

DESCRIPTION

PROCESS FOR PREPARING SULFUR-CONTAINING 2-KETOCARBOXYLATE
COMPOUND

5

Technical Field

[0001]

The present invention relates to a process for preparing a sulfur-containing 2-ketocarboxylate compound.

10

Background Art

[0002]

It is known that sulfur-containing 2-ketocarboxylate compounds such as 4-methylthio-2-oxobutyric acid are, for example, useful intermediates for preparing medicaments and agrochemicals.

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[0003]

A conventional process for preparing a sulfur-containing 2-ketocarboxylate compound is disclosed in, for example, Non-patent Document 1. In particular, Table 4 thereof discloses a process of oxidizing D-2-hydroxy-4-(methylthio)butyric acid with an enzyme to prepare 4-(methylthio)-2-oxobutyric acid.

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25 (Prior Art Documents)

[0004]

Non-patent Document 1: Applied Microbiology and
Biotechnology, 1988, vol.28, p.433-439

5 Summary of Invention
(Technical Problem)

[0005]

In the above-mentioned process, it is necessary to use
an enzyme as a reagent. On the other hand, the purpose of
10 the present invention is to provide a novel process for
preparing a sulfur-containing 2-ketocarboxylate compound
without using any enzyme.

(Solution to Problem)

15 [0006]

The present inventors have extensively studied on the
process of a sulfur-containing 2-ketocarboxylate, and then
completed the present invention.

[0007]

20 Namely, the present inventions are as follows:

[1] A process for preparing a sulfur-containing 2-
ketocarboxylate compound comprising a step of oxidizing a
hydroxyacetate compound having an optionally-substituted
sulfur-containing hydrocarbon group at 2-position, in the
25 presence of at least one catalyst selected from the group

consisting of a ruthenium metal and a ruthenium compound.
The sulfur-containing hydrocarbon group used herein means a group comprising sulfur, carbon and hydrogen atoms.

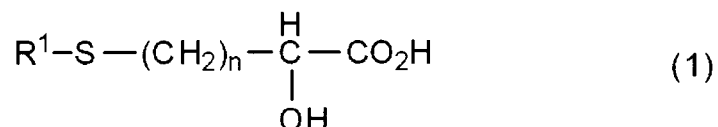
[2] The process of [1] wherein the step of oxidizing
5 a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is carried out under pressurized condition.

[3] The process of [1] or [2] wherein the step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is carried out in the presence of at least one typical metal compound selected from the group consisting
10 of an alkali metal compound and an alkaline earth metal compound.

[4] The process of [3] wherein the typical metal
15 compound is an alkali metal hydroxide.

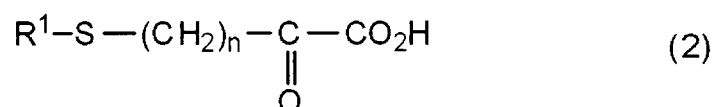
[5] The process of any one of [1] to [4] wherein the step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group
20 at 2-position is carried out in the presence of oxygen.

[6] The process of any one of [1] to [5] wherein the hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is a compound of Formula (1):



wherein R¹ is an optionally-substituted C₁₋₁₂ alkyl group, or an optionally-substituted C₃₋₁₂ cycloalkyl group; and n is an integer of 1 to 4, and

5 the sulfur-containing 2-ketocarboxylate compound is a compound of Formula (2):



wherein R¹ and n are as defined above.

[7] The process of [6] wherein R¹ is methyl group and
10 n is 2.

(Effects of the Invention)

[0008]

The present invention provides a novel process for
15 preparing a sulfur-containing 2-ketocarboxylate compound without using any enzyme.

Description of Embodiments

[0009]

20 Hereinafter, the present invention is explained in detail.

[0010]

The process for preparing a sulfur-containing 2-

ketocarboxylate compound of the present invention comprises a step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position. Hereinafter, a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is optionally referred to as a sulfur-containing hydroxyacetate compound. The oxidation of the sulfur-containing hydroxyacetate compound is optionally referred to as the present reaction. In the present reaction, $-\text{CH}(\text{OH})-$ in the sulfur-containing hydroxyacetate compound is oxidized to $-\text{CO}-$, and thereby the sulfur-containing hydroxyacetate compound is converted into the correspondent sulfur-containing 2-ketocarboxylate compound.

[0011]

In the present reaction, the sulfur-containing hydroxyacetate compound may be in the form of a free acid or a salt. When it is in the form of a salt, H^+ dissociable from COOH in the hydroxyacetic acid is replaced with a cation. The cation includes, for example, an alkali metal ion such as lithium ion, sodium ion and potassium ion; an alkaline earth metal ion such as calcium ion and magnesium ion; a quaternary ammonium ion such as tetramethylammonium ion and tetrabutylammonium ion; and ammonium ion.

[0012]

In the sulfur-containing hydroxyacetate compound, the sulfur-containing hydrocarbon group comprises sulfur, carbon and hydrogen atoms, and the hydrogen atom included
5 in the sulfur-containing hydrocarbon group may be substituted with any group which is inert in the present reaction.

The sulfur-containing hydrocarbon group may be a saturated sulfur-containing hydrocarbon group without any
10 double/multiple bond or an unsaturated sulfur-containing hydrocarbon group with one or more double bonds.

[0013]

The saturated sulfur-containing hydrocarbon group may be in a straight or branched chain form or in a cyclic form.
15 Hereinafter, the straight or branched saturated sulfur-containing hydrocarbon group is optionally referred to as a sulfur-containing saturated open-chain hydrocarbon group, and the cyclic saturated sulfur-containing hydrocarbon group is optionally referred to as a sulfur-containing
20 saturated cyclic hydrocarbon group.

[0014]

The sulfur-containing saturated open-chain hydrocarbon group includes, for example, methylthiomethyl group, ethylthiomethyl group, propylthiomethyl group, isopropylthiomethyl group, tert-butylthiomethyl group, 1-

25

(methylthio)ethyl group, 2-(methylthio)ethyl group, 1-(ethylthio)ethyl group, 2-(ethylthio)ethyl group, 1-(propylthio)ethyl group, 2-(propylthio)ethyl group, 2-(isopropylthio)ethyl group, 2-(tert-butylthio)ethyl group, 1-(methylthio)propyl group, 2-(methylthio)propyl group, 3-(methylthio)propyl group, 3-(ethylthio)propyl group, 3-(propylthio)propyl group, 3-(isopropylthio)propyl group and 2,3-(dimethylthio)propyl group.

[0015]

The sulfur-containing saturated cyclic hydrocarbon group includes, for example, cyclopropylthiomethyl group, cyclobutylthiomethyl group, cyclopentylthiomethyl group, cyclohexylthiomethyl group, 2-(methylthio)cyclopropyl group, 2-(methylthio)cyclobutyl group, 2-(methylthio)cyclopentyl group, 2-(methylthio)cyclohexyl group, 4-(methylthio)cyclohexyl group, 2-methyl-4-(methylthio)cyclohexyl group, 2,4-(dimethylthio)cyclohexyl group, 2-thiacyclohexyl group and 4-thiacyclohexyl group.

[0016]

The sulfur-containing unsaturated hydrocarbon group includes, for example, 2-methylthiophenyl group, 3-methylthiophenyl group, 4-methylthiophenyl group, 2-methyl-4-methylthiophenyl group, 2,4-(dimethylthio)phenyl group, phenylthiomethyl group, 1-(phenylthio)ethyl group, 2-(phenylthio)ethyl group, benzylthiomethyl group, 1-

(benzylthio)ethyl group, 2-(benzylthio)ethyl group, 2-thienyl group, 3-thienyl group and 2-methyl-3-thienyl group.
[0017]

Examples of the inert group which does not interfere
5 with the present reaction include at least one substituent selected from the following Group P1:

an alkyloxy group having 1 to 12 carbon atoms such as methoxy group, ethoxy group, propyloxy group, isopropyloxy group, butyloxy group, isobutyloxy group, sec-butyloxy
10 group, tert-butyloxy group, pentyloxy group and hexyloxy group;

an aralkyloxy group having 7 to 12 carbon atoms such as benzyloxy group;

a cycloalkyloxy group having 3 to 8 carbon atoms such
15 as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group and cyclohexyloxy group;

an aryloxy group having 6 to 12 carbon atoms such as phenoxy group, 2-methylphenoxy group, 4-methylphenoxy group and 4-phenylphenyl group;

20 a perfluoroalkyloxy group having 1 to 6 carbon atoms such as trifluoromethoxy group and pentafluoroethoxy group;

a substituted or unsubstituted amino group (wherein the substituted amino group has, for example, 1 to 12 carbon atoms) such as amino group, methylamino group,
25 dimethylamino group, benzylamino group, tert-

butoxycarbonylamino group and benzyloxycarbonylamino group;

an acyl group having 2 to 12 carbon atoms such as acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group and
5 benzoyl group;

an acyloxy group having 2 to 12 carbon atoms such as acetyloxy group, propionyloxy group, butyryloxy group, isobutyryloxy group, valeryloxy group, isovaleryloxy group, pivaloyloxy group and benzoyloxy group; and

10 a halogen atom such as fluorine atom and chlorine atom.
[0018]

Among the above-defined Group P1, the alkyloxy (alkoxy) group having 1 to 12 carbon atoms and the aryloxy group having 6 to 12 carbon atoms may be substituted with,
15 for example, at least one substituent selected from the following Group P2:

an alkyloxy group having 1 to 12 carbon atoms such as methoxy group, ethoxy group, propyloxy group, isopropyloxy group, butyloxy group, isobutyloxy group, sec-butyloxy
20 group, tert-butyloxy group, pentyloxy group and hexyloxy group;

an aryloxy group having 6 to 12 carbon atoms such as phenoxy group, 2-methylphenoxy group, 4-methylphenoxy group and 4-phenylphenyl group; and

25 a halogen atom such as fluorine atom and chlorine atom.

[0019]

The optionally-substituted sulfur-containing hydrocarbon group is preferably an optionally-substituted sulfur-containing saturated hydrocarbon group; more preferably an optionally-substituted sulfur-containing saturated open-chain hydrocarbon group; and even more preferably a group represented by $R^1-S-(CH_2)_n-$ wherein R^1 is an optionally-substituted C_{1-12} alkyl group or an optionally-substituted C_{3-12} cycloalkyl group, and n is an integer of 1 to 4.

[0020]

In the above-defined $R^1-S-(CH_2)_n-$, the C_{1-12} alkyl group indicated in the definition of R^1 includes, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, tert-butyl group and octyl group. The C_{3-12} cycloalkyl group indicated in the definition of R^1 includes, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group.

The substituent used in the definition of R^1 , i.e. in "the optionally-substituted C_{1-12} alkyl group and the optionally-substituted C_{3-12} cycloalkyl group" includes, for example, an inert group which does not interfere with the present reaction. Preferably, the inert substituent may be at least one selected from the following Group P3:

an aryl group having 6 to 20 carbon atoms such as

phenyl group, 1-naphthyl group, 2-naphthyl group and 4-methylphenyl group;

an alkyloxy group having 1 to 12 carbon atoms such as methoxy group, ethoxy group, propyloxy group, isopropyloxy group, butyloxy group, isobutyloxy group, sec-butyloxy group, tert-butyloxy group, pentyloxy group and hexyloxy group;

an aralkyloxy group having 7 to 12 carbon atoms such as benzyloxy group;

a cycloalkyloxy group having 3 to 8 carbon atoms such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group and cyclohexyloxy group;

an aryloxy group having 6 to 12 carbon atoms such as phenoxy group, 2-methylphenoxy group, 4-methylphenoxy group and 4-phenylphenoxy group;

a perfluoroalkyloxy group having 1 to 6 carbon atoms such as trifluoromethoxy group and pentafluoroethoxy group;

a substituted or unsubstituted amino group (wherein the substituted amino group has, for example, 1 to 12 carbon atoms) such as amino group, methylamino group, dimethylamino group, benzylamino group, tert-butoxycarbonylamino group and benzyloxycarbonylamino group;

an acyl group having 2 to 12 carbon atoms such as acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaloyl group and

benzoyl group;

an acyloxy group having 2 to 12 carbon atoms such as acetyloxy group, propionyloxy group, butyryloxy group, isobutyryloxy group, valeryloxy group, isovaleryloxy group, pivaloyloxy group and benzoyloxy group; and

a halogen atom such as fluorine atom and chlorine atom.

[0021]

Among the above-defined Group P3, the aryl group having 6 to 20 carbon atoms, the alkyloxy (alkoxy) group having 1 to 12 carbon atoms and the aryloxy group having 6 to 12 carbon atoms may be substituted with, for example, at least one substituent selected from the above-defined Group P2.

[0022]

The substituted C₁₋₁₂ alkyl group and the substituted C₃₋₁₂ cycloalkyl group in R¹ includes, for example, benzyl group, naphthalene-1-ylmethyl group, naphthalene-2-ylmethyl group, 4-methylbenzyl group, 3,4-dimethylbenzyl group, 4-methoxybenzyl group, 3,4-dimethoxybenzyl group, 4-phenylbenzyl group, 4-phenoxybenzyl group, methoxymethyl group, ethoxymethyl group, isopropoxyloxymethyl group, butyloxymethyl group, isobutyloxymethyl group, sec-butyloxymethyl group, tert-butyloxymethyl, phenoxymethyl group, 2-methylphenoxymethyl group, 4-methylphenoxymethyl group, 1-phenylethyl group, 2-phenylethyl group, 1-

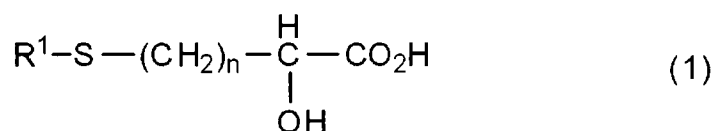
(naphthalene-1-yl)ethyl group, 1-(naphthalene-2-yl)ethyl group,
 1-(4-methylphenyl)ethyl group, 1-(3,4-dimethylphenyl)ethyl group,
 1-(4-methoxyphenyl)ethyl group, 1-(3,4-dimethoxyphenyl)ethyl group,
 1-(4-phenylphenyl)ethyl group,
 5 1-(4-phenoxyphenyl)ethyl group, 2-(methoxy)ethyl group,
 2-(ethoxy)ethyl group, 2-(isopropoxy)ethyl group,
 2-(butyloxy)ethyl group, 2-(isobutyloxy)ethyl group, 2-(sec-butyloxy)ethyl group,
 2-(tert-butyloxy)ethyl group, 2-(phenoxy)ethyl group, 2-(2-methylphenoxy)ethyl group,
 10 2-(4-methylphenoxy)ethyl group, 2-phenylcyclopropyl group and 4-phenylcyclohexyl group.

[0023]

R¹ is preferably a substituted or unsubstituted alkyl group having 1 to 12 carbon atoms; more preferably an alkyl group having 1 to 4 carbon atoms which may be optionally substituted with phenyl group; and even more preferably methyl group.

[0024]

When the optionally-substituted sulfur-containing hydrocarbon group at 2-position of the hydroxyacetate compound is represented by R¹-S-(CH₂)_n-, the hydroxyacetate compound is depicted as a compound of Formula (1):



wherein R¹ and n are as defined above. Hereinafter, the

compound of Formula (1) is optionally referred to as Compound (1). A preferred example of the sulfur-containing hydroxyacetate compound is Compound (1).

[0025]

5 Compound (1) includes, for example, 2-hydroxy-3-methylthiopropionic acid, 3-tert-butylthio-2-hydroxypropionic acid, 3-benzylthio-2-hydroxypropionic acid, 3-ethylthio-2-hydroxypropionic acid, 2-hydroxy-4-(methylthio)butyric acid, 4-ethylthio-2-hydroxybutyric acid,
10 2-hydroxy-4-propylthiobutyric acid, 4-benzylthio-2-hydroxybutyric acid, 2-hydroxy-5-(methylthio)pentanoic acid, 5-(ethylthio)-2-hydroxypentanoic acid, 2-hydroxy-5-(propylthio)pentanoic acid, 5-(benzylthio)-2-hydroxypentanoic acid, 2-hydroxy-6-(methylthio)hexanoic
15 acid, 6-(ethylthio)-2-hydroxyhexanoic acid, 2-hydroxy-6-(propylthio)hexanoic acid, 6-(benzylthio)-2-hydroxyhexanoic acid and salts thereof.

Compound (1) may be commercially available or may be prepared according to the process described in, for example,
20 JP-2006-109834 A.

[0026]

Hereinafter, the step of oxidizing the sulfur-containing hydroxyacetate compound is explained. In the step, the sulfur-containing hydroxyacetate compound is
25 converted into the correspondent sulfur-containing 2-

ketocarboxylate compound through the present reaction.

[0027]

The present reaction is carried out in the presence of at least one catalyst selected from the group consisting of ruthenium metal and a ruthenium compound. Hereinafter, at least one catalyst selected from the group consisting of ruthenium metal and the ruthenium compound is optionally referred to as a ruthenium catalyst.

[0028]

The ruthenium compound includes, for example, ruthenium oxide and ruthenium hydroxide.

[0029]

Regarding the ruthenium catalyst, at least one catalyst selected from the group consisting of ruthenium metal and a ruthenium compound is preferably a carrier-supported catalyst (hereinafter, optionally referred to as a carrier-supported ruthenium catalyst).

The carrier includes at least one selected from the group consisting of, for example, active carbon, alumina (Al_2O_3), silica (SiO_2), zeolite, diatomaceous earth, magnesium oxide, titanium oxide, zirconium oxide, hydroxyapatite, and hydrotalcite. The carrier preferably has a large surface area in order to increase the activity of the catalyst.

The carrier-supported ruthenium catalyst may be

commercially available. Alternatively, it may be prepared by supporting ruthenium metal or a derivative thereof (e.g. ruthenium nitrate, sulfate, formate, acetate, carbonate, halogen, hydroxide or oxide) on the above-mentioned carrier
5 by coprecipitation method or impregnation method, and if necessary, the resultant is treated by burning or hydrogen reduction.

[0030]

The amount of the ruthenium catalyst used herein may
10 vary depending on the form thereof. For example, it may be in the range of 0.1 wt% to 100 wt% of the sulfur-containing hydroxyacetate compound. The amount of ruthenium contained in the ruthenium catalyst is preferably 0.001 mol or more per 1 mol of the sulfur-containing hydroxyacetate compound;
15 and from a practical viewpoint, it should be 0.5 mol or less per 1 mol thereof.

[0031]

Preferably, the present reaction is carried out in the presence of at least one typical metal compound selected
20 from the group consisting of an alkali metal compound and an alkaline earth metal compound.

[0032]

The alkali metal compound includes, for example, an alkali metal carbonate such as sodium carbonate, sodium
25 bicarbonate, potassium carbonate, potassium bicarbonate,

lithium carbonate and lithium hydrogen carbonate, and an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide and lithium hydroxide.

The alkaline earth metal compound includes, for
5 example, an alkaline earth metal carbonate such as magnesium carbonate and calcium carbonate, and an alkaline earth metal hydroxide such as magnesium hydroxide and calcium hydroxide.

Preferably, the typical metal compound is at least one
10 compound selected from the group consisting of an alkali metal hydroxide and an alkaline earth metal. More preferably, the typical metal compound is an alkali metal hydroxide, and even more preferably sodium hydroxide or potassium hydroxide.

15 [0033]

The amount of the typical metal compound used herein is preferably 0.5 mol or more per 1 mol of the sulfur-containing hydroxyacetate compound, and there is no upper limit thereof. However, from a practical viewpoint, it
20 should be 2 mol or less per 1 mol thereof.

[0034]

Preferably, the present reaction is carried out in the presence of oxygen.

The oxygen used herein may be oxygen gas which is
25 undiluted or diluted with an inert gas such as nitrogen, or

oxygen from the air. In addition, the oxygen from the air may be diluted with an inert gas such as nitrogen.

The amount of oxygen used herein is preferably 1 mol or more per 1 mol of the sulfur-containing hydroxyacetate compound, and there is no upper limit thereof.

[0035]

Preferably, the present reaction is carried out in the presence of a solvent.

The solvent includes, for example, a ketone solvent such as acetone and methylethylketone, a nitrile solvent such as acetonitrile and propionitrile, an aromatic solvent such as toluene and benzotrifluoride, water, and a mixed solvent thereof. The solvent is preferably water, a ketone solvent or an aromatic solvent; and more preferably water or toluene.

The amount of the solvent used herein is not limited to a particular amount, but from the viewpoint of volumetric efficiency, the amount is preferably not more than 100 parts by weight per 1 part by weight of the sulfur-containing hydroxyacetate compound.

[0036]

In the present reaction, the addition order of each reagent is not limited. A preferred embodiment of the procedure includes, for example, a procedure which comprises mixing the sulfur-containing hydroxyacetate

compound, solvent, a typical metal compound and a ruthenium catalyst, and then mixing the mixture and oxygen.

[0037]

The present reaction may be carried out under a
5 reduced pressure condition, a normal pressure condition or
a pressurized condition. Preferably, it is carried out
under a normal pressure condition or a pressurized
condition; and more preferably, it is carried out under a
pressurized condition. The pressurized condition is, for
10 example, 0.2 to 10 MPaG (gauge pressure).

[0038]

The reaction temperature of the present reaction may
vary depending on factors such as the concentration of the
sulfur-containing hydroxyacetate compound contained in the
15 reaction mixture and the amount of the ruthenium catalyst.
Preferably, the reaction temperature is in the range of
20°C to 150°C. When the reaction temperature is lower than
20°C, the present reaction tends to proceed slowly, while
when it is higher than 150°C, the selectivity rate of the
20 present invention tends to decrease.

[0039]

The reaction can be monitored by analytical methods
such as gas chromatography, high performance liquid
chromatography, thin-layer chromatography, nuclear magnetic
25 resonance spectrum analysis, and infrared absorption

spectrum analysis.

[0040]

For example, the sulfur-containing 2-ketocarboxylate compound can be isolated as follows. After the reaction is completed, the resultant reaction mixture is filtered to remove the ruthenium catalyst, and the filtrate is optionally neutralized with mineral acids such as sulfuric acid and hydrochloric acid. Then, the mixture can be concentrated, cooled, or mixed with for example, acetone to isolate the sulfur-containing 2-ketocarboxylate compound as a solid. In case that the sulfur-containing 2-ketocarboxylate compound is a lipophilic compound, it may be isolated as follows. After the reaction is completed, the resultant reaction mixture is filtered to remove the ruthenium catalyst; the filtrate is mixed with a water-immiscible solvent, extracted, concentrated, and cooled to isolate the sulfur-containing 2-ketocarboxylate compound. The water-immiscible solvent includes, for example, an ester solvent such as ethyl acetate and an ether solvent such as methyl tert-butyl ether. In addition, the amount of the water-immiscible solvent used herein is not limited to a particular amount.

The isolated sulfur-containing 2-ketocarboxylate compound can be purified by methods such as distillation, column chromatography and crystallization.

[0041]

The sulfur-containing 2-ketocarboxylate compound prepared by the above-mentioned process has an optionally-substituted sulfur-containing hydrocarbon group. The optionally-substituted sulfur-containing hydrocarbon group in the sulfur-containing 2-ketocarboxylate compound is the same as that of the above-mentioned sulfur-containing hydroxyacetate compound. The sulfur-containing 2-ketocarboxylate compound may be in the form of a free acid or a salt. When it is in the form of a salt, H^+ dissociable from COOH in the sulfur-containing 2-ketocarboxylate is replaced with a cation which is the same as the above-listed cation in the sulfur-containing hydroxyacetate compound.

[0042]

The sulfur-containing 2-ketocarboxylate compound includes, for example, 3-methylthio-2-oxopropionic acid, 3-tert-butylthio-2-oxopropionic acid, 3-benzylthio-2-oxopropionic acid, 3-ethylthio-2-oxopropionic acid, 4-methylthio-2-oxobutyric acid, 4-ethylthio-2-oxobutyric acid, 2-oxo-4-propylthiobutyric acid, 4-benzylthio-2-oxobutyric acid, 5-methylthio-2-oxopentanoic acid, 5-(ethylthio)-2-oxopentanoic acid, 2-oxo-5-(propylthio)pentanoic acid, 5-(benzylthio)-2-oxopentanoic acid, 6-methylthio-2-oxohexanoic acid, 6-(ethylthio)-2-oxohexanoic acid, 2-oxo-

6-(propylthio)hexanoic acid, 6-(benzylthio)-2-oxohexanoic acid and salts thereof.

(Example)

5 [0043]

Hereinafter, the present invention is illustrated in more detail with some examples.

[0044]

10 In the following examples, each reaction mixture was analyzed with high performance liquid chromatograph (manufactured by Shimadzu Corporation) under the analysis conditions shown below, and each conversion rate and each selectivity rate were calculated using the formulae shown below.

15 [0045]

Analysis Conditions:

LC column: Lichrosorb-RP-8

Column temperature: 40°C

Mobile phase: acetonitrile/water = 5/95

20 Additive agent: sodium 1-pentanesulfonate

Concentration of additive agent: 2.5 mmol/L

pH of mobile phase; pH 3 (adjusted by adding 40 % phosphoric acid)

Flow rate: 1.5 mL/min

25 Detection wavelength: 210 nm

Measurement time: 60 min

[0046]

Calculation of conversion rate:

Conversion rate (%) =

5 100 (%) - [Peak area of Compound (1) (%)]

[0047]

Calculation of Selectivity rate:

Selectivity rate (%) =

[Peak area of Compound (2)] /

10 (Peak area of all products) x 100

[0048]

Example 1

A 60 mL autoclave was charged with 150 mg of 2-hydroxy-4-(methylthio)butyric acid, 2.29 g of water, 45 mg
15 of potassium hydroxide and 100 mg of 5 % Ru/Al₂O₃ (manufactured by Wako Pure Chemical Industries, Ltd.), and the mixture was stirred. After the autoclave was pressurized to 2 MPaG (gauge pressure) with 30 % oxygen / 70 % nitrogen, the mixture was heated to 80°C and stirred
20 for 6 hours. A portion of the reaction mixture was filtered to remove Ru/Al₂O₃, and the filtrate was analyzed by high performance liquid chromatography to find that the conversion rate of 2-hydroxy-4-(methylthio)butyric acid was 11 % and the selectivity rate of 4-(methylthio)-2-oxobutyric acid was 42 %.
25

[0049]

Example 2

A 60 mL autoclave was charged with 150 mg of 2-hydroxy-4-(methylthio)butyric acid, 2.25 g of toluene and
5 100 mg of 5 % Ru/Al₂O₃ (manufactured by Wako Pure Chemical Industries, Ltd.), and the mixture was stirred. After the autoclave was pressurized to 2 MPaG (gauge pressure) with 30 % oxygen / 70 % nitrogen, the mixture was heated to 80°C and stirred for 6 hours. A portion of the reaction mixture
10 was filtered to remove Ru/Al₂O₃, and the filtrate was analyzed by high performance liquid chromatography to find that the conversion rate of 2-hydroxy-4-(methylthio)butyric acid was 2 % and the selectivity rate of 4-(methylthio)-2-oxobutyric acid was 49 %.

[0050]

Example 3

A 60 mL autoclave was charged with 150 mg of 2-hydroxy-4-(methylthio)butyric acid, 2.25 g of water, 45 mg of potassium hydroxide and 100 mg of 5 % Ru/Al₂O₃, and the
20 mixture was stirred. After the autoclave was pressurized to 2 MPaG (gauge pressure) with nitrogen, the mixture was heated to 80 °C and stirred for 6 hours. A portion of the reaction mixture was filtered to remove Ru/Al₂O₃, and the filtrate was analyzed by high performance liquid
25 chromatography to find that the conversion rate of 2-

hydroxy-4-(methylthio)butyric acid was 2 % and the selectivity rate of 4-(methylthio)-2-oxobutyric acid was 61 %.

[0051]

5 Example 4

A 60 mL autoclave was charged with 150 mg of 2-hydroxy-4-(methylthio)butyric acid, 2.25 g of water, 45 mg of potassium hydroxide and 220 mg of $\text{Ru(OH)}_x/\text{Al}_2\text{O}_3$ (see, Angewandte Chemie International Edition 2002, Vol.41, 10 p.4538-4542), and the mixture was stirred. After the autoclave was pressurized to 2 MPaG (gauge pressure) with nitrogen, the mixture was heated to 80 °C and stirred for 6 hours. A portion of the reaction mixture was filtered to remove $\text{Ru(OH)}_x/\text{Al}_2\text{O}_3$, and the filtrate was analyzed by high 15 performance liquid chromatography to find that the conversion rate of 2-hydroxy-4-(methylthio)butyric acid was 2.5 % and the selectivity rate of 4-(methylthio)-2-oxobutyric acid was 39 %.

20 (Industrial Applicability)

[0052]

It is known that sulfur-containing 2-ketocarboxylic acid compounds such as 4-methylthio-2-oxobutyric acid are, for example, useful intermediates for preparing medicaments 25 and agrochemicals. The present invention is an

industrially applicable process for preparing sulfur-containing 2-ketocarboxylic acid compounds.

CLAIMS

1. A process for preparing a sulfur-containing 2-ketocarboxylate compound comprising a step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position in the presence of at least one catalyst selected from the group consisting of a ruthenium metal and a ruthenium compound.

2. The process of claim 1 wherein the step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is carried out under pressurized condition.

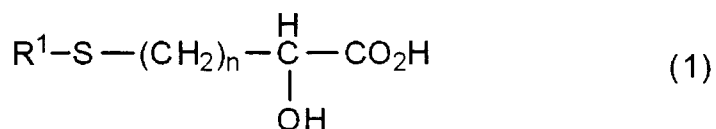
3. The process of claim 1 or 2 wherein the step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is carried out in the presence of at least one typical metal compound selected from the group consisting of an alkali metal compound and an alkaline earth metal compound.

4. The process of claim 3 wherein the typical metal compound is an alkali metal hydroxide.

5. The process of any one of claims 1 to 4 wherein the step of oxidizing a hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is carried out in the presence of oxygen.

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6. The process of any one of claims 1 to 5 wherein the hydroxyacetate compound having an optionally-substituted sulfur-containing hydrocarbon group at 2-position is a compound of Formula (1):

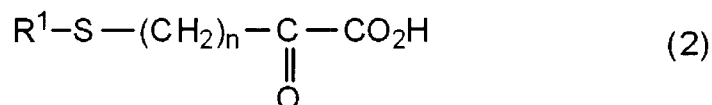


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wherein R^1 is an optionally-substituted C_{1-12} alkyl group, or an optionally-substituted C_{3-12} cycloalkyl group; and n is an integer of 1 to 4, and

the sulfur-containing 2-ketocarboxylate compound is a compound of Formula (2):

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wherein R^1 and n are as defined above.

7. The process of claim 6 wherein R^1 is methyl group and n is 2.

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