracted with 200ml toluene. The combined organic phases were washed with 200g sodium hydroxide solution (5%) and the lower aqueous phase was separated. The organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 126.4g of a slightly brown product (purity: 91.5%, 0.34mol, 88.6% of the theoretical yield).

Example 1-2: Synthesis of [4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-cyclopropyl-methanone

Step 1-2a Synthesis of cyclopropyl-[4-fluoro-2-(trifluoromethyl)phenyl]methanone

[0137] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 94.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 0.38mol) and 150g toluene. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 60min this solution was added to a mixture of 150g toluene, 61.0g cyclopropanecarbonyl chloride (0.57mol), and 1.1g copper(I)chloride (0.01 mol) in a 1000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After half of the Grignard solution was dosed another 1.1g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 2h at 40°C. 300g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with a mixture of 250g water and 60g 25%-ammonia solution. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 89.9g of a dark brown product (purity: 92.4%, 0.36mol, 93.4% of the theoretical yield).

Step 1-2b: Synthesis of [4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-cyclopropyl-methanone

[0138] A 4l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 91 g [4-fluoro-2-(trifluoromethyl)phenyl]-cyclopropyl-methanone (purity 97%, 0.38mol), 200g of DMF, and 68g potassium carbonate (0.49mol). A mixture of 54g 4-chlorophenol (0.42mol) and 20g DMF was added at ambient temperature, the vessel was heated to 130°C and kept at this temperature for 2h. The vessel was cooled to 25°C, 400ml of MTBE followed by 750g of water were added under stirring. The phases were

separated and the aqueous phase was extracted with 300ml MTBE. The combined organic phases were washed with 200ml sodium hydroxide solution (5%) and the lower aqueous phase was separated. The organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 130.4g of a slightly brown product (purity: 94.0%, 0.36mol, 94.6% of the theoretical yield).

Example 2-1: Synthesis of 1-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one

Steps 2-1a and 2-1b:

[0139] A 2l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 270.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 1.1mol) and 1000ml toluene. A solution of isopropylmagnesium chloride in THF (2M, 700g, 1.44mol) was added keeping the temperature between 25 and 30°C. After stirring for 30 min this solution was added to a mixture of 1000ml toluene, 167.0g isobutyric acid chloride (1.57mol), and 3.5g copper(I)chloride (0.035mol) in a 4l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After half of the Grignard solution was dosed another 3.5g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 1h at 40°C. 500g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with 500g 10%-ammonia solution. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave a brown product. This was dissolved in 700g DMF, and transferred to a 4l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel. 200g potassium carbonate (1.45mol) and a mixture of 160g 4-chlorophenol (0.42mol) and 60g DMF was added at ambient temperature, the vessel was heated to 130°C and kept at this temperature for 1.5h. The vessel was cooled to 25°C, 1000ml of MTBE followed by 1000g of water were added under stirring. The phases were separated and the aqueous phase was extracted with 500ml MTBE. The combined organic phases were washed with 500g sodium hydroxide solution (5%) and the lower aqueous phase was separated. The organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 339.4g of a slightly brown product (purity: 87.3%, 0.86mol, 78.8% of the theoretical yield).

Example 2-2 Synthesis of 1-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one

Step 2-2a1: Synthesis of 1-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one

[0140] A 1m^3-vessel equipped with a 3-level 2-blade stirrer was charged with 100kg 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 407mol) and 150kg toluene. A solution of isopropylmagnesium chloride in THF (2M, 272kg, 530mol) was added keeping the temperature between 25 and 33°C. After stirring for 60 min this solution was transferred to a 1m^3-IBC. The vessel was charged with 150kg toluene, 65kg isobutyric acid chloride (611mol), and 1.2kg copper(I)chloride (12.2mol), and the Grignard solution in the IBC was added keeping the temperature between 25 and 40°C. After half of the Grignard solution was dosed another 1.2kg of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 90min at 40°C. The vessel was cooled to 10°C and 200kg water with a temperature of 5°C were added, the solution was stirred for 10min and the phases allowed to separate for 1h. The lower aqueous phase was separated and the organic phase was washed with a mixture of 100kg water and 50kg 25%-ammonia solution. After separation of the phases the organic phase was transferred to an industrial bulk container(IBC). Three identical batches were run, the organic phases of all four batches were combined and the solvents and other volatiles were distilled off at 10mbar and 40°C to leave 393kg of a brown product (purity: 86.7%, 1455mol, 89.3% of the theoretical yield).

Step 2-2a2: Synthesis of 1-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one

[0141] A 1000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 200.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 0.81mol) and 300g toluene. A solution of isopropylmagnesium chloride in THF (2M, 544g, 1.12mol) was added keeping the temperature between 25 and 30°C. After stirring for 60min this solution was added to a mixture of 300g toluene, 165,7g isobutyric acid chloride (1.59mol), and 0.243g copper(I)chloride (0.0025mol) in a 2000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After half of the Grignard solution was dosed another 0.243g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 2h at 40°C. 500g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with 500g of a 5%-ammonia solution. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 194.0g of a dark brown product (purity: 86.2%, 0.71mol, 87.6% of the theoretical yield).

Step 2-2b1:Synthesis of 1-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one

[0142] A 1m^3-vessel equipped with a 3-level 2-blade stirrer was charged with 100kg potassium carbonate (723.6mol) and 128kg DMF. Technical 1-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one (131kg, 86.7%, 485mol) was added at ambient temperature, followed by

132kg of a solution of 4-chlorophenol in DMF (56.7%, 581.9mol, 57.16 kg DMF). The feed lines were rinsed with a total of 15kg DMF. The content of the vessel was heated to 130°C and kept at this temperature for 3.5h. The vessel was cooled to 25°C and a vacuum of 10mbar was applied. The temperature was raised slowly to 100°C to distill off most of the DMF and other volatiles. When no more condensate was formed the vessel was flushed with nitrogen and 400kg of toluene were added followed by 400kg of water. After 30min the stirrer was stopped and after additional 60min the lower aqueous phase was separated. The remaining organic phase was washed with 115kg sodium hydroxide solution (5%) and the lower aqueous phase was separated. The organic phase was discharged to an IBC to yield 580kg of a solution containing 27.8% of the desired product (161.2kg, 470mol, 97% of the theoretical yield).

Step 2-2b2: Synthesis of 1-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one

[0143] A 100ml-four-necked flask equipped with a Teflon-blade stirrer, Dean-Stark-trap, and a dropping funnel was charged with 5g 1-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-propan-1-one (purity 84.7%, 0.0181mol), 10g o-xylene, 3.49g 4-chlorophenol (0.03mol), and 1.52g potassium hydroxide solution (50%, 0.03mol), and was heated to reflux (151°C) for 5h. The vessel was cooled to 25°C, 20ml o-xylene and 20g water were added under stirring and acidified to pH 4 with 20% hydrochloric acid. The phases were separated and the aqueous phase was twice extracted with 20ml o-xylene .The combined aqueous phases were extracted with 20ml o-xylene. The combined organic phases were transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 7.5g of a slightly brown product (purity: 78.5%, 0.02mol, 95.0% of the theoretical yield).

Example 3-1: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

Steps 3-1a and 3-1b:

[0144] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 94.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 0.38mol) and 150g toluene. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 30 min this solution was added to a mixture of 150g toluene, 46.0g acetyl chloride (0.57mol), and 1.1g copper(I)chloride (0.01mol) in a 1000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After half of the Grignard solution was dosed another 1.1g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 1h at 40°C. 300g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with a mixture of 250g water and 60g 25%-ammonia solution. After

separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave a brown product. This was dissolved in 220g DMF, and transferred to a 2l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel. 68.0g potassium carbonate (0.49mol) and a mixture of 54.0g 4-chlorophenol (0.42mol) and 14g DMF was added at ambient temperature, the vessel was heated to 130°C and kept at this temperature for 2h. The vessel was cooled to 25°C, 750g water followed by 400ml toluene were added under stirring. The phases were separated. The organic phase was washed with 200g sodium hydroxide solution (5%) and the lower aqueous phase was separated. The organic phase was transferred to a rotary evaporator and the solvent was removed at 60°C and 5mbar to leave 109.7g of a slightly brown product (purity: 83.8%, 0.29mol, 76.3% of the theoretical yield).

Example 3-2: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

Step 3-2a1: Synthesis of 4-fluoro-2-trifluoromethyl-acetophenone

[0145] A 1l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 96.0g 2-bromo-5-fluoro-benzotrifluoride (purity 95%, 0.38mol) and 150g MTBE. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 30 min this solution was added to a mixture of 150g MTBE, 45.0g acetyl chloride (0.56mol), and 1.1g copper(I)chloride (0.01 mol) in a 2l-double-walled glass reactor equipped with a 3-level 2-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After half of the Grignard solution was dosed another 1.1g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 1h at 40°C. 200g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with a mixture of 250g water and 50g 25%-ammonia solution. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 78.5g of a dark brown oil (purity: 95.0%, 0.36mol, 96.4% of the theoretical yield).

Step 3-2a2: Synthesis of 4-chloro-2-trifluoromethyl-acetophenone

[0146] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 94.0g 2-bromo-5-chloro-benzotrifluoride (purity 96%, 0.35mol) and 150g toluene. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 60 min this solution was added to a mixture of 150g toluene, 61.0g acetyl chloride (0.57mol), and 0.5g copper(I)chloride (0.005mol) in a 1l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. After

half of the Grignard solution was dosed another 0.5g of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 2.5h at 40°C. 300g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with a mixture of 250g water and 60g 25%-ammonia solution. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 94.0g of a dark brown product (purity: 79.3%, 0.30mol, 86.2% of the theoretical yield).

Step 3-2a3: Synthesis of 4-fluoro-2-trifluoromethyl-acetophenone

[0147] A 2,5m^3-vessel equipped with a 3-level 2-blade stirrer was charged with 250kg 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 1019mol) and 375kg toluene. A solution of isopropylmagnesium chloride in THF (2M, 681kg, 1397mol) was added keeping the temperature between 25 and 33°C. After stirring for 45 min this solution was transferred to 1m^3-IBCs. The vessel was charged with 375kg toluene, 120kg acetyl chloride (1498mol), and 3.0kg copper(I)chloride (30.3mol), and the Grignard solution in the IBCs was added keeping the temperature between 25 and 40°C. After half of the Grignard solution was dosed another 3.0kg of copper(I)chloride were added. When the Grignard addition was completed the mixture was stirred for 90min at 40°C. The vessel was cooled to 10°C and 500kg water precooled to 10°C were added, the solution was stirred for 10min and the phases allowed to separate for 1h. The lower aqueous phase was separated and the organic phase was washed with a mixture of 250kg water and 25kg 25%-ammonia solution. After separation of the phases the organic phase was transferred to IBCs and gave 1677kg of a slightly brown solution containing 10.4% of the desired product (846mol, 82.8% of the theoretical yield).

Step 3-2a4: Synthesis of 4-fluoro-2-trifluoromethyl-acetophenone

[0148] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 94.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 0.38mol) and 150g toluene. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 30 min this solution was added to a mixture of 150g toluene, 46.0g acetyl chloride (0.57mol), and 0.76g copper(I)chloride (0.0077mol) in a 1000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. 300g water were added, the mixture was stirred for 10min and the phases allowed to separate. The organic phase was washed with 300g water. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 81.4g of a brown oil (purity: 81.6%, 0.32mol, 84.1% of the theoretical yield). The condensate contained 3.9g of the product (additional 5.0% yield).

Step 3-2a5: Synthesis of 4-fluoro-2-trifluoromethyl-acetophenone

[0149] A 1l-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 94.0g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 0.38mol) and 150g toluene. A solution of isopropylmagnesium chloride in THF (2M, 243g, 0.5mol) was added keeping the temperature between 25 and 30°C. After stirring for 30 min this solution was added to a mixture of 150g toluene, 6.0g acetyl chloride (0.076mol), and 0.76g copper(I)chloride (0.0077mol) in a 1000ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. Parallel to this dosing 40g acetyl chloride (0.51 mol) were added. When the addition was completed the mixture was stirred for 1h at 40°C. 300g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with 300g water. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 81.8g of a brown oil (purity: 80.5%, 0.32mol, 83.4% of the theoretical yield). The condensate contained 3.3g of the product (4.2% yield).

Step 3-2b1: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

[0150] A 2.5m^3-vessel equipped with a 3-level 2-blade stirrer was charged with 250kg potassium carbonate (1809mol) and 460kg DMF. Technical 4-fluoro-2-trifluoromethyl-acetophenone (260kg, 77.7%, 979mol) was added at ambient temperature, followed by 310kg of a solution of 4-chlorophenol in DMF (57%, 1375mol, 133.3 kg DMF). The feed lines were rinsed with a total of 25kg DMF. The content of the vessel was heated to 130°C and kept at this temperature for 3.5h. The vessel was cooled to 25°C and a vacuum of 10mbar was applied. The temperature was raised slowly to 100°C to distill off most of the DMF and other volatiles. When no more condensate was formed the vessel was flushed with nitrogen and 1000kg of toluene were added followed by 1000kg of water. After 30min the stirrer was stopped and after additional 60min the lower aqueous phase was separated. The remaining organic phase was washed with 350kg sodium hydroxide solution (5%) and the lower aqueous phase was separated. The organic phase was discharged to IBCs to yield 1381kg of a solution containing 22.0% of the desired product (304.2kg, 967mol, 98.7% of the theoretical yield).

Step 3-2b2: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

[0151] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, Dean-Stark-trap, and a dropping funnel was charged with 100g 4-fluoro-2-trifluoromethyl-acetophenone (purity 78%, 0.38mol), 100g o-xylene, 54g 4-chlorophenol (0.42mol), and 78,5g potassium carbonate (0.57mol). The vessel was heated to reflux for 5h removing 4.8g of water. The vessel was cooled to 25°C, 250ml o-xylene and 320g of water were added under stirring. The phases were separated and the aqueous phase was extracted with 100ml o-xylene .The combined

organic phases were washed with 100g sodium hydroxide solution (10%) and the lower aqueous phase was separated. The organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 137.2g of a slightly brown product (purity: 82.6%, 0.36mol, 95.2% of the theoretical yield).

Step 3-2b3: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

[0152] A 100ml pressure vessel (Premex) equipped with a mechanical stirrer was charged with 20g 4-fluoro-2-trifluoromethyl-acetophenone (purity 78%, 0.08mol), 20g toluene, 13.6g 4-chlorophenol (0.11 mol), and 6.4g potassium hydroxide (0.11 mol). The vessel was sealed and heated to 153°C for 5h. After cooling and depressurizing the reaction mixture was transferred to a separating funnel containing 20g toluene and 40g water and acidified to pH 4 with 20% hydrochloric acid. The aqueous phase was separated and the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 28.5g of a slightly brown product (purity: 73.3%, 0.07mol, 87.7% of the theoretical yield).

Step 3-2b4: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

[0153] A 100ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 5.7g 4-chloro-2-trifluoromethyl-acetophenone (purity 81.0%, 20.7mmol), 10g N-methyl pyrrolidone, 3.2g 4-chlorophenol (24.9mmol), and 3.3g sodium carbonate (31.1mmol), and was heated 180°C for 17h. The vessel was cooled to 25°C and the solvent was removed at a rotary evaporator at 60°C/8mbar. 50ml toluene and 40g water were added under stirring, the phases were separated and the organic phase was washed with 10g water. The combined aqueous phases were extracted with 10ml toluene . The combined organic phases were transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 8.1g of a slightly brown product (purity: 66.7%, 17.2mmol, 82.8% of the theoretical yield).

Step 3-2b5: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

[0154] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 9.0g 4-chloro-2-trifluoromethyl-acetophenone (purity 78.8%, 31.9mmol), 15g Dimethyl imidazolidinone, 5.3g 4-chlorophenol (41.2mmol), and 7.4g potassium carbonate (53.5mmol), and was heated 170°C for 6h. The vessel was cooled to 25°C and 40ml toluene and 35g water were added under stirring, the phases were separated and the organic phase was washed with 20g 5% sodium hydroxide solution. The phases were separated, the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 16.0g of a brownish product (purity: 50.2%, 25,5mmol, 80.1% of the theoretical yield).

Step 3-2b6: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

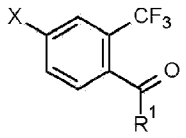
[0155] A 20ml microwave vial equipped with a magnetic stirring bar was charged with 6.0g 4-fluoro-2-trifluoromethyl-acetophenone (purity 78.0%, 22.7mmol), and 4.8g sodium 4-chloro phenolate (31.8mmol), and was heated in a microwave oven to 160°C for 3h. The vessel was cooled to 25°C, and rinsed with 30ml toluene and 20g 10% hydrochloric acid into a separating funnel. The phases were separated, the aqueous phase was extracted with 6ml toluene, the combined organic phases were transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 8.7g of a brownish product (purity: 75.52%, 20.9mmol, 91.9% of the theoretical yield).

Step 3-2b7: Synthesis of 4-(4-chlorophenyloxy)-2-trifluoromethyl-acetophenone

[0156] A 20ml microwave vial equipped with a magnetic stirring bar was charged with 6.0g 4-fluoro-2-trifluoromethyl-acetophenone (purity 78.0%, 22.7mmol), 6g toluene, and 5.3g potassium 4-chloro phenolate (31.8mmol), and was heated in a microwave oven to 160°C for 3h. The vessel was cooled to 25°C, and rinsed with 20g toluene and 20g 10% hydrochloric acid into a separating funnel. The phases were separated, the aqueous phase was extracted with 5ml toluene, the combined organic phases were transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 9.3g of a brownish product (purity: 74.0%, 21.9mmol, 96.3% of the theoretical yield).

Example 4 Preparation of 2-Acyl-5-halogeno-benzotrifluorides using Mg

[0157]



Example 4a: 4-fluoro-2-(trifluoromethyl)-acetophenone

[0158] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 1.10g magnesium metal chips (45 mmol) and 50g THF. 1g of a 2M solution of isopropyl magnesium chloride was added for activation. 10 g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 41mmol) were added within 60 min, the temperature rose to 52°C. After stirring for 60min this Grignard solution was decanted from the remaining metal, transferred to a dropping funnel, and added within 60min to a mixture of 50g toluene, 4,8g

acetyl chloride (61mmol), and 0.08g copper(I)chloride (0,8mmol) in a 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. When the Grignard addition was completed the mixture was stirred for 1h at 40°C. 50g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with 25g water. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 9.2g of a dark brown product (purity: 59,5%, 27mmol, 65% of the theoretical yield).

Example 4b: 4-fluoro-2-(trifluoromethyl)-acetophenone

[0159] A 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel was charged with 0,90g magnesium metal chips (37mmol) and 40g THF. 1g of a 2M solution of isopropyl magnesium chloride was added for activation. 10 g 2-bromo-5-fluoro-benzotrifluoride (purity 99%, 41mmol) were added within 60 min, the temperature rose to 50°C. After stirring for 60min all magnesium had vanished and the Grignard solution was transferred to a dropping funnel, and added within 60min to a mixture of 40g toluene, 4,0g acetyl chloride (51 mmol), and 0,08g copper(I)chloride (0,8mmol) in a 500ml-four-necked flask equipped with a Teflon-blade stirrer, reflux condenser, and a dropping funnel keeping the temperature between 38 and 42°C. When the Grignard addition was completed the mixture was stirred for 1h at 40°C. 30g water were added, the solution was stirred for 10min and the phases allowed to separate. The organic phase was washed with 25g water. After separation of the phases the organic phase was transferred to a rotary evaporator and the solvent was removed at 40°C and 10mbar to leave 9,2g of a dark brown product (purity: 60,9%, 27mmol, 74% of the theoretical yield based on Mg).

REFERENCES CITED IN THE DESCRIPTION

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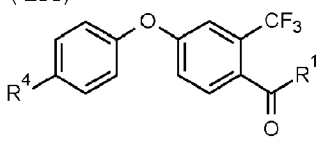
Patentkrav

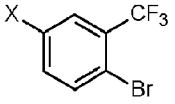
1. Fremgangsmåde til fremstilling af ketonforbindelserne (IA)



(IA)

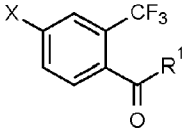
som omfatter følgende trin:

(i) reaktion af en forbindelse med formel (III)



(III)

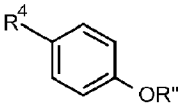
med R'-Mg-Hal (IV) eller Mg og $R^1C(=O)Cl$ (V) i nærvær af en Cu(I)-katalysator i en mængde på 0,005 til 0,065 molækvivalenter pr. 1 mol af forbindelse (III) til opnåelse af forbindelse II



(II)

og

(ii) reaktion af forbindelse (II) som defineret i trin (i) med et phenolderivat med formel (VI)



(VI)

i nærvær af en base, hvis R" er hydrogen;

hvor variablerne defineres som følger:

X er F eller Cl;

R^1 er C_1-C_6-alkyl eller C_3-C_8-cycloalkyl; og

R^4 er F eller Cl;

R' er C_1-C_4-alkyl eller C_3-C_6-cycloalkyl;

Hal er halogen; og

R" er hydrogen eller en alkalimetalkation.

2. Fremgangsmåde ifølge krav 1, hvor Cu(I)-katalysatoren er Cu(I)Cl.

3. Fremgangsmåde ifølge krav 1 eller 2, hvor R' er isopropyl.

4. Fremgangsmåde ifølge et hvilket som helst af kravene 1

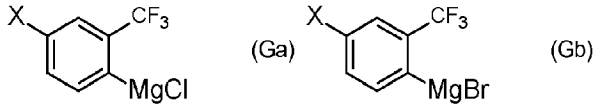
til 3, hvor Hal er Br eller Cl, især Br.

5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 4, hvor X er F.

6. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 5, hvor R^1 er valgt blandt CH_3, $CH(CH_3)_2$ og cyclopropyl.

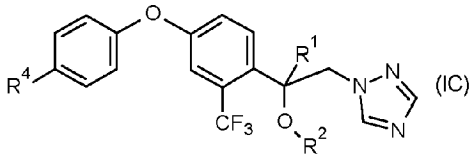
7. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 6, hvor R^4 er Cl.

8. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 7, hvor Grignard-forbindelsen/forbindelserne Ga og/eller Gb



dannes i fremgangsmådens trin (i), hvor X er F eller Cl.

9. Fremgangsmåde til fremstilling af triazolforbindelser med formel (IC)



hvor R^1 og R^4 er som defineret i et hvilket som helst af kravene 1 til 7; og

R^2 er hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenyl, phenyl-C_1-C_4-alkyl, phenyl-C_2-C_4-alkenyl eller phenyl-C_2-C_4-alkynyl;

hvor de alifatiske dele af R^2 ikke er yderligere substitueret eller bærer en, to, tre eller op til det maksimale mulige antal identiske eller forskellige grupper R^{12a}, der er valgt uafhængigt blandt:

halogen, OH, CN, nitro, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl, C_3-C_8-halogencycloalkyl og C_1-C_4-halogenalkoxy;

hvor cycloalkyl- og/eller phenyldelene i R^2 ikke er yderligere substitueret eller bærer en, to, tre, fire, fem eller op til det maksimale antal identiske eller forskellige grupper R^{12b}, der er valgt uafhængigt blandt:

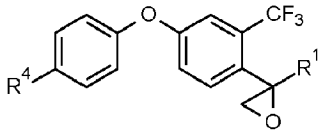
halogen, OH, CN, nitro, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-halogenalkyl, C_3-C_8-cycloalkyl, C_3-C_8-halogencycloalkyl og C_1-C_4-halogenalkoxy;

som omfatter følgende trin:

(i) ifølge krav 1;

(ii) ifølge krav 1;

(iii) reaktion af en keton med formel (IA) som defineret i trin (ii) til oxiraner (IB);



(IB)

og

(iv) reaktion af oxiranen (IB) som defineret i trin (iii) med 1H-1,2,4-triazol i nærvær af en base til opnåelse af forbindelser (IC), hvor R^2 er hydrogen (forbindelser IC-1);

og til opnåelse af forbindelser, hvor R^2 er forskellig fra hydrogen:

(v) derivatisering af forbindelsen med formel (IC-1) som defineret i trin (iv) under basiske betingelser med R^2-LG, hvor LG er en nukleofilt udskiftelig fraspaltelig enhed; til opnåelse af forbindelser (IC-2).

10. Fremgangsmåde ifølge krav 9, hvor reaktionen til oxiranen (IB) udføres med en trimethylsulf(ox)oniumhalid ($(CH_3)_3S^+(O)Hal^-$) (VII), hvor Hal er halogen, eller trimethylsulfoniummethylsulfat med formel (VIII) $(CH_3)_3S^+CH_3SO_4^-$.