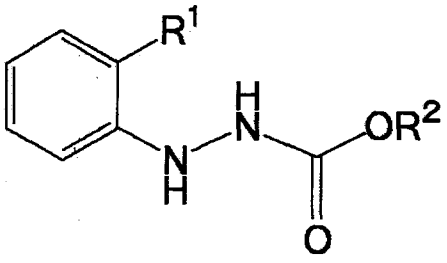
ABSTRACT OF THE DISCLOSURE

Provided is a method for purification to obtain a purified product of a phenylhydrazine-β-carboxylate compound (I) having a reduced concentration of a chloroaniline compound (II) by efficiently separating and removing the chloroaniline compound (II) contained in a crude product of the phenylhydrazine-β-carboxylate compound (I) while preventing loss of the phenylhydrazine-β-carboxylate compound (I). The method for purification of the phenylhydrazine-β-carboxylate compound (I) includes mixing the crude product of the phenylhydrazine-β-carboxylate compound (I) containing the chloroaniline compound (II) with water and an organic solvent separable from water in the presence of an inorganic acid, and then separating the mixture into an oil layer containing the phenylhydrazine-β-carboxylate compound (I) and an aqueous layer.

WHAT IS CLAIMED IS:

1. A method for purification of a phenylhydrazine-β-carboxylate compound represented by the formula (I):

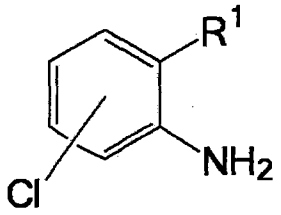
[Chemical Formula 1]



(I)

wherein R^1 represents a hydrogen atom, an alkyl group, a cycloalkyl group, an alkenyl group, an aralkyl group, an alkoxy group, an aryl group, an aralkyloxy group, an aryloxy group or a carboxyalkyl group, and R^2 represents an alkyl group with 1 to 4 carbon atoms, the method comprising mixing a crude product of the phenylhydrazine-β-carboxylate compound represented by the formula (I) containing a compound represented by the formula (II):

[Chemical Formula 2]



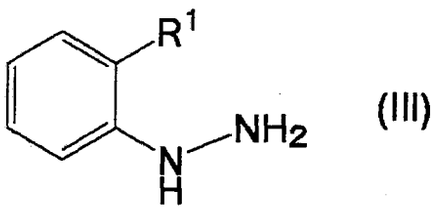
(II)

wherein R^1 represents the same meaning as described above, with water and an organic solvent separable from water in the presence of an inorganic acid, and then separating the mixture into an oil layer containing the phenylhydrazine-β-carboxylate compound represented by the

formula (I) and an aqueous layer.

2. The method for purification according to claim 1, wherein the crude product is obtained by reacting a phenylhydrazine compound represented by the formula (III):

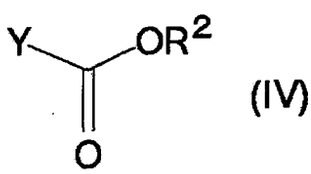
[Chemical Formula 3]



(III)

wherein R^1 represents the same meaning as described above, with an alkyl halide carbonate represented by the formula (IV):

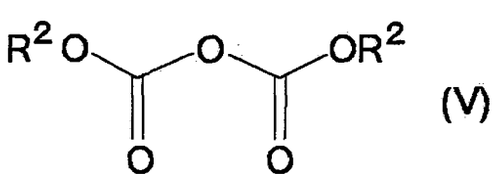
[Chemical Formula 4]



(IV)

wherein R^2 represents the same meaning as described above, and Y represents a halogen atom, or a dialkyldicarbonate represented by the formula (V):

[Chemical Formula 5]

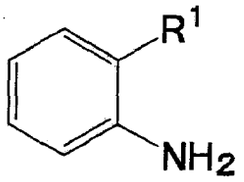


(V)

wherein R^2 represents the same meaning as described above, the phenylhydrazine compound represented by the

formula (III) being obtained by reacting a compound represented by the formula (VI):

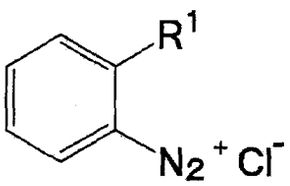
[Chemical Formula 6]



(VI)

wherein R^1 represents the same meaning as described above, with a diazotization agent in the presence of hydrogen chloride to obtain a diazonium salt represented by the formula (VII):

[Chemical Formula 7]



(VII)

wherein R^1 represents the same meaning as described above, reacting the diazonium salt represented by the formula (VII) with at least one selected from the group consisting of sulfites and bisulfites in the presence of water, and then subjecting the reactant to a contact treatment with an acid.

3. The method for purification according to claim 1 or 2, wherein the mixing is carried out at 30 to 90°C.

4. The method for purification according to any of

claims 1 to 3, wherein the inorganic acid is hydrogen chloride or sulfuric acid.

5. The method for purification according to any of claims 1 to 4, wherein R^1 in the formulas (I), (II) and (III), (VI) and (VII) is an alkoxy group.

6. The method for purification according to any of claims 1 to 5, wherein R^2 in the formulas (I), (IV) and (V) is a methyl group.

Dated this 12 day of February 2013.

Shakira

(Shakira N)
REG. No.: IN/PA-~~174~~ 972
of De Penning & De Penning
Agent For The Applicants

DESCRIPTION

METHOD FOR PURIFICATION OF PHENYLHYDRAZINE-BETA-CARBOXYLATE COMPOUND

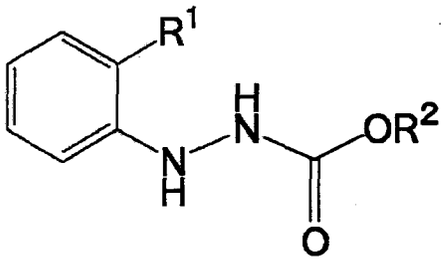
BACKGROUND OF THE INVENTION

[0001]

The present invention relates to a method for purification of a phenylhydrazine-β-carboxylate compound represented by the formula (I) [hereinafter, sometimes referred to as a phenylhydrazine-β-carboxylate compound (I)]:

[0002]

[Chemical Formula 1]

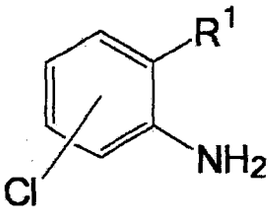


(I)

wherein R^1 represents a hydrogen atom, an alkyl group, a cycloalkyl group, an alkenyl group, an aralkyl group, an alkoxy group, an aryl group, an aralkyloxy group, an aryloxy group or a carboxyalkyl group, and R^2 represents an alkyl group with 1 to 4 carbon atoms, containing a compound represented by the formula (II) [hereinafter, sometimes referred to as a chloroaniline compound (II)]:

[0003]

[Chemical Formula 2]



(II)

wherein R^1 represents the same meaning as described above.

[0004]

It is known that the phenylhydrazine-β-carboxylate compound (I) is useful as an intermediate material for the production of medicines and agricultural chemicals. For example, it is known that the phenylhydrazine-β-carboxylate compound (I) is produced by reacting a phenylhydrazine compound with an alkyl halide carbonate, and the resulting phenylhydrazine-β-carboxylate compound (I) contains various impurities. As a method for purification of a crude product of the phenylhydrazine-β-carboxylate compound (I), for example, National Publication of International Patent Application No. H07-502267 describes a method of washing the crude product with water.

[0005]

However, in the above-mentioned conventional method, there is a problem that when the chloroaniline compound (II) derived from impurities contained in a phenylhydrazine compound as a raw material is contained in the crude product of the phenylhydrazine-β-carboxylate compound (I),

the chloroaniline compound (II) cannot necessarily be sufficiently removed.

SUMMARY OF THE INVENTION

[0006]

Thus, an object of the present invention is to provide a method for purification to obtain a purified product of the phenylhydrazine-β-carboxylate compound (I) having a reduced concentration of the chloroaniline compound (II) by efficiently separating and removing the chloroaniline compound (II) contained in the crude product of the phenylhydrazine-β-carboxylate compound (I) while preventing loss of the phenylhydrazine-β-carboxylate compound (I).

[0007]

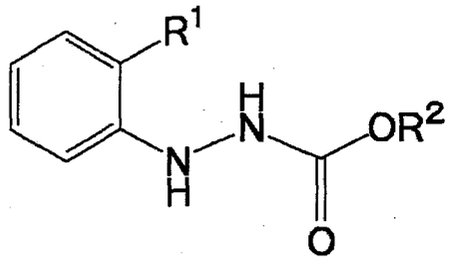
As a result of intensive studies for solving the above-mentioned problem, the present inventors have completed the present invention. That is, the present invention includes the following constitutions.

[0008]

(1) A method for purification of a phenylhydrazine-β-carboxylate compound represented by the formula (I):

[0009]

[Chemical Formula 3]

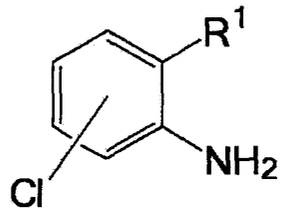


(I)

wherein R^1 represents a hydrogen atom, an alkyl group, a cycloalkyl group, an alkenyl group, an aralkyl group, an alkoxy group, an aryl group, an aralkyloxy group, an aryloxy group or a carboxyalkyl group, and R^2 represents an alkyl group with 1 to 4 carbon atoms, the method comprising mixing a crude product of the phenylhydrazine-β-carboxylate compound represented by the formula (I) containing a compound represented by the formula (II):

[0010]

[Chemical Formula 4]



(II)

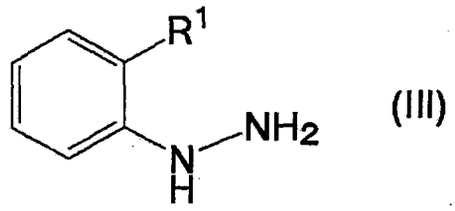
wherein R^1 represents the same meaning as described above with water and an organic solvent separable from water in the presence of an inorganic acid, and then separating the mixture into an oil layer containing the phenylhydrazine-β-carboxylate compound represented by the formula (I) and an aqueous layer.

(2) The method for purification according to (1), wherein the crude product is obtained by reacting a

phenylhydrazine compound represented by the formula (III):

[0011]

[Chemical Formula 5]

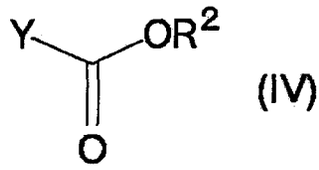


(III)

wherein R^1 represents the same meaning as described above, with an alkyl halide carbonate represented by the formula (IV):

[0012]

[Chemical Formula 6]

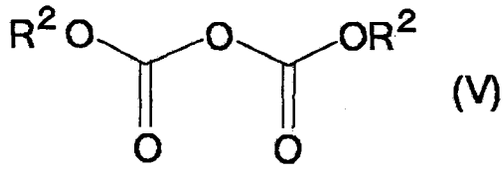


(IV)

wherein R^2 represents the same meaning as described above, and Y represents a halogen atom, or a dialkyldicarbonate represented by the formula (V):

[0013]

[Chemical Formula 7]



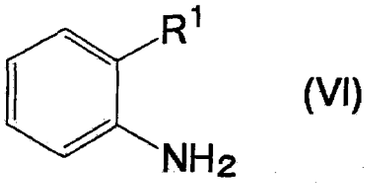
(V)

wherein R^2 represents the same meaning as described above, the phenylhydrazine compound represented by the formula (III) being obtained by reacting a compound

represented by the formula (VI):

[0014]

[Chemical Formula 8]

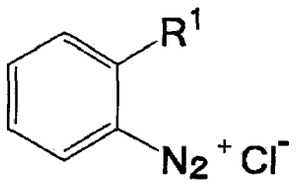


(VI)

wherein R^1 represents the same meaning as described above, with a diazotization agent in the presence of hydrogen chloride to obtain a diazonium salt represented by the formula (VII):

[0015]

[Chemical Formula 9]



(VII)

wherein R^1 represents the same meaning as described above, reacting the diazonium salt represented by the formula (VII) with at least one selected from the group consisting of sulfites and bisulfites in the presence of water, and then subjecting the reactant to a contact treatment with an acid.

(3) The method for purification according to (1) or (2), wherein the mixing is carried out at 30 to 90°C.

(4) The method for purification according to any of (1) to (3), wherein the inorganic acid is hydrogen chloride

or sulfuric acid.

(5) The method for purification according to any of (1) to (4), wherein R^1 in the formulas (I), (II) and (III), (VI) and (VII) is an alkoxy group.

(6) The method for purification according to any of (1) to (5), wherein R^2 in the formulas (I), (IV) and (V) is a methyl group.

[0016]

Effect of the Invention

It is made possible by the present invention to efficiently separate and remove the chloroaniline compound (II) contained in the crude product of the phenylhydrazine-β-carboxylate compound (I) while preventing loss of the phenylhydrazine-β-carboxylate compound (I), and to obtain a purified product of the phenylhydrazine-β-carboxylate compound (I) having a reduced concentration of the chloroaniline compound (II).

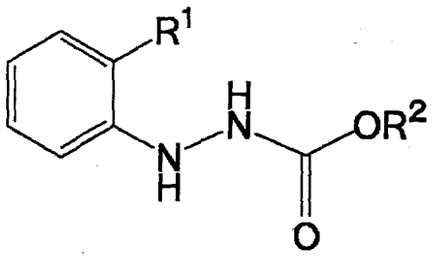
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0017]

In the present invention, the phenylhydrazine-β-carboxylate compound (I) is a compound represented by the formula (I):

[0018]

[Chemical Formula 10]



(I)

wherein R^1 represents a hydrogen atom, an alkyl group, a cycloalkyl group, an alkenyl group, an aralkyl group, an alkoxy group, an aryl group, an aralkyloxy group, an aryloxy group or a carboxyalkyl group, and R^2 represents an alkyl group with 1 to 4 carbon atoms.

[0019]

The alkyl group as R^1 in the formula (I) is preferably an alkyl group with 1 to 6 carbon atoms, and examples thereof include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a s-butyl group, a t-butyl group, a pentyl group, a 2-methyl butyl group, a 3-methyl butyl group, a hexyl group, a 2-methyl pentyl group, a 3-methyl pentyl group and the like. The cycloalkyl group is preferably a cycloalkyl group with 3 to 6 carbon atoms, and examples thereof include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group and the like. The alkenyl group is preferably an alkenyl group with 2 to 6 carbon atoms, and examples thereof include a vinyl group, an allyl group, a 2-methyl allyl group, an isopropenyl group, a 1-propenyl group, a 1-butenyl group, a 2-butenyl

group, a 3-butenyl group, a 1-methyl-1-propenyl group, a 1-methyl-2-propenyl group, a 2-methyl-1-propenyl group, a 2-methyl-2-propenyl group, a 1-pentenyl group, a 2-pentenyl group, a 3-pentenyl group, a 4-pentenyl group, a 1-methyl-1-butenyl group, a 2-methyl-1-butenyl group, a 3-methyl-1-butenyl group, a 1-methyl-2-butenyl group, a 2-methyl-2-butenyl group, a 3-methyl-2-butenyl group, a 2-methyl-3-butenyl group, a 2-methyl-2-pentenyl group, a 3-methyl-2-pentenyl group and the like. Examples of the aralkyl group include a benzyl group, a phenethyl group, a 3-phenyl propyl group, a benzhydryl group, a trityl group, a triphenyl ethyl group, a (1-naphthyl)methyl group, a (2-naphthyl)methyl group and the like. The alkoxy group is preferably an alkoxy group with 1 to 6 carbon atoms, and examples thereof include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a s-butoxy group, a t-butoxy group, a pentyloxy group, a hexyloxy group and the like. Examples of the aryl group include a phenyl group, a naphthyl group, an anthranil group, a phenanthryl group, a tolyl group, a xylyl group and the like. Examples of the aralkyloxy group include a benzyloxy group, a phenethyloxy group and the like. Examples of the aryloxy group include a phenyloxy group, a naphthyloxy group and the like. Examples of the carboxyalkyl group include a carboxymethyl group, a 1-

carboxyethyl group, a 2-carboxyethyl group and the like. Of these, in the case of the phenylhydrazine-β-carboxylate compound (I) in which R^1 is the alkoxy group, the method according to the present invention is advantageously adopted. Among these alkoxy groups, preferred is a methoxy group.

[0020]

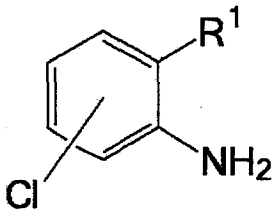
Examples of the alkyl group with 1 to 4 carbon atoms as R^2 in the formula (I) include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a s-butyl group and a t-butyl group. Of these, in the case of the phenylhydrazine-β-carboxylate compound (I) in which R^2 is the methyl group, the method according to the present invention is advantageously adopted.

[0021]

The crude product of the phenylhydrazine-β-carboxylate compound (I) to be subjected to the method for purification according to the present invention contains various impurities depending on its preparation method, and contains at least a compound represented by the formula (II) [a chloroaniline compound (II)]:

[0022]

[Chemical Formula 11]



(II)

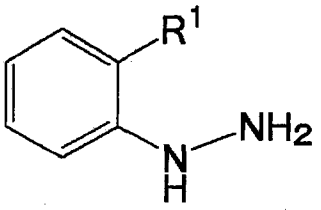
wherein R^1 represents the same meaning as described above. In the present invention, the crude product to be subjected to purification preferably has a chloroaniline compound (II) content of 0.1 to 10 parts by weight based on 100 parts by weight of the phenylhydrazine-β-carboxylate compound (I).

[0023]

Although the preparation method for the crude product of the phenylhydrazine-β-carboxylate compound (I) is not particularly limited as long as the crude product is composed mainly of the phenylhydrazine-β-carboxylate compound (I) and contains the chloroaniline compound (II) as an impurity, an example thereof includes a method of reacting a phenylhydrazine compound represented by the formula (III) [hereinafter, sometimes referred to as a phenylhydrazine compound (III)]:

[0024]

[Chemical Formula 12]



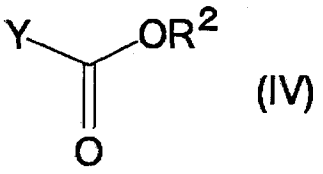
(III)

wherein R^1 represents the same meaning as described

above, with an alkyl halide carbonate represented by the formula (IV) [hereinafter, sometimes referred to as an alkyl halide carbonate (IV)]:

[0025]

[Chemical Formula 13]

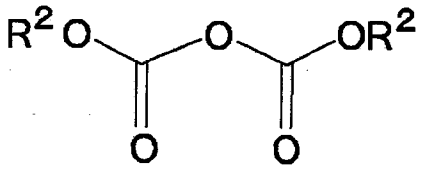


(IV)

wherein R^2 represents the same meaning as described above, and Y represents a halogen atom, or a dialkyldicarbonate represented by the formula (V) [hereinafter, sometimes referred to as a dialkyldicarbonate (V)]:

[0026]

[Chemical Formula 14]

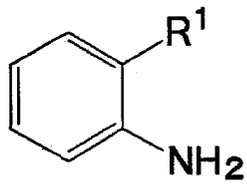


(V)

wherein R^2 represents the same meaning as described above, the phenylhydrazine compound represented by the formula (III) being obtained by reacting a compound represented by the formula (VI) [hereinafter, sometimes referred to as ortho-substituted anilines (VI)]:

[0027]

[Chemical Formula 15]

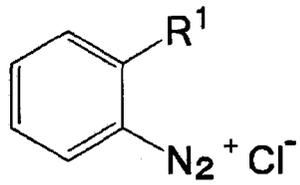


(VI)

wherein R^1 represents the same meaning as described above, with a diazotization agent in the presence of hydrogen chloride to obtain a diazonium salt represented by the formula (VII) [hereinafter, sometimes referred to as a diazonium salt (VII)]:

[0028]

[Chemical Formula 16]



(VII)

wherein R^1 represents the same meaning as described above, reacting the diazonium salt represented by the formula (VII) with at least one selected from the group consisting of sulfites and bisulfites in the presence of water, and then subjecting the reactant to a contact treatment with an acid.

[0029]

In the reaction of the ortho-substituted anilines (VI) with the diazotization agent [hereinafter, sometimes referred to as a diazotization reaction] in the presence of hydrogen chloride, examples of the diazotization agent include nitrogen oxides, nitrites, nitrite esters and the

like. Examples of the nitrogen oxides include nitrous acid, nitrogen monoxide, nitrogen dioxide and the like, examples of the nitrites include sodium nitrite, potassium nitrite and the like, and examples of the nitrite esters include n-butyl nitrite, i-butyl nitrite, n-pentyl nitrite, i-pentyl nitrite and the like. The reaction temperature of the diazotization reaction is in the range of usually -20 to 20°C, preferably -10 to 10°C, and more preferably -5 to 5°C. In the diazotization reaction, a solvent containing water is usually used. As the solvent containing water, water alone may be used, or a mixed solvent of water and an organic solvent may be used, but a solvent including water alone is preferred. Examples of the organic solvent include alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons and the like, and two or more thereof may also be used in combination if necessary. By the diazotization reaction, a chloroaniline compound (II) is produced as a by-product, so that the chloroaniline compound (II) is contained in the finally obtained crude product of the phenylhydrazine-β-carboxylate compound (I).

[0030]

In the reaction of the diazonium salt (VII) with at least one selected from the group consisting of sulfites and bisulfites in the presence of water [hereinafter,

sometimes referred to as a reductive reaction], examples of the sulfite as at least one selected from the group consisting of sulfites and bisulfites include sulfurous acid, ammonium sulfite, sodium sulfite, potassium sulfite and the like. Moreover, examples of the bisulfites include ammonium bisulfite, sodium bisulfite, potassium bisulfite and the like. The temperature of the reductive reaction is usually 45 to 100°C. In the reductive reaction, an organic solvent may be used. Examples of the organic solvent include alcohols, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons and the like, and two or more thereof may also be used in combination if necessary.

[0031]

In the contact treatment of the reaction mixture obtained by the reductive reaction and an acid, examples of the contact treatment include a method of mixing the reaction mixture with an acid, and the like. The temperature upon the contact treatment is preferably 0 to 30°C. Examples of the acid include inorganic acids such as hydrogen chloride, sulfuric acid, phosphoric acid and nitric acid, and among these inorganic acids, hydrogen chloride or sulfuric acid is preferably used. In the contact treatment, an organic solvent may be used. Examples of the organic solvent include alcohols, aliphatic

hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons and the like, and two or more thereof may be used in combination if necessary. After the contact treatment with an acid, the pH may be adjusted by mixing with a base.

[0032]

The phenylhydrazine compound (III) is obtained by the contact treatment with an acid. The phenylhydrazine-β-carboxylate compound (I) is obtained by reacting the obtained phenylhydrazine compound (III) with the alkyl halide carbonate (IV) or the dialkyldicarbonate (V). The reaction is usually carried out in the presence of a base such as sodium hydroxide, potassium hydroxide or potassium carbonate. Examples of the halogen atom represented by Y in the formula (IV) include chlorine, fluorine, bromine and iodine.

[0033]

Examples of the alkyl halide carbonate (IV) include an alkyl chlorocarbonate, an alkyl bromocarbonate, an alkyl iodocarbonate, and of these, preferred is an alkyl chlorocarbonate. Examples of the alkyl chlorocarbonate include methyl chlorocarbonate, ethyl chlorocarbonate, propyl chlorocarbonate, isopropyl chlorocarbonate, butyl chlorocarbonate, isobutyl chlorocarbonate, s-butyl chlorocarbonate and t-butyl chlorocarbonate. Examples of

the alkyl bromocarbonate include methyl bromocarbonate, ethyl bromocarbonate, propyl bromocarbonate, isopropyl bromocarbonate, butyl bromocarbonate, isobutyl bromocarbonate, s-butyl bromocarbonate and t-butyl bromocarbonate. Examples of the alkyl iodocarbonate include methyl iodocarbonate, ethyl iodocarbonate, propyl iodocarbonate, isopropyl iodocarbonate, butyl iodocarbonate, isobutyl iodocarbonate, s-butyl iodocarbonate and t-butyl iodocarbonate.

[0034]

Examples of the dialkyldicarbonate (V) include di-t-butyldicarbonate, dimethyldicarbonate and the like.

[0035]

In the present invention, the crude product of the phenylhydrazine-β-carboxylate compound (I) containing the chloroaniline compound (II) is mixed with water and an organic solvent separable from water in the presence of an inorganic acid.

[0036]

Examples of the inorganic acid include hydrogen chloride, sulfuric acid, phosphoric acid, nitric acid and the like. Among these inorganic acids, preferred are hydrogen chloride and sulfuric acid, and more preferred is hydrogen chloride.

[0037]

The amount of the inorganic acid used is preferably 0.01 to 1.0 mol, and more preferably 0.05 to 0.5 mol, based on 1 mol of the phenylhydrazine-β-carboxylate compound (I) from the point that the chloroaniline compound (II) can be efficiently removed.

[0038]

In the mixing, the amount of water used is preferably 10 to 1000 parts by weight based on 100 parts by weight of the phenylhydrazine-β-carboxylate compound (I).

[0039]

In the mixing, although the organic solvent separable from water is not particularly limited as long as it is separable from water and capable of dissolving the phenylhydrazine-β-carboxylate compound (I), examples thereof include ketones such as methyl ethyl ketone and methyl isobutyl ketone; aliphatic hydrocarbons such as pentane, hexane, heptane and octane; alicyclic hydrocarbons such as cyclopentane, cyclohexane and methylcyclohexane; aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether and cyclopentyl methyl ether; halogenated hydrocarbons such as dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethylene, 1,1,2,2-tetrachloroethylene, chlorobenzene and o-dichlorobenzene; nitriles such as benzonitrile; nitro compounds such as nitrobenzene; ester

compounds such as ethyl acetate, isopropyl acetate and ethyl benzoate; and aliphatic alcohols with 4 to 12 carbon atoms such as n-butanol, n-hexanol, 2-ethylhexanol and n-dodecanol; and the like, and two or more thereof may also be used in combination if necessary. Of these, preferred is the aromatic hydrocarbon, and the use of toluene is preferred among them.

[0040]

In the mixing, the amount of the organic solvent separable from water used is preferably 10 to 10000 parts by weight, and more preferably 50 to 5000 parts by weight, based on 100 parts by weight of the phenylhydrazine-β-carboxylate compound (I).

[0041]

In the mixing, the mixing temperature is preferably 10 to 100°C, more preferably 30 to 90°C, and still more preferably 50 to 70°C, from the point that the chloroaniline compound (II) can be efficiently removed. The mixing time is appropriately set. Examples of the mixing method include (A) a method of mixing a mixed solution of the organic solvent separable from water and the crude product of the phenylhydrazine-β-carboxylate compound (I) with an aqueous solution of an inorganic acid; (B) a method of mixing a mixed solution of the organic solvent separable from water and the crude product of the

phenylhydrazine-β-carboxylate compound (I) with water and then adding an inorganic acid and mixing the contents; (C) a method of mixing a mixed solution of the organic solvent separable from water and the crude product of the phenylhydrazine-β-carboxylate compound (I) and an aqueous solution of an inorganic acid while simultaneously feeding them into a mixing treatment apparatus; (D) a method of mixing the crude product of the phenylhydrazine-β-carboxylate compound (I), the organic solvent separable from water and an aqueous solution of an inorganic acid in any order, respectively; and (E) a method of mixing the crude product of the phenylhydrazine-β-carboxylate compound (I), the organic solvent separable from water, water and an inorganic acid in any order, respectively; and the like, and preferred is the method of (A). When an aqueous solution of an inorganic acid is used, the inorganic acid content in the aqueous solution is preferably 1 to 30% by weight, and more preferably 2 to 20% by weight. The mixing is usually carried out under around atmospheric pressure, but may be carried out under increased pressure if necessary. The mixing may be carried out by any of a continuous process, a semi-batch process and a batch process.

[0042]

In the present invention, after the mixing, the

mixture is separated into an oil layer containing the phenylhydrazine-β-carboxylate compound (I) and an aqueous layer. It is made possible by the separation to recover a purified product of the phenylhydrazine-β-carboxylate compound (I) as an organic solvent solution. The temperature on the oil-water separation is preferably 10 to 100°C, more preferably 30 to 90°C, and still more preferably 50 to 70°C, from the point that the chloroaniline compound (II) can be efficiently removed. When the oil-water separation is carried out by a batch process, the separation is usually carried out by allowing the mixture to stand, but may be carried out by centrifugation if necessary.

[0043]

By removing the aqueous layer from the oil layer containing the phenylhydrazine-β-carboxylate compound (I) obtained after the oil-water separation, the purified product of the phenylhydrazine-β-carboxylate compound (I) may be recovered as an organic solvent solution. After the oil-water separation, by removing the aqueous layer and then further subjecting the oil layer to an operation such as crystallization, concentration, distillation or chromatography, the purified product of the phenylhydrazine-β-carboxylate compound (I) may be recovered. Moreover, a series of treatment, in which the oil layer

obtained after the aqueous layer is removed is mixed with water and an inorganic acid, the mixture is subjected to the oil-water separation, and then the aqueous layer is removed, may be further repeated one or more times. In addition, before and/or after the series of treatment, washing with water may be carried out. When insoluble matters are generated owing to the mixing or the water washing, it is preferred that the matters be removed by filtration.

[0044]

Examples of an impurity recoverable in the separated aqueous layer include the chloroaniline compound (II) and the like. In the separated aqueous layer, an inorganic acid may be contained, but the aqueous layer may be appropriately purified to be recycled as water or an aqueous solution of an inorganic acid for the mixing. Furthermore, when a trace amount of the phenylhydrazine-β-carboxylate compound (I) is contained in the aqueous layer, an oil layer containing the phenylhydrazine-β-carboxylate compound (I) may be recovered by mixing the aqueous layer with an organic solvent separable from water and subjecting the mixture to the oil-water separation. From the recovered oil layer, the phenylhydrazine-β-carboxylate compound (I) may be recovered by subjecting the oil layer to an operation such as crystallization, concentration,

distillation or chromatography if necessary, and the oil layer may be subjected to the mixing.

[0045]

Examples

Hereinafter, Examples according to the present invention will be shown, but the present invention is not limited thereto. It should be noted that in Examples, a 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester [a compound represented by the formula (I) wherein R^1 is a methoxy group and R^2 is a methyl group] content, an area percentage of chloro-o-anisidine [a compound represented by the formula (II) wherein R^1 is a methoxy group], an o-methoxyphenylhydrazine [a compound represented by the formula (III) wherein R^1 is a methoxy group] content, an o-anisidine [a compound represented by the formula (VI) wherein R^1 is a methoxy group] content, and an o-methoxybenzenediazonium chloride [a compound represented by the formula (VII) wherein R^1 is a methoxy group] content were analyzed and calculated by high performance liquid chromatography.

[0046]

Reference Example 1

[Preparation of o-Methoxybenzenediazonium chloride]

In a 300-mL flask, 20.07 g (0.16 mol) of o-anisidine, 24.63 g of water, and 61.14 g (0.34 mol) of 20% by weight

hydrochloric acid were placed and stirred at room temperature to prepare a solution. The solution was cooled to 0°C with stirring, and 29.20 g (0.17 mol) of a 40% by weight aqueous sodium nitrite solution was added dropwise over 1 hour while maintaining the temperature of the liquid mixture at 0°C to obtain 135.04 g of a liquid mixture (i) containing o-methoxybenzenediazonium chloride. The liquid mixture (i) was analyzed by high performance liquid chromatography, whereupon the o-methoxybenzenediazonium chloride content in the liquid mixture (i) was 20.60% by weight.

[0047]

[Preparation of o-Methoxyphenylhydrazine]

In a 1-L flask, 107.21 g (0.34 mol) of a 33% by weight aqueous sodium bisulfite solution, 34.59 g (0.59 mol) of sodium chloride, and 83.05 g of water were placed and stirred at room temperature to prepare a solution. The solution was added with a 25% by weight aqueous ammonia solution with stirring and adjusted to pH 6.0 to obtain a liquid mixture (A). The obtained liquid mixture (A) was heated to 60°C with stirring, and the whole amount of the liquid mixture (i) obtained in [Preparation of o-Methoxybenzenediazonium chloride] was added at 60°C over 0.5 hours while the 25% by weight aqueous ammonia solution was added to maintain the mixture at pH 6.0. The mixture

was then heated to 75°C and stirred at 75°C for 1 hour, after which it was cooled to 5°C to obtain a reaction mixture (A). The reaction mixture (A) was stirred while maintaining the temperature at 5°C and 84.60 g (0.81 mol) of 35% by weight hydrochloric acid was added dropwise over 2 hours. After the completion of the dropwise addition of hydrochloric acid, the mixture was heated to 25°C and stirred for 1 hour at 25°C to obtain a reaction mixture (B). The obtained reaction mixture (B) was adjusted to pH 9.8 by adding a 48% by weight aqueous sodium hydroxide solution to obtain 598.95 g of a reaction mixture (C). To 454.34 g of the reaction mixture (C), 149.20 g of toluene was added and stirred for 0.5 hours. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand for 0.2 hours, and as an organic phase, 160.64 g of a toluene solution of o-methoxyphenylhydrazine was obtained. The solution was analyzed by high performance liquid chromatography, whereupon the o-methoxyphenylhydrazine content in the solution was 11.19% by weight.

[0048]

[Preparation of Crude Product of 2-(2-Methoxyphenyl)hydrazine-1-carboxylic acid methyl ester]

To 160.64 g (the o-methoxyphenylhydrazine content: 0.13 mol) of the solution of o-methoxyphenylhydrazine in toluene obtained above, 55.39 g (3.07 mol) of water and

20.85 g (0.13 mol) of a 25% by weight aqueous sodium hydroxide solution were added and stirred at 3°C for 0.1 hours. After the stirring, while the obtained liquid mixture was maintained at 3°C with stirring, 11.39 g (0.12 mol) of methyl chlorocarbonate was added dropwise over 0.5 hours. Furthermore, the mixture was stirred at 3°C for 0.5 hours and then heated to 65°C and stirred at 65°C for 0.5 hours. After the stirring, the stirring was stopped, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 0.2 hours, after which the obtained oil layer was added with 16.03 g of water and stirred at 65°C for 0.5 hours. After the stirring, the stirring was stopped, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 0.2 hours, after which the obtained oil layer was added with 101.62 g of toluene and stirred at 65°C for 0.5 hours to obtain 269.72 g of a crude product (i) as a solution of 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester in toluene. The crude product (i) was analyzed by high performance liquid chromatography, whereupon in the crude product (i), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.83% by weight, the area percentage of chloro-o-anisidine was 4.56%, and the o-methoxyphenylhydrazine content was 0% by weight. The yield of 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl

ester based on o-anisidine was 65.0%.

[0049]

Example 1

The crude product (i) (6.30 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 2.51 mmol] was stirred while maintaining the temperature at 65°C, 0.41 g (0.56 mmol) of 5% by weight hydrochloric acid was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.29 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 6.18 g of an oil layer (A) was recovered. The oil layer (A) was analyzed by high performance liquid chromatography, whereupon in the oil layer (A), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.76% by weight (2.44 mmol), and the area percentage of chloro-o-anisidine was 0.23%. From the analyzed values obtained, a 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate and a chloro-o-anisidine removal rate were calculated according to the following equations and shown in Table 1.

[0050]

· 2-(2-Methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate (%) = (2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content in recovered oil layer (mmol)) / (2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content in crude product (mmol)) × 100

· Chloro-o-anisidine removal rate (%) = 100 - [(area percentage of chloro-o-anisidine in recovered oil layer (%)) / (area percentage of chloro-o-anisidine in crude product (%))× 100]

[0051]

Example 2

The crude product (i) (4.45 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 1.78 mmol] was stirred while maintaining the temperature at 65°C, 0.31 g (0.16 mmol) of a 5% by weight aqueous sulfuric acid solution was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.33 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 4.25 g of an oil layer (B) was recovered. The

oil layer (B) was analyzed by high performance liquid chromatography, whereupon in the oil layer (B), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.76% by weight (1.68 mmol), and the area percentage of chloro-o-anisidine was 1.03%. From the analyzed values obtained, the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate and the chloro-o-anisidine removal rate were calculated in the same manner as in Example 1 and shown in Table 1.

[0052]

Comparative Example 1

The crude product (i) (4.49 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 1.79 mmol] was stirred while maintaining the temperature at 65°C, 0.30 g of water was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.29 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 4.34 g of an oil layer (C) was recovered. The oil layer (C) was analyzed by high performance liquid chromatography, whereupon in the oil layer (C), the 2-(2-

methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.80% by weight (1.73 mmol), and the area percentage of chloro-o-anisidine was 3.95%. From the analyzed values obtained, the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate and the chloro-o-anisidine removal rate were calculated in the same manner as in Example 1 and shown in Table 1.

[0053]

Comparative Example 2

The crude product (i) (4.50 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 1.80 mmol] was stirred while maintaining the temperature at 65°C, 0.39 g (0.33 mmol) of a 5% by weight aqueous acetic acid solution was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.30 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 4.26 g of an oil layer (D) was recovered. The oil layer (D) was analyzed by high performance liquid chromatography, whereupon in the oil layer (D), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester

content was 7.73% by weight (1.68 mmol), and the area percentage of chloro-o-anisidine was 2.13%. From the analyzed values obtained, the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate and the chloro-o-anisidine removal rate were calculated in the same manner as in Example 1 and shown in Table 1.

[0054]

Comparative Example 3

The crude product (i) (4.88 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 1.95 mmol] was stirred while maintaining the temperature at 65°C, 0.37 g (0.46 mmol) of a 5% by weight aqueous sodium hydroxide solution was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.32 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 4.67 g of an oil layer (E) was recovered. The oil layer (E) was analyzed by high performance liquid chromatography, whereupon in the oil layer (E), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.51% by weight (1.79 mmol), and the area

percentage of chloro-o-anisidine was 3.04%. From the analyzed values obtained, the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate and the chloro-o-anisidine removal rate were calculated in the same manner as in Example 1 and shown in Table 1.

[0055]

Comparative Example 4

The crude product (i) (5.16 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 2.06 mmol] was stirred while maintaining the temperature at 65°C, 0.37 g (0.33 mmol) of a 5% by weight aqueous potassium hydroxide solution was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.32 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 5.04 g of an oil layer (F) was recovered. The oil layer (F) was analyzed by high performance liquid chromatography, whereupon in the oil layer (F), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.34% by weight (1.89 mmol), and the area percentage of chloro-o-anisidine was 3.02%. From the

analyzed values obtained, the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester recovery rate and the chloro-o-anisidine removal rate were calculated in the same manner as in Example 1 and shown in Table 1.

[0056]

Comparative Example 5

The crude product (i) (5.06 g) [the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content: 2.02 mmol] was stirred while maintaining the temperature at 65°C, 0.34 g (0.12 mmol) of a 5% by weight aqueous potassium carbonate solution was added and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute. The obtained oil layer was stirred while maintaining the temperature at 65°C, added with 0.34 g of water and stirred at 65°C for 1 minute. After the stirring, the mixture was subjected to the oil-water separation by allowing it to stand at 65°C for 1 minute, and 5.06 g of an oil layer (G) was recovered. The oil layer (G) was analyzed by high performance liquid chromatography, whereupon in the oil layer (G), the 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester content was 7.41% by weight (1.91 mmol), and the area percentage of chloro-o-anisidine was 2.03%. From the analyzed values obtained, the 2-(2-methoxyphenyl)hydrazine-

1-carboxylic acid methyl ester recovery rate and the chloro-o-anisidine removal rate were calculated in the same manner as in Example 1 and shown in Table 1.

[0057]

[Table 1]

	Treatment liquid	Recovered oil layer		Compound (I) [1] recovery rate (%)	Compound (II) [2] removal rate (%)
		Compound (I) [1] content (% by weight)	Area percentage of compound (II) [2] (%)		
Reference Example 1	-	7.83	4.56	-	-
Example 1	Hydrochloric acid	7.76	0.23	97.2	95.0
Example 2	Aqueous sulfuric acid	7.76	1.03	94.7	77.4
Comparative Example 1	Aqueous acetic acid	7.80	3.95	96.3	13.4
Comparative Example 2	Water	7.73	2.13	93.5	53.3
Comparative Example 3	Aqueous NaOH	7.51	3.04	91.8	33.3
Comparative Example 4	Aqueous KOH	7.34	3.02	91.6	33.8
Comparative Example 5	Aqueous K_2CO_3	7.41	2.03	94.6	55.5

[0058]

1) Compound (I): 2-(2-Methoxyphenyl)hydrazine-1-carboxylic acid methyl ester

2) Compound (II): Chloro-o-anisidine

[0059]

As shown in Table 1, in Examples 1 to 2, it is made possible to recover 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester at high recovery rates by mixing a solution of 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester in organic solvent as a crude product with an inorganic acid and water, that is, it is

made possible to prevent loss of 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester and efficiently separate and remove chloro-o-anisidine as an impurity. In contrast, in Comparative Example 1 in which a solution of 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester in organic solvent as a crude product was treated with water, and Comparative Examples 2 to 5 in which a solution of 2-(2-methoxyphenyl)hydrazine-1-carboxylic acid methyl ester in organic solvent as a crude product was mixed with an organic acid or base and water, it is understood that the chloro-o-anisidine removal rates are lower.