

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 August 2004 (19.08.2004)

PCT

(10) International Publication Number
WO 2004/069821 A1

(51) International Patent Classification⁷: **C07D 311/54**

TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:

PCT/EP2004/001786

(22) International Filing Date: 28 January 2004 (28.01.2004)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

03356014.5

3 February 2003 (03.02.2003) EP

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

(71) Applicant (for all designated States except US): **BAYER CROPSCIENCE S.A.** [FR/FR]; 16 Rue Jean-Marie Leclair, F-69009 Lyon (FR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DELAMARE, Madeleine** [FR/FR]; 6 Rue Ternois, F-69003 Lyon (FR). **CASADO, Michel** [FR/FR]; Les Magnolias N° 14, Route De Corbas, F-69360 Saint Symphorien d'Ozon (FR).

(74) Agent: **BALMEFREZOL, Ludovic**; Bayer Cropscience S.A., Patent & Licensing Department, 14-20 Rue Pierre Baizet, BP 9163, F-69263 Lyon Cedex 09 (FR).

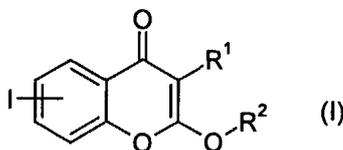
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,

Published:

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR PREPARING DERIVATIVES OF FUNGICIDAL IODOCHROMONES

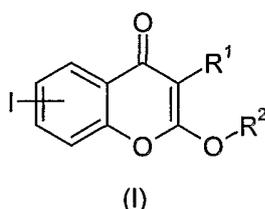


(57) Abstract: This invention relates to new methods for preparing chemical compounds, in particular fungicidal compounds, especially iodinated derivatives of chromones, preferably compounds of formula (I), and intermediate compounds useful for these methods.

WO 2004/069821 A1

METHOD FOR PREPARING DERIVATIVES OF FUNGICIDAL IODOCHROMONES**DESCRIPTION**

This invention relates to new methods for preparing chemical compounds, in particular fungicidal compounds, especially iodinated derivatives of chromones, preferably compounds of formula (I), and intermediate compounds useful for these methods.



The subject of the present invention is also a method for preparing vinylalkoxides from vinylamines; it relates more particularly to the preparation of 2-halo and 2-alkoxychromones by the reaction of a 2-aminochromone with a copper halide or alkoxide.

The subject of the present invention is also a method for preparing 2-aminochromones by reacting an alkyl salicylate with an alkylnitrile and a base, followed by cyclization in an aqueous acid medium.

European patent application EP-861 242, which relates to fungicidal compounds derived from coumarin or chromone, generically reviews methods for preparing some of these compounds. However, even though two examples of iodinated compounds are disclosed, no specific method for preparing such iodinated derivatives is mentioned, nor is such an improved method suggested.

There are known from the prior art various methods allowing the preparation of aromatic halides from primary aromatic amines via a Sandmeyer reaction. There is known in particular the preparation of aromatic diazonium salts (March's Advanced Organic Chemistry, 5th edition, John Wiley & Sons, Inc., (2001), p816-817 and 936) and the chemical reactions associated with such diazonium salts (Chem. Rev.,

(1988), 88, 765-792). However, none of the known methods describes such conversions to a vinyl ether series according to the scheme below in which * represents a free site, G¹ represents a halogen atom or an alkoxide and for which the structures are linear or cyclic which may be aromatic or otherwise:

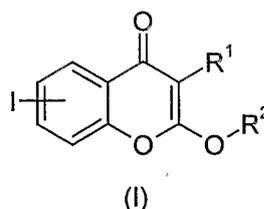


During the preparation of the fungal compounds covered by the present invention, the following problems are often encountered:

- difficulty of improving the methods both from a technical point of view and from an economic point of view;
- low yield;
- insufficient purity;
- difficulty of recycling the reagents used;
- low rate of conversion;
- reduction in the number of steps;
- use of more economical agents;
- improvement in the simplicity and safety of the reactions used;
- limiting the number of by-products formed;
- limiting side reactions.

The present invention makes it possible to solve all or some of these problems or disadvantages. It makes it possible in particular to avoid or to limit the substitution of halogen atoms by an alcoholate group when it is present, in particular when the structure comprises two halogen atoms.

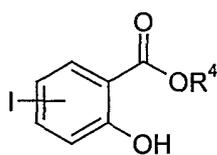
A first aspect of the invention relates to the preparation of a compound of formula (I)



according to the following steps:

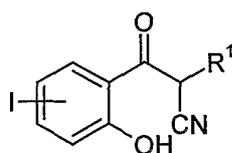
step A:

reaction of a compound of formula (V)



(V)

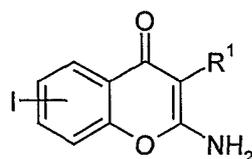
with a nitrile of formula R^1CH_2CN and a base to form the compound of formula (IV);



(IV)

step B:

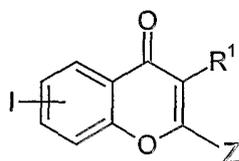
compound of formula (IV) which is then cyclized in an aqueous acid medium to form the compound of formula (III):



(III)

step C:

compound of formula (III) which gives the compound of formula (II) via a diazotization reaction by means of a compound chosen from sodium nitrite in the form of a mixture with an acid, alkyl nitrites, alkyl thionitrites and alkyl thionitrates, and decomposition by means of a compound AZ_n ;



(II)

step D:

compound of formula (II) which gives the compound of formula (I) by the action of an alcohol in the form of a mixture with a base;

in the formulae (I) to (V)

- R^1 , R^2 , R^3 and R^4 , which are identical or different, represent a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbo- or heterocycles having 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted;
- A represents a metal or a metal salt;
- Z represents a group chosen from Cl, Br or $-OR^3$;
- n is equal to 0, 1 or 2.

For R^1 , noncyclic substituents or optionally aromatic cyclic substituents are preferred, and for Z, Cl is preferred.

When the groups or radicals of the compounds of formula (I) to (V) are substituted, they are preferably substituted with one or more groups which may be chosen, independently of each other, from an alkyl radical, alkenyl radical, alkynyl radical, a halogen atom, a cyano radical, trialkylsilyl radical, alkoxy radical, alkylthio radical, hydroxyl radical, nitro radical, amino radical, acyl radical, acyloxy radical, phenyl radical, heterocyclyl radical, phenylthio radical, phenoxy radical, heterocycloxy radical, heterocyclylthio radical and oxidized and optionally substituted derivatives of chemical entities containing a thio group.

The term heterocyclyl comprises heteroaryl groups and nonaromatic heterocyclyl groups, which may be saturated or unsaturated.

The heteroaryl groups are generally 5- or 6-membered rings containing up to 4 heteroatoms chosen from nitrogen, oxygen and sulfur, optionally fused with a benzene ring. As examples of heteroaryl groups, there may be mentioned groups derived from thiophene, furan, pyrrole, thiazole, oxazole, imidazole, isothiazole, oxazole, pyrazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,4-triazole, 1,2,3-triazole, tetrazole, benzo[b]thiophene, benzo[b]furan, indole, benzo[c]thiophene, benzo[c]furan, isoindole, benzoxazole, benzothiazole, benzimidazole, benzisoxazole, benzisothiazole, indazole, benzothiadiazole, benzotriazole, dibenzofuran, dibenzothiophene, carbazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,3,5-triazine, 1,2,4-triazine, 1,2,4,5-tetrazine, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, 1,8-naphthyridine, 1,5-naphthyridine, 1,6-naphthyridine, 1,7-naphthyridine, phthalazine, pyridopyrimidine, purine or pteridine.

The nonaromatic heterocyclyl groups are generally 3-, 5-, 6- or 7-membered rings containing up to 3 heteroatoms chosen from nitrogen, oxygen and sulfur, for example oxiranyl, thiiranyl, thiazolinyl, dioxolanyl, 1,3-benzoxazinyl, 1,3-benzothiazinyl, morpholino, pyrazolinyl, sulfolanyl, dihydroquinazolinyl, piperidinyl, phthalimido, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, indolinyl, 2-oxopyrrolidino, 2-oxobenzoxazolin-3-yl or tetrahydroazepinyl.

The substituents, when they are present, on the phenyl or heterocyclyl groups may be for example halogen atoms, CN, NO₂, SF₅, B(OH)₂, trialkylsilyl, acyl, O-acyl or a radical E, OE or S(O)_nE as defined above for R¹ or alternatively an optionally substituted amino radical; or alternatively two adjacent groups on the ring, together with the atoms to which they are attached form a carbocyclic or heterocyclic ring, which may be optionally substituted in a similar manner.

The term acyl comprises acid residues containing sulfur or phosphorus and carboxylic acid residues. Examples of acyl groups are thus -COR⁵, -COOR⁵, -CONR⁵R⁶, -CON(R⁵)OR⁶, -COONR⁵R⁶, -CON(R⁵)NR⁶R⁷, -COSR⁵, -CSSR⁵, -S(O)_qR⁵, -S(O)₂OR⁶, -S(O)_qNR⁵R⁶, -P(=L)(OR⁵)(OR⁶) or -COOR⁵, in which R⁵, R⁶ and R⁷, which may be identical or different, represent a hydrogen atom, an optionally substituted alkyl radical, optionally substituted cycloalkyl radical, optionally substituted cycloalkenyl radical, optionally substituted alkenyl radical, optionally substituted alkynyl radical, optionally substituted phenyl group or optionally substituted heterocyclyl group, or alternatively R⁵ and R⁶, or R⁶ and R⁷, together with the atom(s) to which they are attached, may form a ring, q represents 1 or 2 and L represents O or S.

Where appropriate, the amino radicals may be substituted for example with one or two optionally substituted alkyl or optionally substituted acyl radicals, or alternatively two substituents may form a ring, preferably a 5- to 7-membered ring, which may be substituted and which may contain other heteroatoms, such as for example morpholine.

Where appropriate, persons skilled in the art will know how to adapt the reaction conditions according to the groups present, in particular by suitably protecting them.

The combination of steps A and B, as well as the combination of steps C and D, taken separately constitute methods which also form part of the

present invention as such. The reagents, the reaction conditions and the optional variant steps are similar to those described for the method of the invention comprising steps A to D.

The compounds of formula (V) may be prepared in a manner similar to what has been reported in the literature for alkyl 3-halosalicylates from equivalent alkyl salicylates, see for example Pharm. J., (1947), 159, 182.

During the condensation reaction of step A using the compound of formula (V) to give the compound of formula (IV), a homogeneous or heterogeneous inorganic or organic base, preferably a lithium alkylamide, for example lithium diisopropylamide, is advantageously used.

Advantageously, the base useful for this step may consist of a mixture of such bases. Persons skilled in the art will know how to determine the number and the relative quantities of these bases used as a mixture.

The compound of formula (IV) can be characterized but is generally not isolated.

According to a variant A' of this step A, the nitrile of formula R^1CH_2CN may be replaced by a nitrile of formula R^1CXHCN in which X represents a halogen atom and the base is then replaced by a metal, in particular magnesium or zinc, see in particular Synth. Commun. (1989), 19(9-10), 1649-53.

During step B, the compound of formula (IV) gives the compound of formula (III). An inorganic or organic acid is used; ammonium chloride, hydrochloric acid or acetic acid are suitable. Aqueous acetic acid is preferred.

During step C, the compound of formula (III) gives the compound of formula (II) via a diazotization reaction, see for example March's Advanced Organic Chemistry, 5th edition, John Wiley & Sons, Inc. (2001), p.816, followed by a decomposition reaction.

As preferred reagents used for this diazotization reaction, sodium nitrite, and alkyl nitrites, in particular t-butyl or methyl nitrites, may be mentioned.

During the use of $NaNO_2$, the preferred acids are HCl, HBr, H_2SO_4 .

Preferably, the diazo intermediate may be decomposed by means of a compound AZ_n chosen from a metal halide or alkoxide, preferably $CuCl$, $CuBr$, $CuCl_2$, $CuBr_2$, $CuOR^3$ or $Cu(OR^3)_2$; $CuCl_2$ and $CuBr_2$ may also be used in their hydrated form.

The following combinations are particularly advantageous:

- t-butyl or methyl nitrites and $Cu(OR^3)_2$ or $CuCl_2$;
- sodium nitrite with HCl or H_2SO_4 and $CuOR^3$ or $CuCl$.

During this step C A therefore preferably represents copper. Other metals useful for this step are mentioned in Chem. Rev., (1988), 88, 765-792.

This step C may also be carried out using $NaNO_2$ with $ClSiMe_3$ in order to prepare a compound in which Z represents Cl; persons skilled in the art will know how to adapt the conditions for such a Sandmeyer reaction known per se (Tet. Letters, 33 (22), 3167-3168 (1992)).

Likewise, $NaNO_2$, as a mixture with copper metal and KI may be used during this step C, in this case Z represents I.

Likewise, BF_4 as a mixture with $NaNO_2$ may be used. Z then represents F.

During step D, the compounds of formula (II) give the compound of formula (I). An alcohol of formula R^2OH , in which R^2 represents a group such as those defined above, preferably a C_1 - C_{10} alkyl, still more preferably an n-butyl group, is used. The choice of the base used to form the alcoholate is within the capability of persons skilled in the art who may in particular use an alkali or alkaline-earth metal hydroxide or hydride, an alkali metal or an alkaline-earth metal, preferably KOH , NaH or sodium metal.

Another aspect of the present invention relates to a further improved method for preparing this same compound of formula (I) obtained directly by diazotization and decomposition of a compound of formula (III) by means of a compound AZ_n which is preferably a metal alkoxide.

In this case, steps C and D of the method of the invention are replaced by a single step C'.

The various substituents of the compounds then have the same meanings as above.

Another variant of the method of the invention consists in replacing step D with step D'. In this case, a compound of formula (II) in which Z represents a group $-OR^3$ is used, it is then possible to displace this group by a more appropriate similar group. For example, in the case where Z is an ethoxy group, it will be possible to displace it by a butoxy group which may be introduced by treating with sodium butoxide. The use of such a substitution constitutes an additional method of the present invention for the preparation of a compound of formula (I) starting from a compound of formula (II).

The methods of the invention which are particularly preferred allow the preparation of compounds of formula (I) by means of the compounds of formulae (II) to (V) in which the following characteristics are present alone or in combination:

- the iodine atom is in the 6-position of the chromone;
- R^1 represents a C_1 - C_{10} alkyl, preferably an n-propyl;
- R^2 represents a C_1 - C_{10} alkyl, preferably an n-butyl;
- R^4 represents a C_1 - C_{10} alkyl, preferably a methyl;
- A represents Cu;
- Z represents a halogen atom, preferably Cl or Br, more preferably Cl, or the group $-OR^3$ in which R^3 represents a methyl or n-butyl group.

Most preferably, the methods of the invention are used for the preparation of a compound of formula (I) in which R^1 represents an n-propyl and R^2 represents an n-butyl.

As compounds which are advantageously prepared by means of the methods of the invention, there may be mentioned in particular

- 2-butoxy-6-iodo-3-propyl-4H-1-benzopyran-4-one
- 2-ethoxy-6-iodo-3-propyl-4H-1-benzopyran-4-one
- 6-iodo-2-propoxy-3-propyl-4H-1-benzopyran-4-one
- 2-but-2-ynyloxy-6-iodo-3-propyl-4H-1-benzopyran-4-one
- 6-iodo-2-(1-methylbutoxy)-3-propyl-4H-1-benzopyran-4-one
- 2-but-3-enyloxy-6-iodo-3-propyl-4H-1-benzopyran-4-one
- 3-butyl-6-iodo-2-isopropoxy-4H-1-benzopyran-4-one
- 6-iodo-3-propyl-2-(tetrahydropyran-4-yloxy)-4H-1-benzopyran-4-one

- 6-iodo-3-propyl-2-(2,2,2-trifluoroethoxy)-4H-1-benzopyran-4-one

Moreover, persons skilled in the art will know how to adapt the methods of the invention to the preparation of the compounds of formula (I) to (V) in the form of their possible geometric and/or optical isomers, pure or as mixtures, in all proportions, including the possible racemic mixture(s), their optional N-oxides, addition salts with an acid, which are acceptable for use in the crop protection field, and their possible metal and/or metalloid complexes, which are acceptable for use in the crop protection field.

The methods of the invention have been described in relation to iodinated chromone derivatives. However, these methods may be adapted for the preparation of other halogenated chromone derivatives.

An additional aspect of the present invention relates to intermediate compounds useful for the methods of preparation according to the invention.

These compounds are the compounds of formula (III) and the compounds of formula (II) in which the various substituents have the same meaning as above.

Excluded however are the compounds of formula (II) for which the iodine atom is in the 6-position, R^1 represents an n-propyl group and R^3 represents a methyl group or an n-propyl group.

Among the intermediate compounds of formula (III), there are preferred those in which the following characteristics are present alone or in combination:

- the iodine atom is in the 6-position of the chromone;
- R^1 represents a C_1 - C_{10} alkyl group, preferably an n-propyl group.

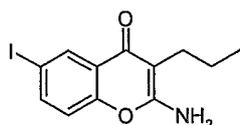
Among the intermediate compounds of formula (II), there are preferred those in which the following characteristics are present alone or in combination:

- the iodine atom is in the 6-position of the chromone;
- R^1 represents a C_1 - C_{10} alkyl group;
- Z represents a halogen atom.

More preferably, R¹ represents an n-propyl group and Z represents chlorine or bromine.

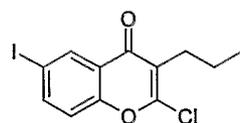
The following examples are given without limitation in order to further illustrate the present invention.

Example 1 : preparation of 2-amino-6-iodo-3-propylchromone



A solution of 8.4 ml (0.06 mol) of diisopropylamine in 20 ml of anhydrous THF, cooled to -20°C , is treated by adding 30 ml (0.06 mol) of 2 M n-butyllithium in solution in hexanes over 15 minutes. The solution is kept stirring at this temperature for 5 minutes and 2.10 ml (0.02 mol) of valeronitrile are added at -20°C over 5 minutes. The solution is kept stirring at -20°C for 15 minutes and a solution of 5.84 g (0.02 mol) of ethyl 4-iodosalicylate in 20 ml of anhydrous THF is added over 15 minutes. The suspension is heated to 5°C and kept stirring for 45 minutes and then hydrolyzed with 15 ml of a saturated aqueous NH_4Cl solution. The biphasic solution is kept stirring for 2 hours. The aqueous phase is then removed, the organic phase is washed with 2×20 ml of water and then 20 ml of a saturated aqueous NaCl solution. The organic phase is dried over MgSO_4 , filtered and concentrated to dryness, which gives 7.25 g of a yellow solid (70%). The product crystallized from acetonitrile has a melting point of $186-188^{\circ}\text{C}$.

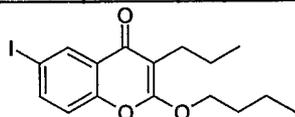
Example 2 : preparation of 2-chloro-6-iodo-3-propylchromone



To a suspension of 1.98 g (6 mmol) of 2-amino-6-iodo-3-propylchromone, 1.22 g (7.2 mmol) of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in 60 ml of acetonitrile, cooled to 0°C is added 0.86 ml (7.2 mmol) of *tert*-butylnitrite over 10 minutes. The reaction mixture is heated to 20°C and kept stirring at this temperature for 3 hours. The solution is hydrolyzed by adding 60 ml of water and extracted with

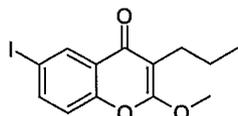
2×50 ml of ethyl acetate. The organic phases are combined and washed with 20 ml of NH₄OH, 2×50 ml of water and then 50 ml of a saturated aqueous NaCl solution. The organic phase is dried over MgSO₄, filtered and concentrated to dryness. This gives 2.04 g of a brown solid (78% theoretical yield) having a melting point of 103-105°C.

Example 3 : preparation of 2-butoxy-6-iodo-3-propylchromone

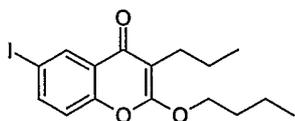


To a solution of 1.05 g (3 mmol) of 2-chloro-6-iodo-3-propylchromone in 10 ml of dichloromethane are added, at 20°C, 2.4 ml (4.3 mmol) of a 20% solution of sodium n-butoxide in n-butanol. The solution is kept at 20°C for 2 hours and then heated at 40°C for 4 hours. The reaction medium is hydrolyzed with 10 ml of water and the organic phase is washed with 2×10 ml of water, dried over MgSO₄, filtered and concentrated to dryness. This gives 0.95 g of a brown oil which crystallizes. The product crystallized from acetonitrile has a melting point of 69-71°C.

Example 4 : preparation of 6-iodo-2-methoxy-3-propylchromone



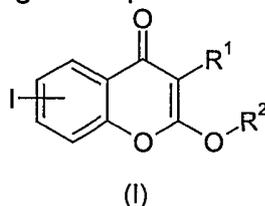
To a suspension of 0.31 g (0.95 mmol) of 2-amino-6-iodo-3-propylchromone, 0.15 g (1.2 mmol) of Cu(OMe)₂ in 2 ml of acetonitrile is added, at 20°C, 0.14 ml (1.2 mmol) of tert-butyl nitrite over 5 minutes. The reaction medium is heated to 60°C and kept stirring at this temperature for 3 hours. After returning to room temperature, the reaction mixture is hydrolyzed by adding 1 ml of water and extracted with 2×5 ml of ethyl acetate. The organic phases are combined and washed with 5 ml of NH₄OH, 2×5 ml of water and then 5 ml of a saturated aqueous NaCl solution. The organic phase is dried over MgSO₄, filtered and concentrated to dryness.

Example 5 : preparation of 2-n-butoxy-6-iodo-3-propylchromone

To a solution of 0.27 g (0.76 mol) of 2-ethoxy-6-iodo-3-propylchromone in 2.5 ml of n-butanol is added, at 20°C, 0.5 ml (0.91 mmol) of a 20% (w/w) solution of sodium n-butoxide in n-butanol over 5 minutes. The reaction medium is kept stirring at 20°C for 2 hours. The reaction mixture is treated by adding 2 ml of an aqueous 0.1 N HCl solution and extracted with 10 ml of dichloromethane. The organic phase is extracted and washed with 2×5 ml of water. The organic phase is dried over MgSO₄, filtered and concentrated to dryness. This gives 0.24 g of a brown oil which crystallizes.

CLAIMS

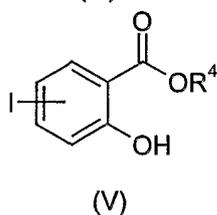
1. A method for preparing a compound of formula (I)



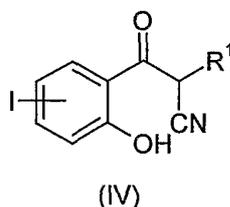
according to the following steps:

step A:

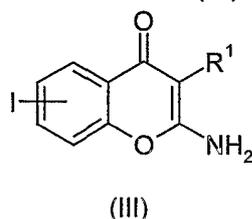
reaction of a compound of formula (V)



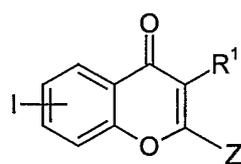
with a nitrile of formula R^1CH_2CN and a base to form the compound of formula (IV);

**step B:**

compound of formula (IV) which is then cyclized in an aqueous acid medium to form the compound of formula (III):

**step C:**

compound of formula (III) which gives the compound of formula (II) via a diazotization reaction by means of a compound chosen from sodium nitrite in the form of a mixture with an acid, alkyl nitrites, alkyl thionitrites and alkyl thionitrates, and decomposition by means of a compound AZ_n ;



(II)

step D:

compound of formula (II) which gives the compound of formula (I) by the action of an alcohol in the form of a mixture with a base;

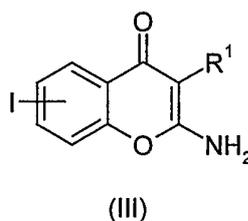
in the formulae (I) to (V)

- R^1 , R^2 , R^3 and R^4 , which are identical or different, represent a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbo- or heterocycles having 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted;
 - A represents a metal or a metal salt;
 - Z represents a group chosen from Cl, Br or $-OR^3$;
 - n is equal to 0, 1 or 2.
2. A method according to claim 1, for which the base used during step A is lithium diisopropylamide.
 3. A method according to claims 1 or 2, for which the acid used during step B is acetic acid.
 4. A method according to 1 to 3, for which A is copper.
 5. A method according to 1 to 4, in which step C uses t-butyl or methyl nitrite.
 6. A method according to claims 1 to 4, for which AZ_n represents $Cu(OR^3)_2$ or $CuCl_2$.
 7. A method according to claims 1 to 4, in which step C uses t-butyl or methyl nitrite and for which AZ_n represents $Cu(OR^3)_2$ or $CuCl_2$.
 8. A method according to claims 1 to 4, in which step C uses sodium nitrite in the form of a mixture with HCl or H_2SO_4 .

9. A method according to claims 1 to 4, for which AZ_n represents $Cu(OR^3)$ or $CuCl$.
10. A method according to claims 1 to 4, in which step C uses sodium nitrite in the form of a mixture with HCl or H_2SO_4 and for which AZ_n represents $Cu(OR^3)$ or $CuCl$.
11. A method according to claims 1 to 10, in which step D uses an alcohol of formula R^2OH in which R^2 is a C_1 - C_{10} alkyl.
12. A method according to claim 11, for which R^2 represents n-butyl.
13. A method according to claims 1 to 11, in which step D is replaced by step D' and in which there is used a compound of formula (II) in which Z represents a group $-OR^3$, which is displaced by a similar, more appropriate group.
14. A method according to claim 13, for which Z is the ethoxy group which is displaced by a butoxy group introduced by treating with sodium butoxide.
15. A method according to claims 1 to 14, in which step A is replaced by step A' and in which there is used a nitrile of formula R^1CXHCN , in which X represents a halogen atom, with, as base, a metal chosen from magnesium or zinc.
16. A method according to claims 1 to 15, for which the following characteristics are present alone or in combination:
- the iodine atom is in the 6-position of the chromone;
 - R^1 represents a C_1 - C_{10} alkyl, preferably an n-propyl;
 - R^2 represents a C_1 - C_{10} alkyl, preferably an n-butyl;
 - R^4 represents a C_1 - C_{10} alkyl, preferably a methyl;
 - A represents Cu;
 - Z represents Cl or Br, or the group $-OR^3$ in which R^3 represents a methyl or n-butyl group.

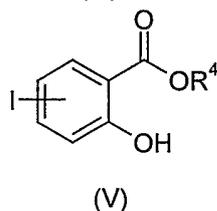
17. The method as claimed in any one of claims 1 to 16, for which the preparation of a compound of formula (I) in which R^1 represents an n-propyl and R^2 represents an n-butyl.

18. A method for preparing a compound of formula (III)

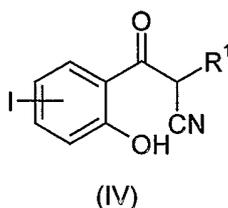


according to the following steps:

reaction of a compound of formula (V)



with a nitrile of formula R^1CH_2CN and a base to form the compound of formula (IV);

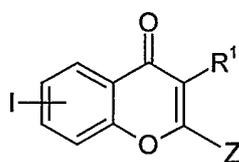


which compound of formula (IV) is then cyclized in an aqueous acid medium to form the compound of formula (III);

in formulae (III) to (V)

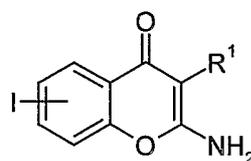
- R^1 , R^2 , R^3 and R^4 , which are identical or different, represent a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbocycles having from 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted.

19. A method for preparing a compound of formula (II)



(II)

from a compound of formula (III) which gives the compound of formula (II) via a diazotization reaction



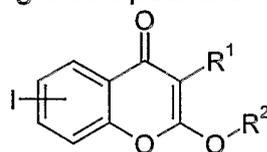
(III)

by means of a compound chosen from sodium nitrite in the form of a mixture with an acid, alkyl nitrites, alkyl thionitrites and alkyl thionitrates; and decomposition by means of a compound AZ_n ;

in the formulae (II) and (III)

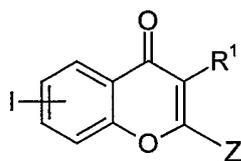
- R^1 and R^3 , which are identical or different, represent a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbo- or heterocycles having 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted;
- A represents a metal or a metal salt;
- Z represents a group chosen from Cl, Br or $-OR^3$;
- n is equal to 0, 1 or 2.

20. A method for preparing a compound of formula (I)



(I)

from a compound of formula (II) which gives the compound of formula (I)

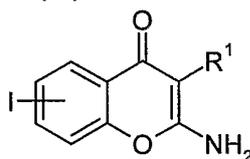


(II)

by the action of an alcohol in the form of a mixture with a base;
in the formulae (I) and (II)

- R^1 and R^2 , which are identical or different, represent a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbo- or heterocycles having 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted;
- Z represents a group chosen from Cl, Br or $-OR^3$.

21. A compound of formula (III)



(III)

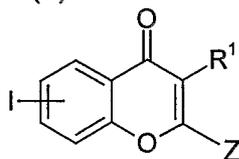
in which R^1 represents a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbo- or heterocycles having from 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted.

22. The compound as claimed in claim 21, of formula (III) in which the following characteristics are present alone or in combination:

- the iodine atom is in the 6-position of the chromone;
- R^1 represents a C_1 - C_{10} alkyl group.

23. The compound as claimed in either of claims 21 and 22, of formula (III) in which R^1 represents the n-propyl group.

24. A compound of formula (II)



(II)

in which

- R^1 and R^3 , which are identical or different, represent a C_1 - C_{10} alkyl, C_1 - C_{10} alkenyl or C_1 - C_{10} alkynyl, one or more carbo- or heterocycles having 5 to 7 atoms, it being possible for these groups to be substituted or unsubstituted;
- Z represents a halogen atom.

25. A compound according to claim 24, of formula (II) in which the following characteristics are present alone or in combination:

- the iodine atom is in the 6-position of the chromone;
- R^1 represents a C_1 - C_{10} alkyl group.

26. A compound according to claims 24 and 25, of formula (II) in which R^1 represents an n-propyl group and Z represents chlorine or bromine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001786

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D311/54				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X A X X	US 6 034 121 A (LINDELL STEPHEN DAVID ET AL) 7 March 2000 (2000-03-07) claim 1; examples 122,195 ----- PATENT ABSTRACTS OF JAPAN vol. 012, no. 096 (C-484), 29 March 1988 (1988-03-29) & JP 62 228001 A (TAKEDA CHEM IND LTD), 6 October 1987 (1987-10-06) column 18; example 23 ----- DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002236953 Database accession no. 578115 abstract -/--	24,25 1-23,26 18,21,22 18		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.				
<input checked="" type="checkbox"/> Patent family members are listed in annex.				
° Special categories of cited documents :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; border: none; vertical-align: top;"> *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family </td> </tr> </table>			*A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family
A document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family			
Date of the actual completion of the international search <p style="text-align: center;">17 May 2004</p>	Date of mailing of the international search report <p style="text-align: center;">27/05/2004</p>			
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <p style="text-align: center;">Seelmann, I</p>			

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001786

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	& BULL.CHEM.SOC.JAP., vol. 31, 1958, page 440, ----- WO 03/014103 A (HUSER NATHALIE ;PEREZ JOSEPH (FR); WEGMANN THOMAS (FR); AVENTIS CR) 20 February 2003 (2003-02-20) examples 10-97	24,25
X	----- JEONG S., ET AL.: "Macrocyclic Triarylethylenes via Heck Endocyclization" J. ORG. CHEM., vol. 63, 1998, pages 8640-8641, XP009008688 Scheme 1, step b	19
X	----- GILL H. S., ET AL.: "Selective Formation and Trapping of Dihalocarbonyl Ylides Derived from Dihalocarbenes and Substituted Benzaldehydes" J. ORG. CHEM., vol. 48, 1983, pages 1051-1055, XP002236951 transformation from compound 9 to 10	20
X	----- MANLY D. G., ET AL.: "Simple Furan Ethers. II: 2-Alkoxy- and 2-Aryloxy-furans" J. ORG. CHEM., vol. 21, 1956, pages 516-519, XP002236952 transformation from compound I to II -----	20

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001786

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6034121	A	07-03-2000	AT 201674 T	15-06-2001
			AU 7223896 A	30-04-1997
			BR 9610970 A	06-04-1999
			CA 2233666 A1	17-04-1997
			CN 1204330 A , B	06-01-1999
			DE 69613139 D1	05-07-2001
			DE 69613139 T2	13-09-2001
			DK 861242 T3	06-08-2001
			EP 0861242 A1	02-09-1998
			ES 2157462 T3	16-08-2001
			WO 9713762 A1	17-04-1997
			GR 3036017 T3	28-09-2001
			HU 9900753 A2	28-07-1999
			IL 123701 A	10-03-2002
			JP 2000500739 T	25-01-2000
			PL 326159 A1	31-08-1998
			PT 861242 T	30-10-2001
			TW 420671 B	01-02-2001
			ZA 9608650 A	15-07-1997

JP 62228001	A	06-10-1987	NONE	

WO 03014103	A	20-02-2003	FR 2828196 A1	07-02-2003
			CA 2451041 A1	20-02-2003
			WO 03014103 A1	20-02-2003
			EP 1412344 A1	28-04-2004
