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Eljárás fenil-acetamid vegyület előállítására

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(54) Method for Producing Phenylacetamide Compound

Verfahren zur Herstellung einer Phenylacetamidverbindung

Procédé de production de composé phénylacétamide

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- **DATABASE CA[Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OOTSUKA, SHUNICHI ET AL: "Preparation of .alpha.-hydroxyphenylacetic acid derivatives as agricultural bactericides", XP002714187, retrieved from STN Database accession no. 1997:371871 -& JP 9 095462 A (SHIONOGI AND CO., LTD., JAPAN) 8 April 1997 (1997-04-08)**
- **DATABASE CA[Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MASUI, MORIYASU ET AL: "Process for producing optically active alcohol by asymmetric hydrogen-transfer reduction of ketones with chiral transition metal complex having amide compound as ligand", XP002714188, retrieved from STN Database accession no. 2002:107282 -& WO 02/10101 A1 (SHIONOGI & CO., LTD., JAPAN) 7 February 2002 (2002-02-07)**
- **DATABASE CA[Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MASUI, MORIYASU ET AL: "Preparation of phenyl ketones from esters and o-(aminomethyl)phenyl halides", XP002714189, retrieved from STN Database accession no. 2003:68569 -& JP 2003 026640 A (SHIONOGI AND CO., LTD., JAPAN) 29 January 2003 (2003-01-29)**

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EP 2 682 382 B1

Description

TECHNICAL FIELD

[0001] The present invention relates to a method for producing a phenylacetamide compound.

BACKGROUND ART

[0002] WO 95/27693 discloses that a 2-substituted phenyl-N-alkylacetamide compound having an alkoxy group at the 2-position typified by

2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide is useful as an agricultural fungicide, and also discloses, as a method for producing the compound, a method in which methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-hydroxyacetate is reacted with methyl iodide to obtain methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxyacetate, and then the methyl 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxyacetate is reacted with methylamine to obtain 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide.

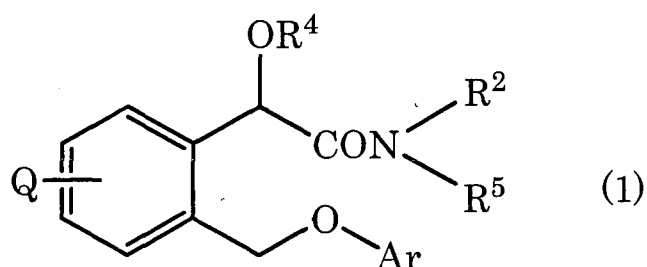
[0003] JP 9 095462 A discloses a method for the preparation of an α -hydroxyphenylacetic acid derivative.

[0004] WO 02/10101 A1 discloses a method for producing an optically active alcohol. JP 2003 026640 A discloses a method for producing an aromatic ketone. The methods may involve the O-methylation of a hydroxy group using dimethyl sulfate.

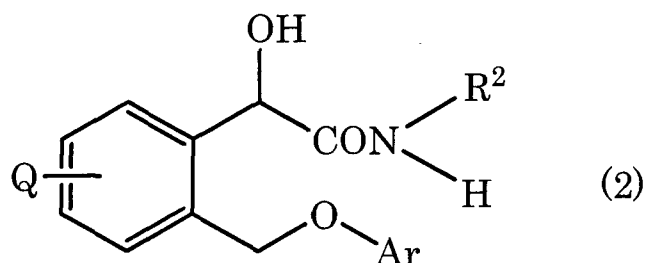
DISCLOSURE OF THE INVENTION

[0005] The present invention provides

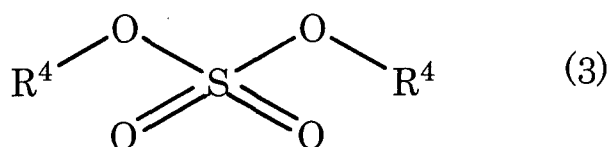
[1] a method for producing a phenylacetamide compound represented by formula (1):



wherein Q represents a hydrogen atom or a halogen atom, R^2 represents a hydrogen atom, R^4 represents an alkyl group having 1 to 4 carbon atoms, Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen, and R^5 represents R^4 ; comprising reacting a phenylacetamide compound represented by formula (2):



wherein Q, R^2 and Ar have the same meanings as defined above; with a dialkyl sulfate represented by formula (3):



wherein R^4 has the same meaning as defined above; in the presence of a base;

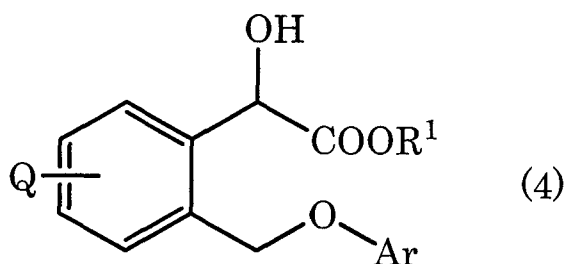
[2] the production method according to [1], wherein Ar is a 2,5-dimethylphenyl group or a 2-methylphenyl group;

[3] the production method according to [1], wherein Ar is a 2,5-dimethylphenyl group;

[4] the production method according to any one of [1] to [3], wherein R^4 is a methyl group;

[5] the production method according to any one of [1] to [4], wherein the base is an alkali metal hydroxide;

[6] the production method according to one of [1] to [5], wherein an acetic acid ester compound represented by formula (4):



wherein Q represents a hydrogen atom or a halogen atom, Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen, and R^1 represents an alkyl group having 1 to 4 carbon atoms; is reacted with an amine compound represented by formula (5):



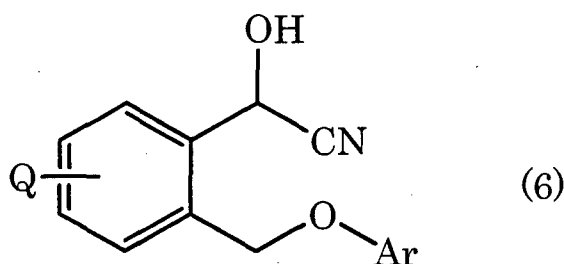
wherein R^2 represents a hydrogen atom;

to obtain the phenylacetamide compound represented by formula (2),

which phenylacetamide compound is subsequently reacted with the dialkyl sulfate in accordance with the production method of [1];

[7] the production method according to [6], wherein the reaction of the acetic acid ester compound represented by formula (4) with the amine compound represented by formula (5) is carried out in the presence of an alcohol solvent having 1 to 4 carbon atoms;

[8] the production method according to [6] or [7], wherein a mandelonitrile compound represented by formula (6):

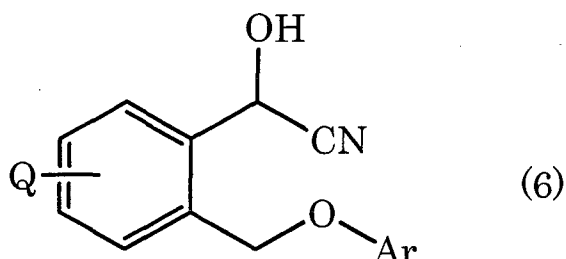


wherein Q represents a hydrogen atom or a halogen atom, and Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen; is reacted with an alcohol compound represented by formula (7):



wherein R^1 represents an alkyl group having 1 to 4 carbon atoms; and an acid, and then the resulting product is

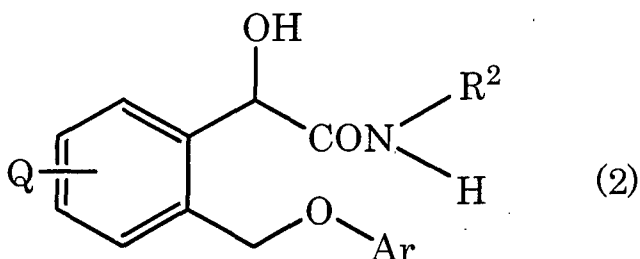
reacted with water; to obtain the acetic ester compound represented by formula (4); which acetic ester compound is subsequently reacted with the amine compound in accordance with the production method of [6] ;
 [9] the production method according to [1], wherein the mandelonitrile compound represented by formula (6):



wherein Q represents a hydrogen atom or a halogen atom, and Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen; is reacted with 0.1 to 1 mol of hydrogen chloride and 1 to 4 mol of water, based on 1 mol of the mandelonitrile compound;
 [10] the production method according to [9], wherein the reaction of the mandelonitrile compound represented by formula (6) with hydrogen chloride and water is carried out in the presence of an aromatic hydrocarbon solvent to obtain the phenylacetamide compound of formula (2); which phenylacetamide compound is subsequently reacted with the dialkyl sulfate in accordance with the production method of [1] .

BEST MODE FOR CARRYING OUT THE INVENTION

[0006] In the phenylacetamide compound represented by formula (2) (hereinafter abbreviated to an acetamide compound (2)), Q represents a hydrogen atom or a halogen atom.



[0007] Examples of the halogen atom include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Q is preferably a hydrogen atom.

[0008] R² in formula (2) represents a hydrogen atom.

[0009] Ar represents an unsubstituted or substituted phenyl group. The substituent may be selected from alkyl groups having 1 to 4 carbon atoms, such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group and a tert-butyl group; and halogen atoms such as a fluorine atom and a chlorine atom. There is no particular limitation on the number of substituents, and the number of substituents is preferably 1 to 3, more preferably 1 or 2, and particularly preferably 2.

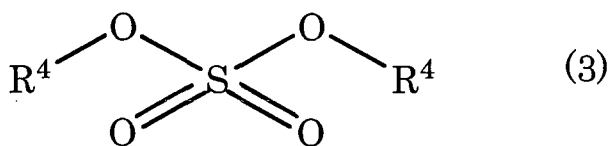
[0010] Examples of the substituted phenyl group include a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2,3-dimethylphenyl group, a 2,4-dimethylphenyl group, a 2,5-dimethylphenyl group, a 2,6-dimethylphenyl group, a 3,4-dimethylphenyl group, a 3,5-dimethylphenyl group, a 2,4,6-trimethylphenyl group, a 2-ethylphenyl group, a 3-ethylphenyl group, a 4-ethylphenyl group, a 2,3-diethylphenyl group, a 2,4-diethylphenyl group, a 2,5-diethylphenyl group, a 2,6-diethylphenyl group, a 3,5-diethylphenyl group, a 2,4,6-triethylphenyl group, a 2-propylphenyl group, a 3-propylphenyl group, a 4-propylphenyl group, a 2,4-dipropylphenyl group, a 2,5-dipropylphenyl group, a 2,6-dipropylphenyl group, a 2,4,6-tripropylphenyl group, a 2-isopropylphenyl group, a 3-isopropylphenyl group, a 4-isopropylphenyl group, a 2,4-isopropylphenyl group, a 2,5-diisopropylphenyl group, a 2,6-diisopropylphenyl group, a 2,4,6-triisopropylphenyl group, a 2-butylphenyl group, a 3-butylphenyl group, a 4-butylphenyl group, a 2,4-dibutylphenyl group, a 2,5-dibutylphenyl group, a 2,6-dibutylphenyl group, a 2,4,6-tributylphenyl group, a 2-isobutylphenyl group, a 3-isobutylphenyl group, a 4-isobutylphenyl group, a 2,4-diisobutylphenyl group, a 2,5-diisobutylphenyl group, a 2,6-diisobutylphenyl group, a 2,4,6-triisobutylphenyl group, a 2-(tert-butyl)phenyl group, a 3-(tert-butyl)phenyl group, a 4-(tert-butyl)phenyl group, a 2,5-di-(tert-butyl)phenyl group, a 2,4-di-(tert-butyl)phenyl group, a 2,6-di-(tert-butyl)phenyl group, a 2,4,6-tri-(tert-

butyl)phenyl group, a 2-fluorophenyl group, a 4-fluorophenyl group, a 2,4-difluorophenyl group, a 2,4,6-trifluorophenyl group, a pentafluorophenyl group, a 2-chlorophenyl group, a 4-chlorophenyl group, a 2,4-dichlorophenyl group, a 2,4,6-trichlorophenyl group, and a pentachlorophenyl group. Among these groups, a 2,5-dimethylphenyl group and a 2-methylphenyl group are preferred, and a 2,5-dimethylphenyl group is more preferred.

[0011] Examples of the acetamide compound (2) include

2-[2-(phenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(3-methylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(4-methylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2-ethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(4-ethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2-isopropylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(4-isopropylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2-tert-butylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(4-tert-butylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,4-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,6-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(3,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,4-diethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,5-diethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,6-diethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,5-diisopropylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,6-diisopropylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,4,5-trimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,4,6-trimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(3,4,5-trimethylphenoxyethyl)phenyl]-2-hydroxyacetamide,
 2-[2-(2,5-dimethylphenoxyethyl)-3-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2-methylphenoxyethyl)-3-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2,5-dimethylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2-methylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2,5-dimethylphenoxyethyl)-5-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2-methylphenoxyethyl)-5-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2,5-dimethylphenoxyethyl)-6-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2-methylphenoxyethyl)-6-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2,5-diethylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2-ethylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetamide,
 2-[2-(2,5-diisopropylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetamide, and
 2-[2-(2-isopropylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetamide.

[0012] In the dialkyl sulfate represented by formula (3) (hereinafter abbreviated to a dialkyl sulfate (3)), R^4 represents an alkyl group having 1 to 4 carbon atoms.



Examples of the alkyl group having 1 to 4 carbon atoms include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, an isobutyl group and a tert-butyl group, and a methyl group is preferred.

[0013] Examples of the dialkyl sulfate (3) include dialkyl sulfates having a linear alkyl group, such as dimethyl sulfate, diethyl sulfate, dipropyl sulfate and dibutyl sulfate; and dialkyl sulfates having a branched alkyl group, such as diisopropyl sulfate and diisobutyl sulfate, and dialkyl sulfates having a linear alkyl group are preferred, and dimethyl sulfate is more preferred.

[0014] As such dialkyl sulfates (3), commercially available dialkyl sulfates or those produced by a known method may be used.

[0015] The amount of the dialkyl sulfate (3) used is usually from 1 to 20 mol, and preferably from 1 to 10 mol, based on 1 mol of the acetamide compound (2).

[0016] The reaction of the acetamide compound (2) with the dialkyl sulfate (3) is carried out in the presence of a base. Examples of the base include alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; and alkaline earth metal hydroxides such as barium hydroxide and calcium hydroxide, and alkali metal hydroxides are preferred, and sodium hydroxide is more preferably.

[0017] The amount of the base used is usually from 2 to 50 mol, and preferably from 2 to 20 mol, based on 1 mol of the acetamide compound (2).

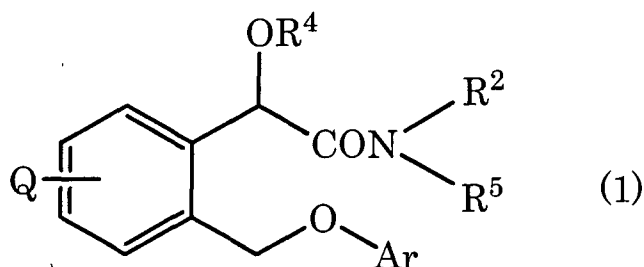
[0018] The reaction of the acetamide compound (2) with the dialkyl sulfate (3) is usually carried out in the presence of a solvent inert in the reaction. Examples of the solvent include alcohol solvents such as methanol and ethanol; aromatic hydrocarbon solvents such as toluene and xylene; ether solvents such as diethyl ether and tetrahydrofuran; and water. These solvents may be used alone, two or more kinds of solvents may be used in combination. Among these solvents, aromatic hydrocarbon solvents are preferred, and toluene or xylene is more preferred. There is no particular limitation on the amount of the solvents used, and it is preferably from 0.5 to 100 parts by weight, and more preferably from 1 to 20 parts by weight, based on 1 part by weight of the acetamide compound (2).

[0019] The reaction of the acetamide compound (2) with the dialkyl sulfate (3) is carried out by mixing the acetamide compound (2), the dialkyl sulfate (3) and the base, and there is no particular limitation on the mixing order of these components. For example, the dialkyl sulfate (3) and the base may be simultaneously added to the acetamide compound (2) adjusted to reaction temperature, or the base may be added to the acetamide compound (2) adjusted to reaction temperature and then the dialkyl sulfate (3) may be added. Among these, it is preferred that the base is added to the acetamide compound (2) adjusted to reaction temperature, and then the dialkyl sulfate (3) may be added. There is no particular limitation on the time of the base and the dialkyl sulfate (3) added.

[0020] The reaction temperature is usually from 0 to 70°C, and preferably from 10 to 50°C. The reaction time depends on the reaction temperature, and is usually from 0.5 to 20 hours, and preferably from 1 to 10 hours.

[0021] The progress of the reaction can be recognized by general analytical means such as high-performance liquid chromatography and gas chromatography.

[0022] After completion of the reaction, for example, the obtained reaction mixture may be washed with water or an aqueous acid solution such as diluted hydrochloric acid, and then concentrated to obtain a phenylacetamide compound represented by formula (1) (hereinafter abbreviated to a phenylacetamide compound (1)):



wherein Q, R², R⁴ and Ar have the same meanings as defined above; and R⁵ represents R⁴. The phenylacetamide compound (1) thus obtained may be further purified by general purification means such as column chromatography.

When the acetamide compound (2) wherein R² is a hydrogen atom is used, the phenylacetamide compound (1) is obtained wherein a hydroxyl group at the 2-position is alkylated and a nitrogen atom on the amide moiety is also monoalkylated. The method of the present invention is advantageous because the phenylacetamide compound (1) wherein a hydroxyl group at the 2-position is alkylated and a nitrogen atom on the amide moiety is also monoalkylated is obtained in one step when the acetamide compound (2) wherein R² is a hydrogen atom is used. Also, the phenylacetamide compound wherein a nitrogen atom on the amide moiety is dialkylated is scarcely generated as a by-product, when the acetamide compound (2) wherein R² is a hydrogen atom is used. Furthermore, a phenylacetamide compound wherein a nitrogen atom on the amide moiety is alkylated is scarcely generated as a by-product, even when the acetamide compound (2) wherein R² is an alkyl group having 1 to 4 carbon atoms is used. Accordingly, the objective phenylacetamide compound (1) can be obtained in good yield. Also, the phenylacetamide compound (1) having good purity can be easily obtained because of less by-products.

[0023] Examples of the phenylacetamide compound (1) thus obtained include

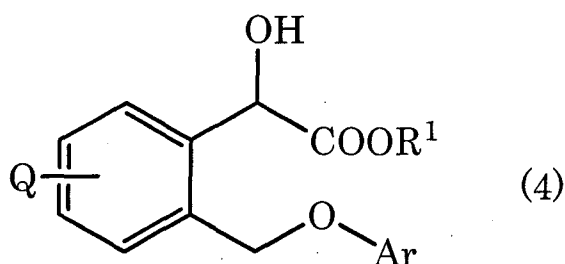
- 2-[2-(phenoxyethyl)phenyl]-2-methoxy-N-methylacetamide,
- 2-[2-(2-methylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide,
- 2-[2-(3-methylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide,

2-[2-(4-methylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-ethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(4-ethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-isopropylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(4-isopropylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-tert-butylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(4-tert-butylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,4-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,6-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(3,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,4-diethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-diethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,6-diethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-diisopropylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,6-diisopropylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,4,5-trimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,4,6-trimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(3,4,5-trimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]-3-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]-4-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-methylphenoxy)methyl]-4-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]-5-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-methylphenoxy)methyl]-5-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]-6-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-methylphenoxy)methyl]-6-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-diethylphenoxy)methyl]-4-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-ethylphenoxy)methyl]-4-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2,5-diisopropylphenoxy)methyl]-4-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-isopropylphenoxy)methyl]-4-chlorophenyl]-2-methoxy-N-methylacetamide,
 2-[2-(2-methylphenoxy)methyl]phenyl]-2-ethoxy-N-ethylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-ethoxy-N-ethylacetamide,
 2-[2-(2-methylphenoxy)methyl]phenyl]-2-propoxy-N-propylacetamide,
 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-propoxy-N-propylacetamide,
 2-[2-(2-methylphenoxy)methyl]phenyl]-2-butoxy-N-butylacetamide, and
 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-butoxy-N-butylacetamide.

Among them,

2-[2-(2-methylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide and
 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-hydroxy-N-methylacetamide are preferred, and
 2-[2-(2,5-dimethylphenoxy)methyl]phenyl]-2-methoxy-N-methylacetamide is more preferred.

[0024] The acetamide compound (2) can be produced by reacting an acetic acid ester compound represented by formula (4) (hereinafter abbreviated to an acetic acid ester compound (4)):



wherein Q and Ar have the same meanings as defined above, and R¹ represents an alkyl group having 1 to 4 carbon

atoms; with an amine compound represented by formula (5) (hereinafter abbreviated to an amine compound (5)):



wherein R^2 has the same meaning as defined above. Examples of the acetic acid ester compound (4) include methyl 2-hydroxyacetate compounds such as methyl 2-[2-(phenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(3-methylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(4-methylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2-ethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(4-ethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2-isopropylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(4-isopropylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2-tert-butylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(4-tert-butylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,4-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,6-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(3,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,4-diethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-diethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,6-diethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-diisopropylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,6-diisopropylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,4,5-trimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,4,6-trimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(3,4,5-trimethylphenoxyethyl)phenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-dimethylphenoxyethyl)-3-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2-methylphenoxyethyl)-3-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-dimethylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2-methylphenoxyethyl)-5-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-dimethylphenoxyethyl)-6-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2-methylphenoxyethyl)-6-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-diethylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2-ethylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetate, methyl 2-[2-(2,5-diisopropylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetate, and methyl 2-[2-(2-isopropylphenoxyethyl)-4-chlorophenyl]-2-hydroxyacetate; ethyl 2-hydroxyacetate compounds such as ethyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate, and ethyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate; propyl 2-hydroxyacetate compounds such as propyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate, and propyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate; isopropyl 2-hydroxyacetate compounds such as isopropyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate, and isopropyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate; butyl 2-hydroxyacetate compounds such as butyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate, and butyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate; isobutyl 2-hydroxyacetate compounds such as isobutyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate; tert-butyl 2-hydroxyacetate compounds such as tert-butyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate, and tert-butyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate; isobutyl 2-hydroxyacetate compounds such as isobutyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate; and the like. Among these compounds, methyl 2-[2-(2-methylphenoxyethyl)phenyl]-2-hydroxyacetate and methyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate are preferred, and methyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate is more preferred.

[0025] As such amine compound (5), commercially available amine compounds or those produced by a known method may be used.

[0026] The amount of the amine compound (5) used is usually from 1 to 10 mol, and preferably from 1 to 6 mol, based on 1 mol of the acetic acid ester compound (4).

[0027] The reaction of the acetic acid ester compound (4) with the amine compound (5) is usually carried out in the presence of a solvent inert in the reaction. Examples of the solvent include alcohol solvents having 1 to 4 carbon atoms, such as methanol and ethanol; aromatic hydrocarbon solvents such as toluene and xylene; ether solvents such as diethyl ether and tetrahydrofuran; and water. These solvents may be used alone, or two or more kinds of solvents may be used in combination. Among these solvents, aromatic hydrocarbon solvents, alcohol solvents having 1 to 4 carbon atoms and mixed solvents thereof are preferred, and alcohol solvents having 1 to 4 carbon atoms and mixed solvents of alcohol solvents having 1 to 4 carbon atoms with aromatic hydrocarbon solvents are more preferred. There is no particular limitation on the amount of the solvent used, and it is usually from 0.5 to 100 parts by weight, and preferably from 1 to 10 parts by weight, based on 1 part by weight of the acetic acid ester compound (4).

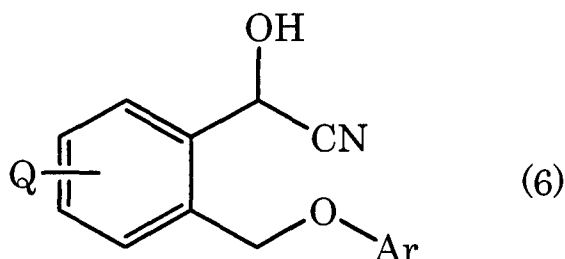
[0028] The reaction temperature is usually from 0 to 100°C, and preferably from 20 to 60°C. The reaction time depends on the reaction temperature, and is usually from 0.5 to 100 hours, and preferably from 1 to 50 hours. The progress of the reaction can be recognized by general analytical methods such as high-performance liquid chromatography and gas chromatography.

[0029] The reaction of the acetic acid ester compound (4) with the amine compound (5) is usually carried out by mixing both compounds. There is no particular limitation on the mixing order and, for example, there is exemplified a method in which the amine compound (5) is usually added to the acetic acid ester compound (4) over 0.5 to 100 hours, and

preferably over 1 to 50 hours.

[0030] After completion of the reaction, the obtained reaction mixture contains the acetamide compound (2). The reaction mixture may be used in the above reaction of the acetamide compound (2) with the dialkyl sulfate (3) directly or after washing. Alternatively, the acetamide compound (2) may be separated from the reaction mixture by concentration, crystallization or the like, and the acetamide compound (2) thus separated may be used in the above reaction of the acetamide compound (2) with the dialkyl sulfate (3). The acetamide compound (2) thus separated may be further purified by general purification means such as column chromatography.

[0031] The acetic acid ester compound (4) can be produced by reacting a mandelonitrile compound represented by formula (6) (hereinafter abbreviated to a mandelonitrile compound (6)):



wherein Q and Ar have the same meanings as defined above; with an alcohol compound represented by formula (7) (hereinafter abbreviated to an alcohol compound (7)):



wherein R¹ has the same meaning defined above; and an acid, and then reacting the obtained product with water.

[0032] Examples of the mandelonitrile compound (6) include 2-(phenoxymethyl)mandelonitrile, 2-(2-methylphenoxymethyl)mandelonitrile, 2-(3-methylphenoxymethyl)mandelonitrile, 2-(4-methylphenoxymethyl)mandelonitrile, 2-(2-ethylphenoxymethyl)mandelonitrile, 2-(4-ethylphenoxymethyl)mandelonitrile, 2-(2-isopropylphenoxymethyl)mandelonitrile, 2-(4-isopropylphenoxymethyl)mandelonitrile, 2-(2-tert-butylphenoxymethyl)mandelonitrile, 2-(4-tert-butylphenoxymethyl)mandelonitrile, 2-(2,4-dimethylphenoxymethyl)mandelonitrile, 2-(2,5-dimethylphenoxymethyl)mandelonitrile, 2-(2,6-dimethylphenoxymethyl)mandelonitrile, 2-(3,5-dimethylphenoxymethyl)mandelonitrile, 2-(2,4-diethylphenoxymethyl)mandelonitrile, 2-(2,5-diethylphenoxymethyl)mandelonitrile, 2-(2,6-diethylphenoxymethyl)mandelonitrile, 2-(2,5-diisopropylphenoxymethyl)mandelonitrile, 2-(2,6-diisopropylphenoxymethyl)mandelonitrile, 2-(2,4,5-trimethylphenoxymethyl)mandelonitrile, 2-(2,4,6-trimethylphenoxymethyl)mandelonitrile, 2-(3,4,5-trimethylphenoxymethyl)mandelonitrile, 2-(2,5-dimethylphenoxymethyl)-3-chloromandelonitrile, 2-(2-methylphenoxymethyl)-3-chloromandelonitrile, 2-(2,5-dimethylphenoxymethyl)-4-chloromandelonitrile, 2-(2-methylphenoxymethyl)-4-chloromandelonitrile, 2-(2,5-dimethylphenoxymethyl)-5-chloromandelonitrile, 2-(2-methylphenoxymethyl)-5-chloromandelonitrile, 2-(2,5-dimethylphenoxymethyl)-6-chloromandelonitrile, 2-(2-methylphenoxymethyl)-6-chloromandelonitrile, 2-(2,5-diethylphenoxymethyl)-4-chloromandelonitrile, 2-(2-ethylphenoxymethyl)-4-chloromandelonitrile, 2-(2,5-diisopropylphenoxymethyl)-4-chloromandelonitrile, and 2-(2-isopropylphenoxymethyl)-4-chloromandelonitrile. Among these compounds, 2-(2-methylphenoxymethyl)mandelonitrile and 2-(2,5-dimethylphenoxymethyl)mandelonitrile are preferred, and 2-(2,5-dimethylphenoxymethyl)mandelonitrile is more preferred.

[0033] The mandelonitrile compound (6) can be produced by reacting a corresponding aldehyde compound with hydrogen cyanide.

[0034] Examples of the alcohol compound (7) include methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, and 2-butanol, and methanol is preferred.

[0035] Examples of the acid include sulfuric acid, hydrogen chloride and p-toluenesulfonic acid, and hydrogen chloride is preferred. The amount of the acid used is usually from 1 to 10 mol, and preferably from 1 to 5 mol, based on 1 mol of the mandelonitrile compound (6). Such an acid may be used by mixing with the alcohol compound (7). In particular, it is preferred to use a solution obtained by dissolving hydrogen chloride in the alcohol compound (7). The content of the hydrogen chloride in the solution obtained by dissolving the hydrogen chloride in the alcohol compound (7) is preferably from 20 to 60 parts by weight, and more preferably from 40 to 55 parts by weight, based on 100 parts by weight of the solution. When hydrogen chloride is used as the acid, the amount of the hydrogen chloride used is preferably from 1 to 5 mol, more preferably from 1.2 to 3 mol, and particularly preferably from 1.2 to 2.5 mol, based on 1 mol of the mandelonitrile compound (6).

[0036] The reaction of the mandelonitrile compound (6), the alcohol compound (7) and the acid is usually carried out in the presence of an organic solvent. Examples of the organic solvent include aromatic hydrocarbon solvents such as

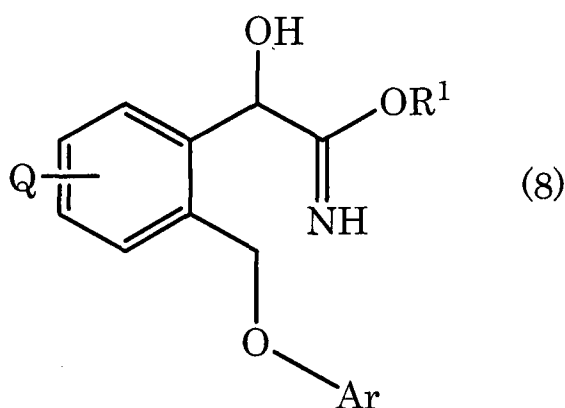
benzene, toluene, xylene and chlorobenzene; aliphatic hydrocarbon solvents such as hexane and heptane; alicyclic hydrocarbon solvents such as cyclopentane and cyclohexane; ketone solvents such as methyl ethyl ketone and methyl isobutyl ketone; and ether solvents such as diethylether, dibutylether, tetrahydrofuran and tetrahydropyran. These solvents may be used alone, or two or more kinds of solvents may be used in combination. Among these solvents, aromatic hydrocarbon solvents are preferred. The amount of the organic solvent used is usually from 0.5 to 10 parts by weight, and preferably from 1 to 5 parts by weight, based on 1 part by weight of the mandelonitrile compound (6).

[0037] The reaction of the mandelonitrile compound (6), the alcohol (7) and the acid is usually carried out by mixing these three components in the presence of an organic solvent, and it is preferable to add a mixture of the acid and the alcohol compound (7) to a mixture of the organic solvent and the mandelonitrile compound (6). The acid may be added at a time, and is preferably added gradually over 0.5 to 20 hours, and more preferably over 1 to 10 hours.

[0038] The reaction temperature is usually from -20 to 50°C, and preferably from 0 to 30°C. The reaction time depends on the reaction temperature, and is usually from 0.5 to 20 hours, and preferably from 1 to 10 hours.

[0039] The progress of the reaction can be recognized by general analytical means such as high-performance liquid chromatography and gas chromatography.

[0040] The reaction mixture thus obtained contains an imino ester compound represented by formula (8) or a salt thereof (hereinafter abbreviated to an imino ester compound (8)):



wherein Q, R¹ and Ar have the same meanings as defined above. The acetic acid ester compound (4) can be obtained by reacting the imino ester compound (8) with water. The imino ester compound (8) may be separated from the reaction mixture and reacted with water, and it is preferable to react the reaction mixture as it is with water.

[0041] The amount of water used is usually from 0.1 to 10 parts by weight, preferably from 0.5 to 5 parts by weight, and more preferably from 0.5 to 3 parts by weight, based on 1 part by weight of the mandelonitrile compound (6).

[0042] The reaction of the imino ester compound (8) with water is usually carried out by mixing both components, and there is no particular limitation on the mixing order. It is preferable to carry out the reaction by gradually adding water to a reaction mixture. The time of water added is usually from 0.5 to 20 hours, and preferably from 1 to 10 hours.

[0043] The reaction temperature is usually 0 to 70°C, and preferably 5 to 60°C. The reaction time depends on the reaction temperature, and is usually from 0.5 to 20 hours, and preferably from 1 to 10 hours.

[0044] The progress of the reaction can be recognized by general analytical means such as high-performance liquid chromatography and gas chromatography.

[0045] After completion of the reaction, the obtained reaction mixture containing the acetic acid ester compound (4) may be used in the above reaction of the acetic acid ester compound (4) with the amine compound (5) directly or after washing. Alternatively, the acetic acid ester compound (4) may be separated from the reaction mixture by concentration, crystallization or the like to use in the above reaction of the acetic acid ester compound (4) with the amine compound (5). The acetic acid ester compound (4) thus separated may be further purified by general purification means such as column chromatography.

[0046] Also, the acetamide compound (2) wherein R² is a hydrogen atom can be produced by reacting the mandelonitrile compound (6) with 0.1 to 1 mol of hydrogen chloride and 1 to 4 mol of water, based on 1 mol of the mandelonitrile compound (6). In the reaction, the formation of a carboxylic acid compound produced by the hydrolysis of the acetamide compound (2) tends to be suppressed, and thus it is a preferred method for producing the acetamide compound (2) wherein R² is a hydrogen atom.

[0047] Hydrochloric acid, an aqueous solution of hydrogen chloride, may be used instead of hydrogen chloride. When hydrochloric acid is used, the concentration of hydrogen chloride is usually from 10 to 36% by weight, and preferably from 25 to 36% by weight. As described above, the amount of hydrogen chloride used is from 0.1 to 1 mol, and preferably from 0.5 to 1 mol, based on 1 mol of the mandelonitrile compound (6). When the amount of hydrogen chloride used is

0.1 mol or more based on 1 mol of the mandelonitrile (6), the yield of the acetamide compound (2) wherein R² is a hydrogen atom tends to be improved. On the other hand, when the amount is 1 mol or less based on 1 mol of the mandelonitrile compound (6), the progress of hydrolysis reaction of the acetamide compound (2) tends to be suppressed.

[0048] Water may be used alone or simultaneously with hydrogen chloride in the form of hydrochloric acid. As described above, the amount of water used is from 1 to 4 mol, and preferably from 2 to 4 mol, based on 1 mol of the mandelonitrile compound (6). When the amount of water used is 1 mol or more based on 1 mol of the mandelonitrile compound (6), the conversion rate of the mandelonitrile compound (6) tends to be improved. On the other hand, when the amount is 4 mol or less based on 1 mol of the mandelonitrile compound (6), the progress of hydrolysis reaction of the acetamide compound (2) tends to be suppressed.

[0049] The reaction of the mandelonitrile compound (6), hydrogen chloride and water is preferably carried out in the presence of an organic solvent. Examples of the organic solvent include aromatic hydrocarbon solvents such as benzene, toluene, xylene and chlorobenzene; aliphatic hydrocarbon solvents such as hexane and heptane; alicyclic hydrocarbon solvents such as cyclopentane and cyclohexane; ketone solvents such as methyl ethyl ketone and methyl isobutyl ketone; and ether solvents such as diethyl ether, dibutyl ether, tetrahydrofuran and tetrahydropyran. These solvents may be used alone, or two or more kinds of solvents may be used in combination. Among these solvents, aromatic hydrocarbon solvents are preferred.

[0050] The amount of the organic solvent used is usually from 0.5 to 10 parts by weight, and preferably from 1 to 5 parts by weight, based on 1 part by weight of the mandelonitrile compound (6).

[0051] The reaction is carried out by mixing the mandelonitrile compound (6), hydrogen chloride and water. For example, hydrogen chloride and water may be added to the mandelonitrile compound (6), or the mandelonitrile compound (6) may be added to hydrogen chloride and water. Alternatively, the mandelonitrile compound (6) may be diluted with an organic solvent before the diluted solution is mixed with hydrogen chloride and water.

[0052] The reaction temperature is usually from -20 to 100°C, and preferably from 20 to 80°C. The reaction time depends on the reaction temperature, and is usually from 0.5 to 20 hours, and preferably from 1 to 10 hours.

[0053] The progress of the reaction can be recognized by general analytical means such as high-performance liquid chromatography and gas chromatography.

[0054] The obtained reaction mixture may be used in the above reaction of the acetamide compound (2) with the dialkyl sulfate (3) directly or after washing. Alternatively, the acetamide compound (2) may be separated from the reaction mixture by concentration, crystallization or the like, and the acetamide compound (2) separated may be used in the above reaction of the acetamide compound (2) with the dialkyl sulfate (3). The acetamide compound (2) thus separated may be further purified by general purification means such as column chromatography.

EXAMPLES

[0055] The present invention will be described in more detail below by way of Examples, but the invention is not limited thereto. The analysis was carried out using high-performance liquid chromatography according to an internal standard method.

Example 1 (Reference Example)

[0056] To 10.0 g of 2-(2,5-dimethylphenoxyethyl)-mandelonitrile (content: 96% by weight), 30 g of xylene, 3.66 g of hydrogen chloride and 0.648 g of water were added. The obtained mixture was heated to 50°C, stirred and maintained at the same temperature for 3 hours to obtain a xylene solution containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide (yield: 65.7%). The formation of by-products generated by the hydrolysis of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was not recognized.

Example 2 (Reference Example)

[0057] A xylene solution containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was obtained by carrying out the reaction in the same manner as in Example 1, except that the obtained mixture was heated to 70°C, stirred and maintained at the same temperature for 1 hour in Example 1. The conversion rate of 2-(2,5-dimethylphenoxyethyl)mandelonitrile was 67.7%, and the yield of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetic acid amide was 46.3%. The formation of by-products generated by the hydrolysis of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was not recognized.

Example 3 (Reference Example)

[0058] To 10.0 g of 2-(2,5-dimethylphenoxyethyl)-mandelonitrile (content: 96% by weight), 30 g of xylene and 1.02

g of 36% by weight hydrochloric acid were added. The obtained mixture was heated to 50°C, stirred and maintained at the same temperature for 7 hours to obtain a reaction mixture containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide. The conversion rate of 2-(2,5-dimethylphenoxyethyl)mandelonitrile was 40.0%, and the yield of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was 30.2%. The formation of by-products generated by the hydrolysis of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was not recognized.

Example 4 (Reference Example)

[0059] A reaction mixture containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was obtained by carrying out the reaction in the same manner as in Example 3, except that the amount of 36% hydrochloric acid used was 2.03 g and the obtained mixture was stirred and maintained at 50°C for 4 hours in Example 3. The conversion rate of 2-(2,5-dimethylphenoxyethyl)mandelonitrile was 68.4%, and the yield of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was 53.1%. The formation of by-products generated by the hydrolysis of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was not recognized.

Example 5

[0060] A xylene solution containing 0.33 g of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetamide was adjusted to 20°C with stirring. To the xylene solution, 1.2 g of a 48% by weight aqueous sodium hydroxide solution was added dropwise over 1 hour, followed by 0.70 g of dimethyl sulfate over 1 hour. The obtained mixture was stirred at 20°C for 5 hours to obtain a reaction mixture containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide.

[0061] To the obtained reaction mixture, 1.3 g of water was added. The obtained mixture was heated to 50°C, and the water layer was then removed. The obtained organic layer was washed at 50°C with 1.3 g of 5% by weight hydrochloric acid. The obtained organic layer was washed at 50°C with 1.3 g of water. The obtained organic layer was concentrated to obtain 0.36 g (content: 96.5%) of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide (yield: 96%). The formation of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-methoxy-N,N'-dimethylacetamide was not recognized.

Example 6 (Reference Example)

[0062] First, 255.9 g (content: 93% by weight) of 2-(2,5-dimethylphenoxyethyl)mandelonitrile was mixed with 469.0 g of xylene. The obtained mixture was adjusted to 7°C with stirring. To the mixture, 160.1 g of a 47% by weight hydrogen chloride/methanol solution was added dropwise over 2 hours. The obtained mixture was stirred and maintained at 7°C for 2 hours to obtain a reaction mixture containing 1-[2-(2,5-dimethylphenoxyethyl)phenyl]-1-hydroxy-2-methoxyethaniminium chloride.

[0063] To the obtained reaction mixture, 320.1 g of water was added dropwise at 7°C over 1 hour. The obtained mixture was stirred and maintained at 50°C for 1 hour, and 312.6 g of an organic layer was then separated. The content of methyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate in the organic layer was 82.4% by weight, and the yield was 96.2%.

Example 7 (Reference Example)

[0064] Then, 30.0 g (content: 25% by weight) of the organic layer containing methyl 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxyacetate was adjusted to 50°C with stirring. To the layer, 5.8 g of a 40% by weight methylamine/methanol solution was added dropwise over 1 hour. The obtained mixture was stirred and maintained at 50°C for 10 hours to obtain a reaction mixture containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxy-N-methylacetamide.

[0065] The obtained reaction mixture was concentrated under reduced pressure conditions to remove low-boiling components. The residue was adjusted to 50°C, and washed with 7.7 g of water and then with 7.7 g of a 5% by weight aqueous sulfuric acid solution to obtain 31.5 g of a solution (content: 23.8% by weight) containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxy-N-methylacetamide. Yield: 100%.

Example 8 (Reference Example)

[0066] Then, 31.1 g of the solution containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-hydroxy-N-methylacetamide obtained in Example 7 was adjusted to 17°C with stirring. To the solution, 7.0 g of a 48% by weight aqueous sodium hydroxide solution was added dropwise over 0.5 hour, followed by 4.2 g of dimethyl sulfate over 2 hours. The obtained mixture was stirred and maintained at 19°C for 5 hours to obtain a reaction mixture containing 2-[2-(2,5-

dimethylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide.

[0067] To the obtained reaction mixture, 7.4 g of water was added. The obtained mixture was heated to 50°C, and an organic layer was obtained at the same temperature. The obtained organic layer was washed at the same temperature with 7.4 g of 5% by weight hydrochloric acid and then with 7.5 g of water to obtain 32.1 g of a solution (content: 24.0% by weight) containing 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide. Yield: 99.1%.

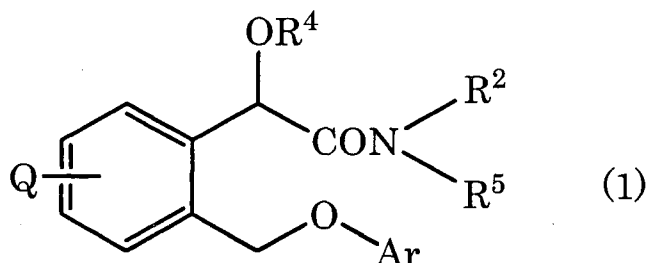
[0068] The obtained solution was concentrated until the content of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide was 42.5% by weight, and then heated to 60°C. The obtained solution was cooled, and crystals precipitated were separated by filtration, washed with heptane, and dried under reduced pressure conditions to obtain crystals of 2-[2-(2,5-dimethylphenoxyethyl)phenyl]-2-methoxy-N-methylacetamide.

Industrial Applicability

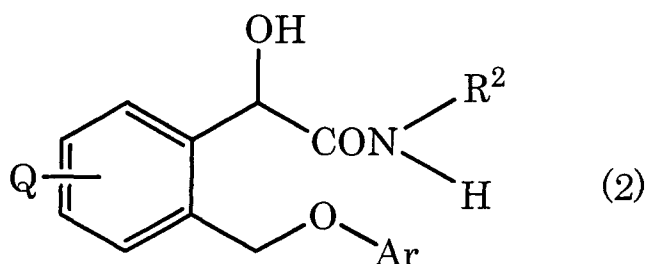
[0069] According to the present invention, a phenylacetamide compound can be produced in a satisfactory yield.

Claims

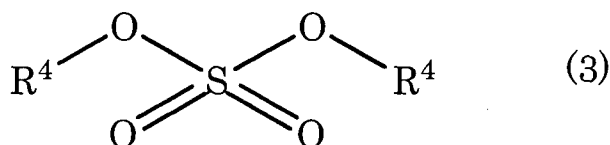
1. A method for producing a phenylacetamide compound represented by formula (1):



wherein Q represents a hydrogen atom or a halogen atom, R² represents a hydrogen atom, R⁴ represents an alkyl group having 1 to 4 carbon atoms, Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen, R⁵ represents R⁴ ;
comprising reacting a phenylacetamide compound represented by formula (2):



wherein Q, R² and Ar have the same meanings as defined above; with a dialkyl sulfate represented by formula (3):

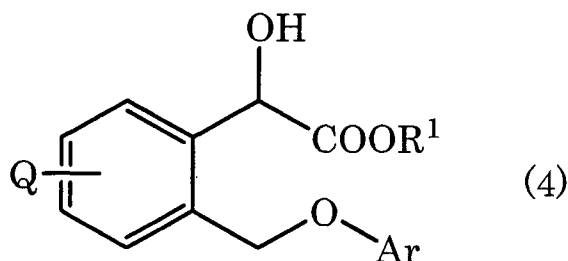


wherein R⁴ has the same meaning as defined above;
in the presence of a base.

2. The production method according to claim 1, wherein Ar is a 2,5-dimethylphenyl group or a 2-methylphenyl group.

3. The production method according to claim 1, wherein Ar is a 2,5-dimethylphenyl group.

4. The production method according to claim 1, wherein R⁴ is a methyl group.
5. The production method according to claim 1, wherein the base is an alkali metal hydroxide.
6. The production method according to claim 1, wherein an acetic acid ester compound represented by formula (4):



wherein Q represents a hydrogen atom or a halogen atom, Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen, and R¹ represents an alkyl group having 1 to 4 carbon atoms;

is reacted with an amine compound represented by formula (5):

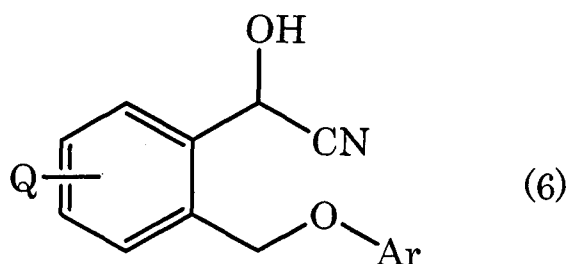


wherein R² represents a hydrogen atom;

to obtain the phenylacetamide compound represented by formula (2),

which phenylacetamide compound is subsequently reacted with the dialkyl sulfate in accordance with the production method of claim 1.

7. The production method according to claim 6, wherein the reaction of the acetic acid ester compound represented by formula (4) with the amine compound represented by formula (5) is carried out in the presence of an alcohol solvent having 1 to 4 carbon atoms.
8. The production method according to claim 6, wherein a mandelonitrile compound represented by formula (6):



wherein Q represents a hydrogen atom or a halogen atom, and Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen; is reacted with an alcohol compound represented by formula (7):



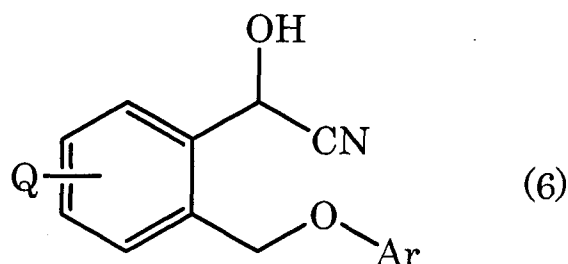
wherein R¹ represents an alkyl group having 1 to 4 carbon atoms;

and an acid, and then the resulting product is reacted with water;

to obtain the acetic ester compound represented by formula (4);

which acetic ester compound is subsequently reacted with the amine compound in accordance with the production method of claim 6.

9. The production method according to claim 1, wherein the mandelonitrile compound represented by formula (6):



wherein Q represents a hydrogen atom or a halogen atom, and Ar represents a phenyl group which may be unsubstituted or substituted with alkyl having 1 to 4 carbon atoms or halogen; is reacted with 0.1 to 1 mol of hydrogen chloride and 1 to 4 mol of water, based on 1 mol of the mandelonitrile compound;

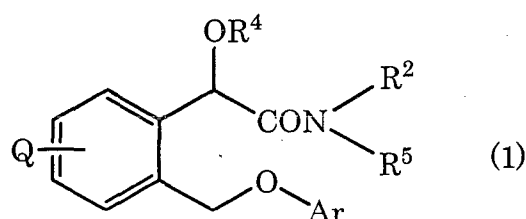
to obtain the phenylacetamide compound of formula (2);

which phenylacetamide compound is subsequently reacted with the dialkyl sulfate in accordance with the production method of claim 1.

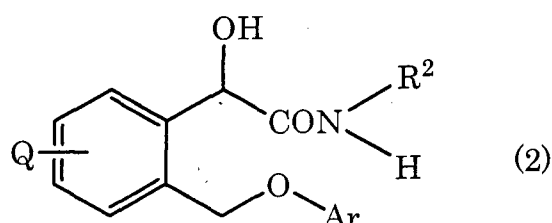
10. The production method according to claim 9, wherein the reaction of the mandelonitrile compound represented by formula (6) with hydrogen chloride and water is carried out in the presence of an aromatic hydrocarbon solvent.

Patentansprüche

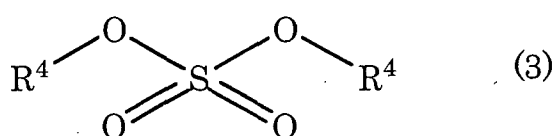
1. Ein Verfahren zur Herstellung einer Phenylacetamidverbindung, dargestellt durch Formel (1):



wobei Q für ein Wasserstoffatom oder ein Halogenatom steht, R² für ein Wasserstoffatom steht, R⁴ für eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen steht, Ar für eine Phenylgruppe steht, die unsubstituiert oder mit Alkyl mit 1 bis 4 Kohlenstoffatomen oder Halogen substituiert sein kann, R⁵ für R⁴ steht; umfassend Umsetzen einer Phenylacetamidverbindung, dargestellt durch Formel (2):

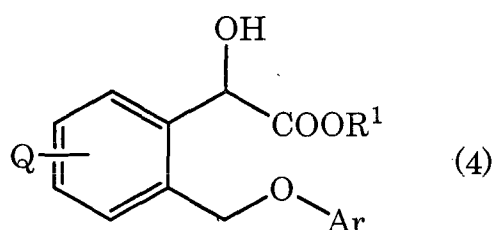


wobei Q, R² und Ar die vorstehend definierten Bedeutungen aufweisen; mit einem Dialkylsulfat, dargestellt durch Formel (3):



wobei R⁴ die vorstehend definierte Bedeutung aufweist;
in Gegenwart einer Base.

2. Das Herstellungsverfahren gemäß Anspruch 1, wobei Ar eine 2,5-Dimethylphenylgruppe oder eine 2-Methylphenylgruppe ist.
3. Das Herstellungsverfahren gemäß Anspruch 1, wobei Ar eine 2,5-Dimethylphenylgruppe ist.
4. Das Herstellungsverfahren gemäß Anspruch 1, wobei R⁴ eine Methylgruppe ist.
5. Das Herstellungsverfahren gemäß Anspruch 1, wobei die Base ein Alkalimetallhydroxid ist.
6. Das Herstellungsverfahren gemäß Anspruch 1, wobei eine Essigsäureesterverbindung, dargestellt durch Formel (4):

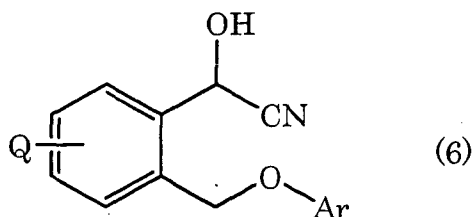


wobei Q für ein Wasserstoffatom oder ein Halogenatom steht, Ar für eine Phenylgruppe steht, die unsubstituiert oder mit Alkyl mit 1 bis 4 Kohlenstoffatomen oder Halogen substituiert sein kann; und R¹ für eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen steht; umgesetzt wird mit einer Aminverbindung, dargestellt durch Formel (5):



wobei R² für ein Wasserstoffatom steht;
um eine Phenylacetamidverbindung, dargestellt durch Formel (2), zu erhalten,
wobei die Phenylacetamidverbindung anschließend mit dem Dialkylsulfat gemäß dem Herstellungsverfahren des Anspruchs 1 umgesetzt wird.

7. Das Herstellungsverfahren gemäß Anspruch 6, wobei die Umsetzung der Essigsäureesterverbindung, dargestellt durch Formel (4), mit der Aminverbindung, dargestellt durch Formel (5), in Gegenwart eines Alkohollösungsmittels mit 1 bis 4 Kohlenstoffatomen durchgeführt wird.
8. Das Herstellungsverfahren gemäß Anspruch 6, wobei eine Mandelonitrilverbindung, dargestellt durch Formel (6):



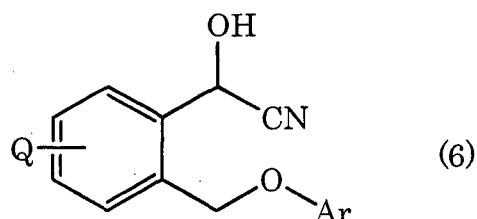
wobei Q für ein Wasserstoffatom oder ein Halogenatom steht, und Ar für eine Phenylgruppe steht, die unsubstituiert oder mit Alkyl mit 1 bis 4 Kohlenstoffatomen oder Halogen substituiert sein kann,
umgesetzt wird mit einer Alkoholverbindung, dargestellt durch Formel (7):



wobei R¹ für eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen steht;
und einer Säure, und dann wird das entstandene Produkt mit Wasser umgesetzt; um eine Essigsäureesterverbindung, dargestellt durch Formel (4), zu erhalten;
wobei die Essigsäureesterverbindung anschließend mit der Aminverbindung gemäß dem Herstellungsverfahren

des Anspruchs 6 umgesetzt wird.

9. Das Herstellungsverfahren gemäß Anspruch 1, wobei die Mandelonitrilverbindung, dargestellt durch Formel (6):



wobei Q für ein Wasserstoffatom oder ein Halogenatom steht, und Ar für eine Phenylgruppe steht, die unsubstituiert oder mit Alkyl mit 1 bis 4 Kohlenstoffatomen oder Halogen substituiert sein kann, umgesetzt wird mit 0,1 bis 1 Mol Chlorwasserstoff und 1 bis 4 Mol Wasser, bezogen auf 1 Mol der Mandelonitrilverbindung;

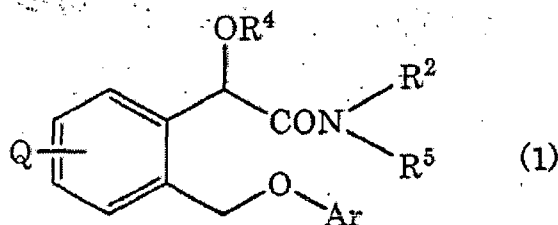
um die Phenylacetamidverbindung der Formel (2), zu erhalten;

wobei die Phenylacetamidverbindung anschließend mit dem Dialkylsulfat gemäß dem Herstellungsverfahren des Anspruchs 1 umgesetzt wird.

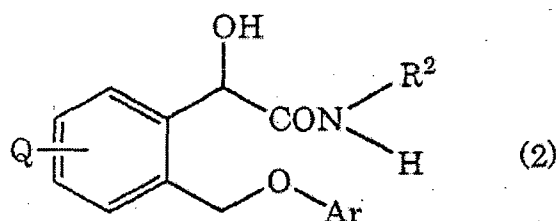
10. Das Herstellungsverfahren gemäß Anspruch 9, wobei die Umsetzung der Mandelonitrilverbindung, dargestellt durch Formel (6), mit Chlorwasserstoff und Wasser in Gegenwart eines aromatischen Kohlenwasserstoff-Lösungsmittels durchgeführt wird.

Revendications

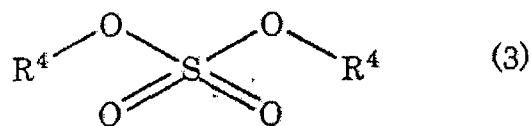
1. Procédé de production d'un composé de phénylacétamide représenté par la formule (1) :



dans laquelle Q représente un atome d'hydrogène ou un atome d'halogène, R² représente un atome d'hydrogène, R⁴ représente un groupe alkyle ayant de 1 à 4 atomes de carbone, Ar représente un groupe phényle qui peut être non substitué ou substitué avec un groupe alkyle ayant de 1 à 4 atomes de carbone ou un halogène, R⁵ représente R⁴ ; comprenant la réaction d'un composé de phénylacétamide représenté par la formule (2)

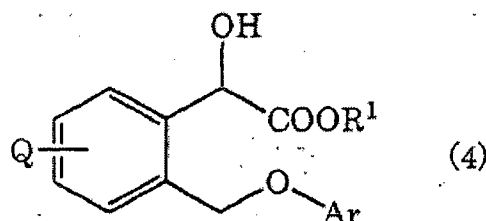


dans laquelle Q, R² et Ar ont les mêmes significations que définies ci-dessus ; avec un sulfate de dialkyle représenté par la formule (3) :



dans laquelle R^4 a la même signification que définie ci-dessus ;
en présence d'une base.

2. Procédé de production selon la revendication 1, dans lequel Ar est un groupe 2,5-diméthylphényle ou un groupe 2-méthylphényle.
3. Procédé de production selon la revendication 1, dans lequel Ar est un groupe 2,5-diméthylphényle.
4. Procédé de production selon la revendication 1, dans lequel R^4 est un groupe méthyle.
5. Procédé de production selon la revendication 1, dans lequel la base est un hydroxyde de métal alcalin.
6. Procédé de production selon la revendication 1, dans lequel un composé d'ester d'acide acétique représenté par la formule (4) :

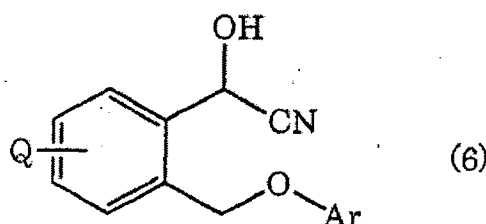


dans laquelle Q représente un atome d'hydrogène ou un atome d'halogène, Ar représente un groupe phényle qui peut être non substitué ou substitué avec un groupe alkyle ayant de 1 à 4 atomes de carbone ou un halogène, et R^1 représente un groupe alkyle ayant de 1 à 4 atomes de carbone ;
réagit avec un composé d'amine représenté par la formule (5) :



dans laquelle R^2 représente un atome d'hydrogène ;
pour obtenir le composé de phénylacétamide représenté par la formule (2),
lequel composé de phénylacétamide réagit ensuite avec le sulfate de dialkyle selon le procédé de production de la revendication 1.

7. Procédé de production selon la revendication 6, dans lequel la réaction du composé d'ester d'acide acétique représenté par la formule (4) avec le composé d'amine représenté par la formule (5) est réalisée en présence d'un solvant d'alcool ayant de 1 à 4 atomes de carbone.
8. Procédé de production selon la revendication 6, dans lequel un composé de mandélonitrile représenté par la formule (6) :

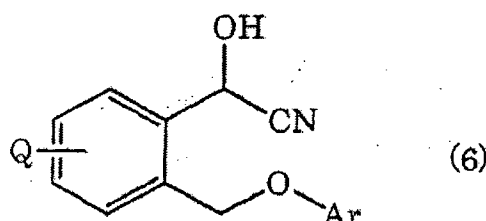


dans laquelle Q représente un atome d'hydrogène ou un atome d'halogène, et Ar représente un groupe phényle qui peut être non substitué ou substitué avec un groupe alkyle ayant de 1 à 4 atomes de carbone ou un halogène ; réagit avec un composé d'alcool représenté par la formule (7) :



dans laquelle R¹ représente un groupe alkyle ayant de 1 à 4 atomes de carbone ; et un acide, et le produit résultant réagit ensuite avec de l'eau ; pour obtenir un composé d'ester d'acide acétique représenté par la formule (4) ; lequel composé d'ester acétique réagit ensuite avec le composé d'amine selon le procédé de production de la revendication 6.

9. Procédé de production selon la revendication 1, dans lequel le composé de mandélonitrile représenté par la formule (6) :



dans laquelle Q représente un atome d'hydrogène ou un atome d'halogène, et Ar représente un groupe phényle qui peut être non substitué ou substitué avec un groupe alkyle ayant de 1 à 4 atomes de carbone ou un halogène ; réagit avec de 0,1 à 1 mole de chlorure d'hydrogène et de 1 à 4 moles d'eau, rapporté à 1 mole du composé de mandélonitrile ;

pour obtenir le composé de phénylacétamide de formule (2) ;

lequel composé de phénylacétamide réagit ensuite avec le sulfate de dialkyle selon le procédé de production de la revendication 1.

10. Procédé de production selon la revendications 9, dans lequel la réaction du composé de mandélonitrile représenté par la formule (6) avec du chlorure d'hydrogène et de l'eau est réalisée en présence d'un solvant hydrocarboné aromatique.

REFERENCES CITED IN THE DESCRIPTION

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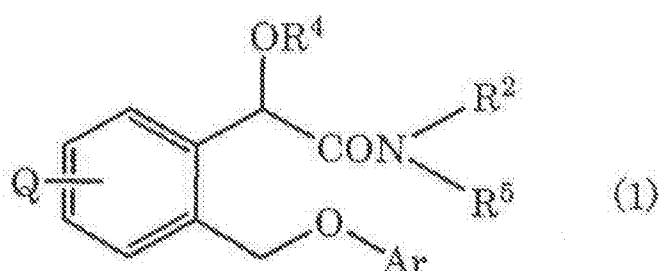
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- WO 9527693 A [0002]
- JP 9095462 A [0003]
- WO 0210101 A1 [0004]
- JP 2003026640 A [0004]

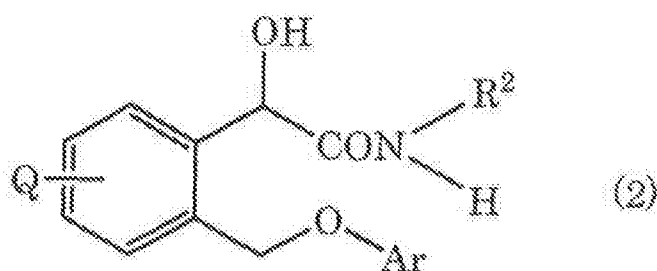
ELJÁRÁS FENIL-ACETAMID VEGYÜLET ELŐÁLLÍTÁSÁRA
SZABADALMI IGÉNYPONTOK



1. Eljárás (1) általános képletű fenil-acetamid vegyület előállítására,

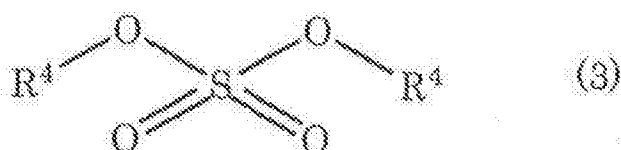


ahol az általános képletben Q jelentése hidrogénatom vagy halogénatom, R² jelentése hidrogénatom, R⁴ jelentése 1-4 szénatommal bíró alkil-csoport, Ar jelentése olyan fenil-csoport, amely lehet nem-szubsztituált vagy szubsztituált 1-4 szénatommal bíró alkil-csoporttal vagy halogénatommal, R⁵ jelentése R⁴;



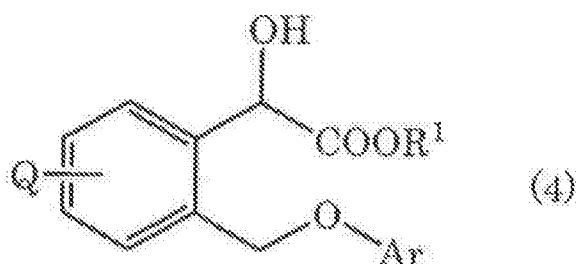
ahol az eljárás tartalmazza egy (2) általános képlettel bíró fenil-acetamid vegyület

ahol az általános képletben Q, R² és Ar ugyanazon jelentéssel bír, ahogyan az előzőekben meghatároztuk; reagáltatását egy (3) általános képletű dialkil-szulfáttal:



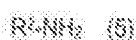
ahol az általános képletben R⁴ ugyanazon jelentéssel bír, ahogyan ezt az előzőekben meghatároztuk; egy bázis jelenlétében.

2. Az 1. igénypont szerinti előállítási eljárás, ahol Ar jelentése 2,5-dimetil-fenil-csoport vagy 2-metil-fenil-csoport.
3. Az 1. igénypont szerinti előállítási eljárás, ahol Ar jelentése 2,5-dimetil-fenil-csoport.
4. Az 1. igénypont szerinti előállítási eljárás, ahol R⁴ jelentése metil-csoport.
5. Az 1. igénypont szerinti előállítási eljárás, ahol a bázis alkálifém-hidroxid.
6. Az 1. igénypont szerinti előállítási eljárás, ahol egy (4) általános képletű ecetsav-észter vegyületet:



ahol az általános képletben Q jelentése hidrogénatom vagy halogénatom, Ar jelentése olyan fenil-csoport, amely lehet nem-szubsztituált vagy szubsztituált 1-4 szénatommal bíró alkil-csoporttal vagy halogénatommal, és R¹ jelentése 1-4 szénatommal bíró alkil-csoport,

reagáltatunk egy (5) általános képletű amin vegyülettel:

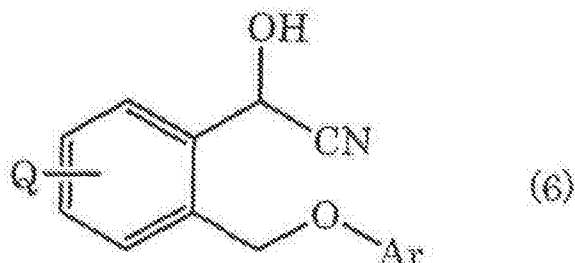


ahol az általános képletben R² jelentése hidrogénatom,

hogy megkapjunk egy (2) általános képlettel bíró fenil-acetamid vegyületet,

amely fenil-acetamid vegyületet ezt követően reagáltatjuk egy dialkil-szulfáttal az 1. igénypont előállításának eljárásával összhangban.

7. A 6. igénypont szerinti előállítási eljárás, ahol a (4) általános képletű ecetsav-észter vegyület reakcióját az (5) általános képletű amin-vegyülettel egy olyan alkoholos oldószer jelenlétében hajtjuk végre, amely 1-4 szénatommal bír.



8. A 6. igénypont szerinti előállítási eljárás, ahol egy (6) általános képletű mandelonitril vegyületet:

ahol az általános képletben Q jelentése hidrogénatom vagy halogénatom, Ar jelentése olyan fenil-csoport, amely lehet nem-szubsztituált vagy szubsztituált 1-4 szénatommal bíró alkil-csoporttal vagy halogénatommal, reagáltatunk egy (7) általános képletű alkohol vegyülettel:



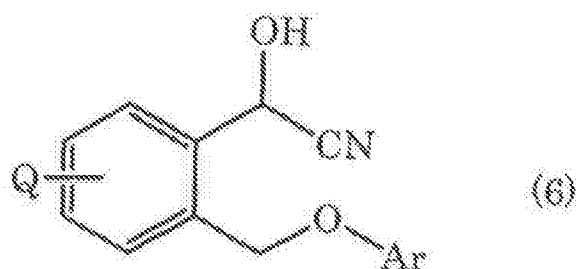
ahol az általános képletben R¹ jelentése 1-4 szénatommal bíró alkil-csoport,

és egy savval, és az így létrejött terméket reagáltatjuk vízzel;

hogy így kapjuk meg a (4) általános képletű ecetsav-észter vegyületet;

amely ecetsav-észter vegyületet ezt követően reagáltatjuk az amin vegyülettel a 6. igénypont előállításának eljárásával összhangban.

9. Az 1. igénypont szerinti előállítási eljárás, ahol a (6) általános képletű mandelonitril vegyületet



ahol az általános képletben Q jelentése hidrogénatom vagy halogénatom, Ar jelentése olyan fenil-csoport, amely lehet nem-szubsztituált vagy szubsztituált 1-4 szénatommal bíró alkil-csoporttal vagy halogénatommal;

reagáltatjuk 0,1-1 mól hidrogén-kloriddal és 1-4 mól vízzel, 1 mól mandelonitril vegyületre alapozva;

és így kapjuk meg a (2) általános képletű fenil-acetamid vegyületet;

amely fenil-acetamid vegyületet ezt követően reagáltatjuk a dialkil-szulfáttal az 1. igénypont előállítási eljárásával összhangban.

10. A 9. igénypont szerinti előállítási eljárás, ahol a (6) általános képletű mandelonitril vegyület reakcióját hidrogén-kloriddal és vízzel egy aromás szénhidrogén oldószer jelenlétében hajtjuk végre.