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(54) Title: PROCESS FOR PRODUCTION OF SUBSTITUTED OR UNSUBSTITUTED CATECHOL O, O-DIACETIC ACID ESTERS

(57) Abstract: A process to produce a substituted or unsubstituted catechol O, O-diacetic acid ester in a relatively mild condition by reacting a substituted or unsubstituted catechol with a haloacetate in the presence of a base in a first solvent, before mixing with a second solvent to precipitate and collect the product.

Process for production of substituted or unsubstituted catechol O,O-diacetic acid esters

TECHNICAL FIELD

The present invention relates to the production of substituted or unsubstituted catechol O,O-diacetic acid esters.

BACKGROUND

It is known in the art that substituted or unsubstituted catechol O,O-diacetic acid esters, such as 4-methyl-catechol O,O-dimethyl acetate, can be produced by the reaction between corresponding catechols and haloacetates.

US3799892 and US3517031 disclose that substituted and unsubstituted catechol O,O-diacetic acid esters can be prepared according to the procedure of W. Carter and W. Trevor Lawrence, J. Chem. Soc., vol. 77, page 1222 (1900).

CN101580470A discloses that catechol O,O-diethyl acetate can be produced from catechol and chloroacetonitrile or ethyl bromoacetate.

CN101544564A discloses that 4-methyl-catechol O,O-dimethyl acetate can be produced from 4-methyl-catechol, methyl chloroacetate, and triethylamine, through filtration, vacuum distillation, and ethyl acetate recrystallization.

Zhang et al, Chemical Papers 67 (6) 586–593 (2013), discloses the synthesis of Calone 1951® via successive Williamson reaction, Dieckmann condensation, and hydrolysis-decarboxylation reaction. In the Williamson reaction, 4-methyl-catechol O,O-dimethyl acetate was synthesized from 4-methylcatechol and methyl bromoacetate with KI as catalyst.

However, existing processes to produce catechol O,O-diacetic acid esters usually involve complicated after-treatments to collect the product, such as vacuum distillation carried out under reduced pressure and/or heat.

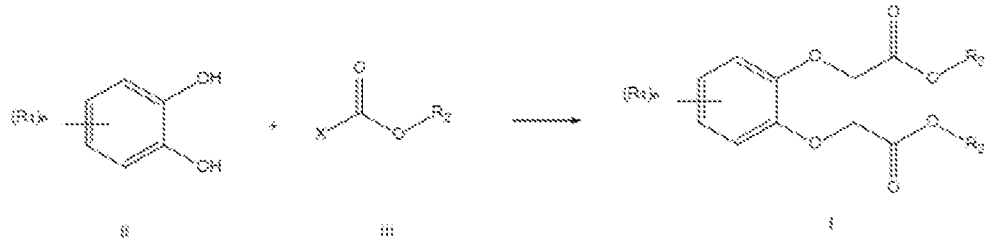
There still exists in the present field a wish to make further improvements to the process for production of substituted or unsubstituted catechol O,O-diacetic acid esters from various aspects.

BRIEF DESCRIPTION OF THE INVENTION

The inventors of the present invention have unexpectedly discovered that a substituted or unsubstituted catechol O,O-diacetic acid ester can be produced in a relatively mild condition by the processes of the present invention.

One subject matter of the present invention is a new process for production of substituted or unsubstituted catechol O,O-diacetic acid esters of formula I, by way of a

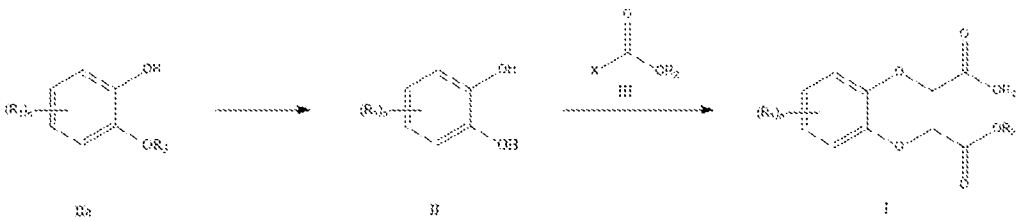
reaction between a substituted or unsubstituted catechol of formula II with a haloacetate of formula III, as shown in the following scheme 1.



Scheme 1

Another subject matter of the present invention is a new process for production of substituted or unsubstituted catechol O,O-diacetic acid esters of formula I as shown in the above scheme 1, wherein the compound of formula II has a bio-based carbon content in the range of 75%-100%.

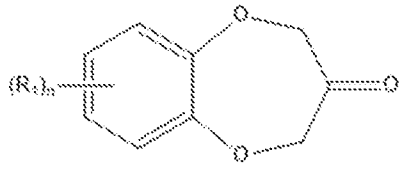
Another subject matter of the present invention is a new process for production of substituted or unsubstituted catechol O,O-diacetic acid esters of formula I, by way of a reaction between a substituted or unsubstituted catechol of formula II with a haloacetate of formula III, wherein the substituted or unsubstituted catechol of formula II is produced by contacting the compound of formula IIa with an aqueous reaction mixture containing an acidic heterogeneous catalyst preferably under an inert gas atmosphere at a temperature of at least 200 °C and a pressure of at least 20 bar, as shown in the following scheme 2.



Scheme 2

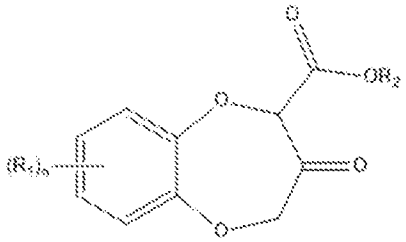
Another subject matter of the present invention is a new process for production of substituted or unsubstituted catechol O,O-diacetic acid esters of formula I as shown in the above scheme 2, wherein the compound of formula IIa has a bio-based carbon content in the range of 75%-100%.

Another subject-matter of the present invention is a new process for production of a compound of formula Ib



Ib

by reacting the compound of formula I with a basic reagent, preferably in an anhydrous organic solvent, to produce the compound of formula Ia



Ia

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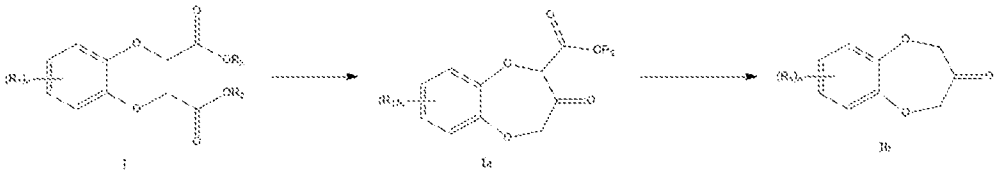
and reacting the compound of formula Ia with an aqueous mineral acid, preferably under reflux of a water-miscible organic solvent, to produce the compound of formula Ib, as shown in the following scheme 3.



Scheme 3

Another subject-matter of the present invention is a new process for production of a compound of formula Ib comprising both the scheme 2 and the scheme 3.

DETAILED DESCRIPTION OF THE INVENTION

For convenience, before further description of the present disclosure, certain terms employed in the specification, and examples are collected here and understood as by a person of skill in the art. The terms used herein have the meanings recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

The articles “a”, “an” and “the” are used to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article.

The term “and/or” includes the meanings “and”, “or” and also all the other possible combinations of the elements connected to this term.

Throughout the description, including the claims, the term "comprising one" should be understood as being synonymous with the term "comprising at least one", unless otherwise specified, and "between" should be understood as being inclusive of the limits. It is specified that, in the continuation of the description, unless otherwise indicated, the values at the limits are included in the ranges of values which are given.

The expression “comprise” should be understood as including equally “consist of” or “consist substantively of”.

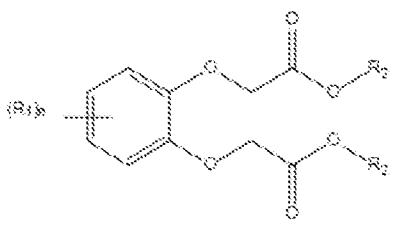
It should be noted that in specifying any numerical range, such as a range of contents or ratios, any particular upper limit can be associated with any particular lower limit, any two particular numerical values can be associated together to form a new numerical range.

If not specified otherwise, a percentage or ppm content is on weight basis.

In the present invention, the expression “bio-based carbon” refers to carbon of renewable origin like agricultural, plant, animal, fungi, microorganisms, marine, or forestry materials living in a natural environment in equilibrium with the atmosphere. The bio-based carbon content is typically evaluated by the means of the carbon-14 dating (also referred to as carbon dating or radiocarbon dating). Furthermore, in the present invention, the “bio-based carbon content” refers to the molar ratio of bio-based carbon to the total carbon of the compound or the product. The bio-based carbon content can preferably be measured by a method consisting in measuring decay process of 14C (carbon-14), in disintegrations per minute per gram carbon (or dpm/gC), through liquid scintillation counting, preferably according to the Standard Test Method ASTM 25 D6866-16. Said American standard test ASTM D6866 is said to be equivalent to the ISO standard 16620-2. According to said standard ASTM D6866, the testing method may preferably utilize AMS (Accelerator Mass Spectrometry) along with IRMS (Isotope Ratio Mass Spectrometry) techniques to quantify the bio-based content of a given product.

In the present invention, the expression “bio-based compound” means the compound is bio-based, or in other words, the compound has a certain bio-based carbon content, as further elaborated below.

Compound of formula I



As specified above, one of the objectives of the present invention is to produce a compound of formula I, which is a substituted or unsubstituted catechol O,O-diacetic acid ester.

In the formula I, each R1 is independently selected from the group consisting of C1-6 alkyl, C2-6 alkenyl, C1-6 alkoxy and C1-6 aldehyde, preferably a C1-4 alkyl, such as methyl, ethyl, propyl, isopropyl or butyl. "C1-6 alkyl" means an alkyl with a carbon number of 1 to 6. "C1-6 alkoxy" means an alkoxy with a carbon number of 1 to 6. "C1-6 aldehyde" means an aldehyde group with a carbon number of 1 to 6. "C2-6 alkenyl" means an alkenyl group with a carbon number of 2 to 6.

In the formula I, n is 0-4, preferably 0-2, such as 0, 1 or 2. When n is 0, formula I is an unsubstituted catechol O,O-diacetic acid ester. When n is 1, R1 can be on any of the two positions on the phenyl group, i.e., on the 3- position or 4- position. When n is 2, the two R1s can be respectively on any of the four positions on the phenyl group, i.e., on the 3-, 4-, 5- or 6- positions. For example, the two R1s can be on the 3- and 4- positions, on the 3- and 5- positions, on the 3- and 6- positions, or on the 4- and 5- positions.

In the formula I, R2 is a C1-6 alkyl, preferably a C1-4 alkyl, such as methyl, ethyl, propyl, isopropyl or butyl.

According to a particular embodiment of the present invention, the compound of formula I may be obtained from a bio-based compound of formula II. In particular the compound of formula II may have a bio-based carbon content above or equal to 75 %, preferably above 80 %, preferably the bio-based carbon content is between 85% and 100%, more preferably between 90% and 100%, more preferably between 98% and 100%, and more preferably between 99% and 100%.

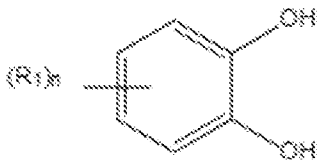
Because of the bio-sourcing of the compound of formula II, the compound of formula I may contain some impurities. Said impurities may be specific to the origin of the compound. For example, the impurities that may be present in the compound of formula I may be the products of a reaction between the impurities present in the compound of formula II with the haloacetate of formula III. Typically the content of each impurity in the bio-based compound of formula I may be comprised between 0.005 and 0.1%, more preferably between 0.01 and 0.08%.

According to a particular embodiment the compound of formula I is 4-methyl catechol dimethylacetate (n=1, R1=R2=Me), the bio-based carbon content of the 4-methyl catechol dimethylacetate is preferably above or equal to 35%, preferably above 40%. In general the bio-based carbon content is between 40% and 100%, more preferably between 40% and 90%, more preferably between 40% and 75%, still more preferably between 40% and 60%, and more preferably between 40% and 55%.

Compound of formula II

According to the present invention, the compound of formula I is produced by a reaction between a compound of formula II and a compound of formula III.

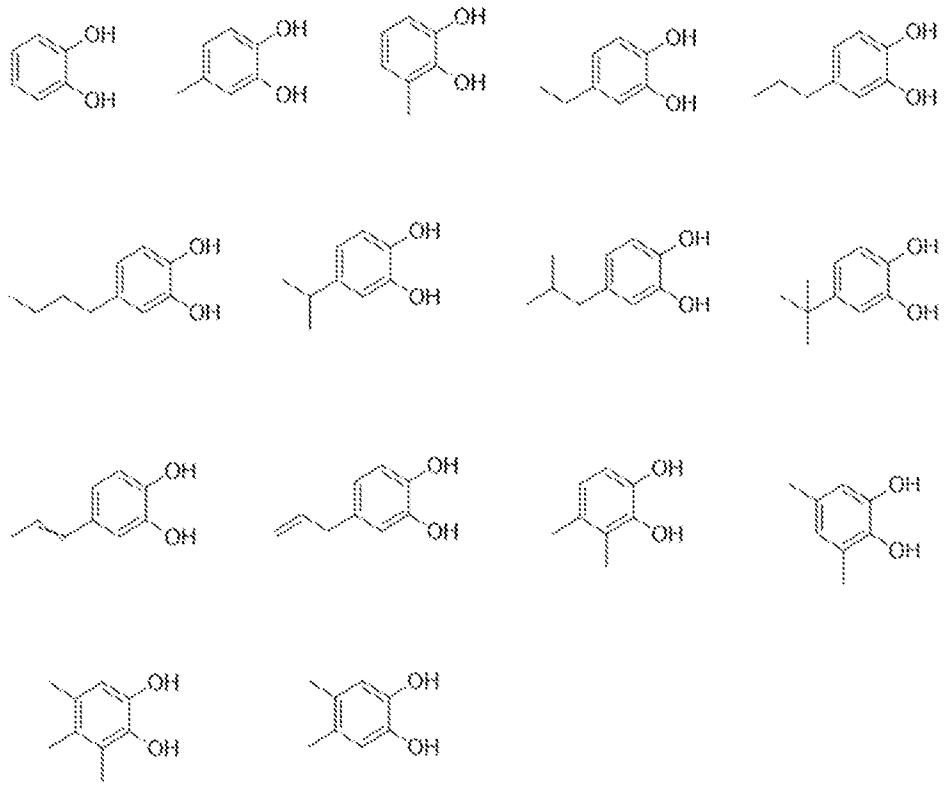
The compound of formula II is a substituted or unsubstituted catechol.



II

In the formula II, the definitions for R1 and n, as well as the specific positions of the R1(s) if any, are the same as in the formula I set forth above.

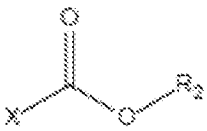
Examples of the compound of formula II comprise:



According to a particular embodiment of the present invention, the compound of formula II may be bio-based. In particular the compound of formula II may have a bio-based carbon content above or equal to 75 %, preferably above 80 %, preferably the bio-based carbon content is between 85% and 100%, more preferably between 90% and 100%, more preferably between 98% and 100%, and more preferably between 99% and 100%.

Because of the bio-sourcing of the raw materials to produce the compound of formula II, said compound of formula II may contain some impurities. Said impurities may be specific to the origin of the compound, Typically the content of each impurity in the bio-based compound of formula II may be comprised between 0.005 and 0.1%, more preferably between 0.01 and 0.08%.

Compound of formula III



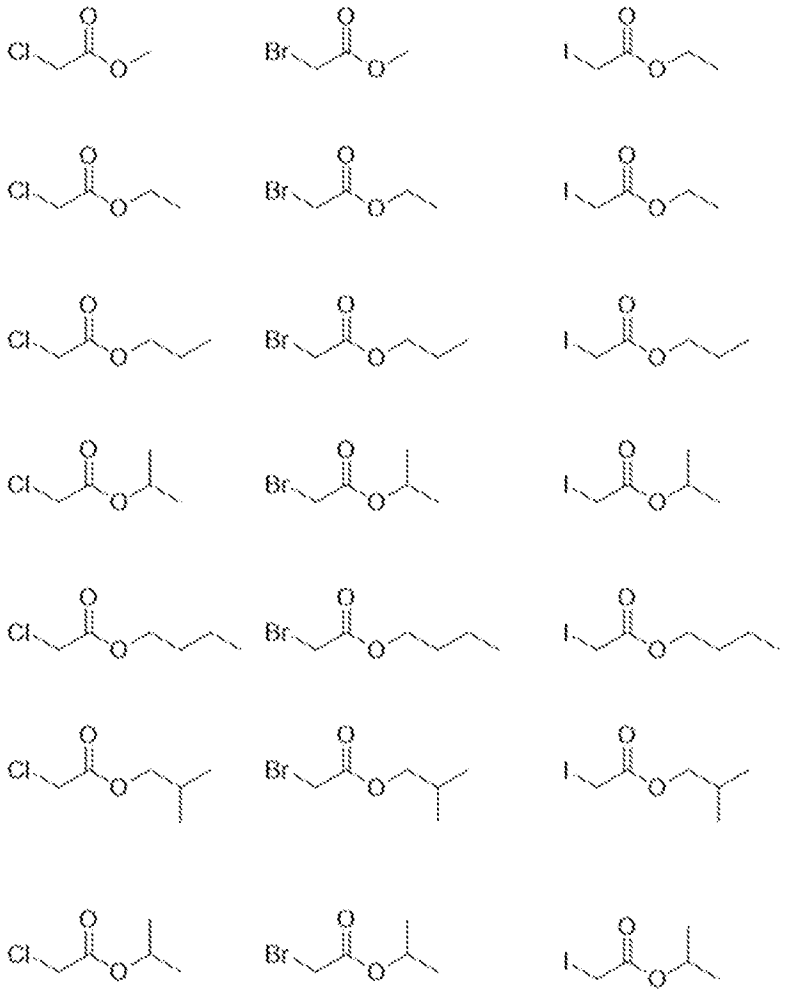
III

In the present invention, the compound of formula III is a haloacetate, or a halogenated acetate.

In the formula III, the definition for R2 is the same as in the formula I set forth above.

In the formula III, X is a halogen, such as F, Cl, Br or I, preferably Cl or Br.

Examples of the compound of formula III comprise:



Production of Compound of formula I

According to the present invention, the compound of formula I is produced by a reaction between a compound of formula II and a compound of formula III, in accordance with scheme 1.

In particular, the process for production of the compound of formula I comprises the following steps:

(i) contacting the compound of formula IIa with an aqueous reaction mixture containing an acidic heterogeneous catalyst to produce the substituted or unsubstituted catechol of formula II;

(ii) reacting the substituted or unsubstituted catechol of formula II with the haloacetate of formula III, to produce the compound of formula I.

Particularly, the step (ii) comprises the following steps:

(ii)(a) reacting the substituted or unsubstituted catechol of formula II with the haloacetate of formula III in the presence of a base in a first solvent;

(ii)(b) mixing the reaction mixture from step (a) with a second solvent to precipitate the compound of formula I, and

(ii)(c) collecting the compound of formula I.

In the step (ii)(a), a base is used in the reaction between the substituted or unsubstituted catechol and the haloacetate. The base can be an inorganic base or an organic base which are customarily used. For example the base can be selected from the group consisting of hydrides, hydroxides and alkoxides of alkali metal and alkali earth metals, such as sodium hydroxide, sodium ethoxide, sodium *tert*-butoxide, potassium *tert*-butoxide or potassium propoxide.

In one aspect of the present invention, the base has a formula of M-OR2, wherein M represents an alkali metal and the definition for R2 is the same as in the formula I set forth above.

In the step (ii)(a), a first solvent is used in the reaction between the compound of formula II and the haloacetate of formula III. The first solvent is a good solvent for the compound of formula I. Preferably, the first solvent is a good solvent for the compound of formula I and the compound of formula II, more preferably the first solvent is a good solvent for the compound of formula I, the compound of formula II, and the compound of formula III. The first solvent is selected from the group consisting of customarily used alcohols, ethers, nitriles, amides, ketones and esters.

In one aspect of the present invention, the first solvent is selected from the group consisting of alcohols such as methanol, ethanol, propanol, isopropanol, 1-butanol and tert-butanol.

In one aspect of the present invention, the first solvent is selected from the group consisting of ethers such as diethyl ether, tetrahydrofuran, methyl tert-butyl ether and diisopropyl ether.

In one aspect of the present invention, the first solvent is selected from the group consisting of esters such as methyl acetate, ethyl acetate, and n-propyl acetate.

In one aspect of the present invention, the first solvent is selected from the group consisting of ethyl nitrile, DMF(N,N-Dimethylformamide), acetone, and MIBK(methyl isobutyl ketone).

In one aspect of the present invention, the first solvent is a mixture of at least two compounds selected from the group consisting of alcohols, ethers, and esters.

In one aspect of the present invention, the reaction of the step (ii)(a) is carried out at a temperature between 25°C and the reflux temperature of the first solvent. In one aspect of the present invention, the reaction mixture of the step (a) is heated to the boiling point of the first solvent.

In one aspect of the present invention, the reaction of the step (ii)(a) is conducted for a period of 1-8 hours, preferably in the range of 2-6 hours, such as 4 or 5 hours.

In one aspect of the present invention, the reaction of the step (ii)(a) is carried out under an inert gas atmosphere, which is in particular selected from the list comprising: N2, CO2, a noble gas, such as He, Ne, Ar, a gaseous alkane such as methane, or a mixture of two or more of the aforementioned gases.

In one aspect of the present invention, the base is added in batches into the reaction mixture of the step (ii)(a). For example, the base, in solid form or in solution form in the first solvent, is added in batches, such as two to four batches, into the mixture of the compound of formula II, haloacetate and first solvent.

In one aspect of the present invention, the compound of formula II, haloacetate and base are added together into the first solvent. In one aspect of the present invention, the compound of formula II, and haloacetate are added together into the first solvent, before addition of the base.

In one aspect of the present invention, the step (ii)(a) is carried out under atmospheric pressure.

In the step (ii)(b), the reaction mixture from step (ii)(a), after completion of the reaction between the compound of formula II and the haloacetate, is mixed with a second solvent to precipitate the compound of formula I. In one aspect of the present invention, the second solvent is charged into the reaction mixture from step (ii)(a).

In one aspect of the present invention, the second solvent is a poor solvent for the compound of formula I.

In one aspect of the present invention, the second solvent is a mixture of the first solvent and a third solvent, which is selected from the group consisting of alcohols, alkanes, esters, ketones and water. In one aspect of the present invention, the third solvent is water.

In the present invention, the term “first solvent” is used equally as the compound formulating the first solvent. For example, in step (ii)(a), a first solvent of methanol is used, and in step (ii)(b), a second solvent, which is a mixture of the first solvent, i.e., methanol, and water, is used.

In one aspect of the present invention, the second solvent is a mixture of the first solvent and water.

In one aspect of the present invention, m1/m2 is in the range of 10-50wt%, preferably 30-45wt%, in which m1 means the total weight of the first solvent in the reaction mixture from step (b), and m2 means the total weight of the first solvent and water in the reaction mixture from step (ii)(b). Notably, m2 is contributed by the weight of the first solvent used in step (ii)(a), the weight of the first solvent comprised in the second solvent used in step (ii)(b), as well as any weight of the first solvent produced during the reaction of the step (ii)(a).

In one aspect of the present invention, m3/m2 is in the range of 1:3 to 1:20, preferably 1:4 to 1:5, by weight, in which m3 means the theoretical weight of the product compound of formula I, and m2 means the total weight of the first solvent and water in the reaction mixture from step (ii)(b).

In the step (ii)(c), the compound of formula I precipitated from the reaction mixture is collected. In one aspect of the present invention, the step (ii)(c) is carried out by filtering the reaction mixture from step (ii)(b), washing the resulting solid and drying the washed solid in vacuum.

According to one aspect of the present invention, the compound of formula I is obtained from a bio-based compound of formula II. Said compound of formula I may therefore contain specific impurities. For example, the impurities that may be present in the compound of formula I may be the products of a reaction between the impurities present in the compound of formula II with the haloacetate of formula III. The purification process may be particularly suitable for the purification of said impurities.

Production of Compound of formula II

In the present invention, the compound of formula II used to produce the compound of formula I can be commercially purchased, or produced in-site. In one aspect of the present invention, the compound of formula II is produced in accordance with WO2019/025535A1, which is incorporated into the present invention by reference.
In one aspect of the present invention, the compound of formula II is produced by contacting the compound of formula IIa (See Scheme 2) with an aqueous reaction mixture containing an acidic heterogeneous catalyst preferably under an inert gas atmosphere at a temperature of at least 200 °C and a pressure of at least 20 bar.
In the formula IIa, R3 is independently selected from an alkyl group which may be linear, branched or cyclic; which may be saturated or containing one or more unsaturated bonds, or which may be an aromatic group; wherein said R3 may optionally further contain one or more heteroatoms and/or one or more substituents.
In one aspect of the present invention, R3 is a C1-6 alkyl, preferably a C1-4 alkyl.
In one aspect of the present invention, the acidic heterogeneous catalyst is selected from the list comprising acidic zeolite, aluminophosphate (AlPO) and silicoaluminophosphate (SAPO).
In one aspect of the present invention, the inert gas is selected from the list comprising: N_2, CO_2, a noble gas, such as He, Ne, Ar, a gaseous alkane such as methane, or a mixture of two or more of the aforementioned gases.
In one aspect of the present invention, the temperature at which the above reaction is carried out is at least 200°C, in particular at least 225 °C, specifically at least 240 °C, more specifically at least 250 °C, and most specifically at least 275 °C. In one aspect of the present invention, the temperature at which the above reaction is carried out is at most 500 °C, and specifically at most 400°C.
In one aspect of the present invention, the pressure at which the above reaction is carried out is at least 20 bar, in particular at least 30 bar, specifically at least 40 bar, and more specifically at least 50 bar.

In one aspect of the present invention, the pressure at which the above reaction is carried out is at most 100 bar, and specifically at most 70 bar.

In one aspect of the present invention, the aqueous reaction mixture may exclusively comprise water as the solvent for the reaction, as this permits minimizing the risk to the occurrence of unwanted side reactions, and this is preferred. The solvent may however also contain one or more organic solvents conventionally used in the reaction of organic compounds, for example an alcohol, for example methanol, ethanol or butanol, dimethylcarbonate, DMSO, DMF or a mixture of two or more of the afore-mentioned solvents. The solvent is preferably selected such that it does not give rise to the formation of unwanted side products, or that it does not show any unwanted reaction with the reactants used. In case the aqueous reaction mixture contains an organic solvent, the volume proportion of the organic solvent will usually be not more than 50 vol. %, preferably not more than 40 or 25 vol. % with respect to the total volume of solvent used, to minimize the risk to the formation of unwanted byproducts caused by the reaction of the solvent with the reaction products or reactants.

The weight percentage of water relative to the mixture of the compound of formula IIa and the aqueous reaction mixture is at least 60%, for example 70%-97%, preferably 80%-90%.

According to a particular embodiment of the present invention, the compound of formula IIa may be bio-based. In particular the compound of formula IIa may have a bio-based carbon content above or equal to 75 %, preferably above 80 %, preferably the bio-based carbon content is between 85% and 100%, more preferably between 90% and 100%, more preferably between 98% and 100%, and more preferably between 99% and 100%.

A compound of formula IIa having a bio-based carbon content above 75% may also be called hereafter “bio-based compound of formula IIa”. It could be naturally obtained from naturally occurring substrates like charcoal oil, lignin, pine wood or alike, by different methods. In particular, different biochemical processes are available. For instance, the US patent application US 2013/0232852 discloses a method for biorefining lignin biomass.

Because of the bio-sourcing, the compound of formula IIa may contain some impurities. Said impurities may be specific to the origin of the compound. For example, the impurities may be selected from the group consisting of phenol, o-cresol, p-cresol, m-cresol, catechol, 4-ethylguaiacol, syringol, eugenol and iso-eugenol. Typically the content of each impurity in the bio-based compound of formula IIa may be comprised between 0.005 and 0.1%, more preferably between 0.01 and 0.08%.

Production of compound of Ib

In the present invention, the compound of formula I can be further processed to produce a compound of formula Ib. In particular, the compound of formula I may be first reacted with a basic reagent to produce a compound of formula Ia, which is then reacted with an aqueous mineral acid to produce the compound of formula Ib.

In one aspect of the present invention, the compound of formula Ib is produced by a process comprising the following steps:

(iii) reacting the compound of formula I with a basic reagent to produce a compound of formula Ia, and

(iv) reacting the compound of formula Ia with an aqueous mineral acid to produce a compound of formula Ib.

In one aspect of the present invention, the compound of formula Ib is produced in accordance with US3799892 or US3517031, which are incorporated into the present invention by reference.

In one aspect of the present invention, the basic reagent is selected from sodamide, sodium alkoxide and potassium alkoxide where alkoxide has from 1 to 4 carbon atoms, trialkylamine where alkyl has from 1 to 4 carbon atoms and sodium hydride.
In one aspect of the present invention, the step (d) is conducted in an anhydrous organic solvent. In one aspect of the present invention, the anhydrous organic solvent is selected from dimethylformamide, tetrahydrofuran, dimethylsulfoxide or ethylene glycol dimethyl ether.

In one aspect of the present invention, the reaction between the compound of formula I with the basic reagent is carried out at a temperature from about 25°C up to the boiling point of said anhydrous organic solvent.

In one aspect of the present invention, the mineral acid is one or more selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid. In one aspect of the present invention, the aqueous mineral acid has a concentration by weight of 2%-10%, preferably 3-7%, more preferably about 5%. For example, the aqueous mineral acid is 5% aqueous hydrochloric acid.

In one aspect of the present invention, the step (iv) is conducted under reflux of a water-miscible organic solvent. The water-miscible organic solvent is preferably selected from ethanol and diethyl ether.

According to a particular embodiment of the present invention, the compound of formula Ib may be bio-based. In particular the compound of formula Ib may have a bio-based carbon content above or equal to 50 %, preferably above 60 %, preferably the bio-based carbon content is between 50% and 100%.

Because of the bio-sourcing of the raw materials and intermediates to produce the compound of formula Ib, the compound of formula Ib may contain some impurities. Said impurities may be specific to the origin of the raw materials and/or intermediates. Typically the content of each impurity in the bio-based compound of formula Ib may be comprised between 0.005 and 0.1%, more preferably between 0.01 and 0.08%.

According to a specific embodiment, the compound of formula Ib is calone (n=1, R1=Me), the bio-based carbon content of calone is preferably above or equal to 40%, preferably above 45%, more preferably above 50%. In general the bio-based carbon

content is between 40% and 100%, more preferably between 50% and 90%, more preferably between 52% and 75%, and more preferably between 52% and 70%.

Processes of the present invention

In one aspect of the present invention, there is provided a new process to produce the compound of formula I starting from the compound of formula II (step (ii)), preferably with a bio-based carbon content in the range of 75%-100%.

In one aspect of the present invention, there is provided a new process to produce the compound of formula I starting from the compound of formula IIa (steps (i)-(ii)), preferably with a bio-based carbon content in the range of 75%-100%, preferably without intermediate purification.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ia starting from the compound of formula I (step (iii)), preferably with a bio-based carbon content in the range of 35%-100%.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ia starting from the compound of formula II (steps (ii)-(iii)), preferably with a bio-based carbon content in the range of 75%-100%, preferably without intermediate purification.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ia starting from the compound of formula IIa (steps (i)-(iii)), preferably with a bio-based carbon content in the range of 75%-100%, preferably without intermediate purification.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ib starting from the compound of formula Ia (step (iv)), preferably with a bio-based carbon content in the range of 35%-100%.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ib starting from the compound of formula I (steps (iii)-(iv)), preferably with a bio-based carbon content in the range of 35%-100%, preferably without intermediate purification.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ib starting from the compound of formula II (steps (ii)-(iv)), preferably with a bio-based carbon content in the range of 75%-100%, preferably without intermediate purification.

In one aspect of the present invention, there is provided a new process to produce the compound of formula Ib starting from the compound of formula IIa (steps (i)-(iv)), preferably with a bio-based carbon content in the range of 75%-100%, preferably without intermediate purification.

Examples

The invention will now be further described in examples. The examples are given by way of illustration and are not intended to limit the specification or the claims in any manner.

The following materials and equipments are used in the examples:

4-methayl guaiacol, also termed as 4-Me GA: AR grade, purchased from Aladdin Chemical Reagent Co., Ltd. and were used without further purification.

β-Zeolite: H and/or ammonium type, purchased from Clariant with a Si/Al ratio of 20-40 and a surface area of 400-800 m2/g.

Autoclave: Parr 300ml Pressure reactor purchased from Parr instrument company.

0.22μm membrane: Hydrophilic PTFE membrane filter, purchased from Shanghai foreneeds biological technology Co., Ltd.

4-methylcatechol: purchased from Shanghai Macklin Biochemical Co.,Ltd., also termed as 4-Me PC.

Methyl chloroacetate: AR grade, purchased from Sinopharm Chemical Reagent Co., Ltd.

Methanol: AR grade, purchased from Sinopharm Chemical Reagent Co., Ltd.

Sodium methoxide: purchased from Shanghai Macklin Biochemical Co.,Ltd.

Example 1 - production of 4-methyl catechol (compound of formula II)

In this example, 4-methyl catechol was produced in accordance with the following process.

205.5g of 4-methyl guaiacol (4-ME-GA), 900.0g of water and 30.0g of β-zeolite were successively charged into a 2 L autoclave at room temperature. Nitrogen gas was pumped into the autoclave until the pressure leveling at 5bar before the autoclave was sealed off from the atmosphere. The autoclave was heated from room temperature to a target temperature of 250°C, in the meantime, the contents inside the autoclave were agitated at a speed of 800rpm. The reaction inside the autoclave was kept at 250°C and 50bar, with agitation, for 3 hours. After this period of time, the autoclave was naturally cooled down to room temperature. The reaction mixture inside the autoclave was obtained and filtrated by a 0.22μm pore size membrane to remove the catalyst zeolite. The resulting reaction mother liquid was purified by distillation to obtain 69.2g of unreacted 4-ME-GA and 116.3g of 4-methyl catechol as a white solid, with a yield of 63% and a selectivity of 95%. The final 4-methyl catechol was analyzed by GC to have a purity of 99.1%.

Example 2 - production of 4-Methyl catechol dimethylacetate (compound of formula I)

In this example, 4-Methyl catechol dimethylacetate was produced from 4-methyl catechol in accordance with the following process.

30.00g of 4-methylcatechol, 91.79g of methyl chloroacetate, and 38.30g of methanol were successively charged into a 500ml flask, which was a jacket reactor equipped with an oil bath, a thermometer, a condenser, a gas absorber, a solid feeding funnel and a magnetic stirrer. Nitrogen was charged into the flask as gas protection. The oil bath in which the flask was immerged was heated until reflux of methanol in the reaction mixture. Agitation was set at a speed of 300 rpm after the start of heating. As the reflux continued, the reaction mixture inside the flask turned into a homogeneous liquid with a light yellow color.

Since the reflux of methanol, a total weight of 46.62g of sodium methoxide was charged into the flask in three batches in a period of two hours, after which, the reaction mixture was aged for an additional 2 hours, before it was cooled to room temperature.

206g of a methanol aqueous solution (methanol 50g+water 156g) was charged into the flask to induce an in-site precipitation at 10 °C for 2 hours under agitation.

The reaction mixture inside the flask was collected, filtrated with a Buchner filter, washed and dried to obtain 55.1 g of an off-white 4-Methylcatecholdimethylacetate product with a purity of 99.5% and a yield of 85%.

Comparative Example 3 - production of 4-Methyl catechol dimethylacetate

Example 2 was repeated, the sodium methoxide was charged into the flask in one batch together with 4-methylcatechol, methyl chloroacetate, and methanol. The reaction mixture inside the flask was refluxed for four hours before cooling to room temperature.

It was discovered that, compared with a 4-Methyl catechol dimethylacetate selectivity of 92% in example 2, the selectivity was reduced to 10% in this example; while the 4-Methyl catechol conversion rate was also reduced from more than 99% to less than 30%.

Comparative Examples 4.1-4.2 - production of 4-Methyl catechol dimethylacetate

Example 2 was repeated, except that different amounts of solvents were used in examples 4.1 and 4.2. In example 4.1, instead of the 206g of a methanol aqueous solution, only 43.95g of water was charged into the flask. Similarly, in example 4.2, 1253.05g of water was charged into a 2L flask instead. The following table 1 shows the impact of m1/m2 to the yield, purity and appearance of the product 4-Methyl catechol dimethylacetate.

Table 1. the impact of m1/m2 to product production.

Ex. No.	m1/m2	yield %	purity %	appearance
Inv. Ex. 2	43%	85%	99.5%	off-white solid
Com. Ex. 4.1	60%	65%	97.0%	black oily solid or yellow semi-solid
Com. Ex. 4.2	5%	91%	95.0%	off-white solid

Examples 5.1-5.3 - production of 4-Methyl catechol dimethylacetate

Example 2 was repeated, except that different amounts of solvents were used in examples 5.1, 5.2 and 5.3. In example 5.1, instead of the 206g of a methanol aqueous solution, only 88.52g of water was charged into the flask. In example 5.2, 45.51g of methanol and 147.74g of water was charged into the flask instead. In Example 5.3, 769.14g of methanol and 1108.08g of water was charged into a 2L flask to replace the 206g of a methanol aqueous solution.

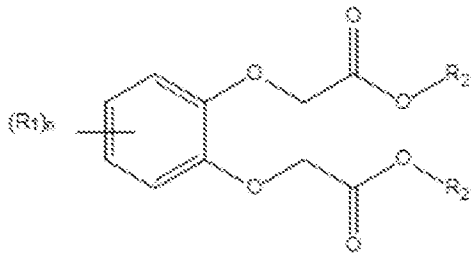
The following table 2 shows the impact of m3/m2 to the yield, purity and appearance of 4-Methyl catechol dimethylacetate.

Table 2. the impact of m3/m2 to 4-Methyl catechol dimethylacetate production.

Ex. No.	m1/m2	m3/m2	yield%	purity%	appearance of product
Inv. Ex. 2	43%	1:4.2	85%	99.5%	off-white solid
Com. Ex. 5.1	43%	1:2.4	50%	95.0%	black oily solid or yellow semi-solid
Inv. Ex. 5.2	43%	1:4	85%	99.0%	off-white solid
Com. Ex. 5.3	43%	1:30	51%	99.0%	off-white solid

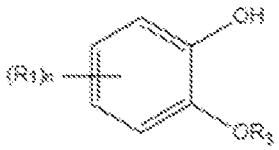
CLAIMS

1. A process for production of the compound of formula I comprising:



I

(i) contacting the compound of formula IIa with an aqueous reaction mixture containing an acidic heterogeneous catalyst,



IIa

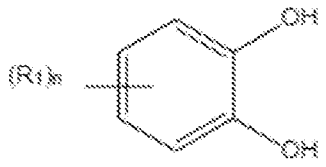
wherein

R1 is independently selected from the group consisting of C1-6 alkyl, C2-6 alkenyl, C1-6 alkoxy and C1-6 aldehyde,

n is 0-4,

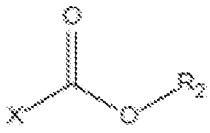
R3 is independently selected from an alkyl group which may be linear, branched or cyclic; which may be saturated or containing one or more unsaturated bonds, or which may be an aromatic group; wherein said R3 may optionally further contain one or more heteroatoms and/or one or more substituents,

to produce the substituted or unsubstituted catechol of formula II;



II

(ii) reacting the substituted or unsubstituted catechol of formula II with the haloacetate of formula III, to produce the compound of formula I;



III

wherein

X is F, Cl, Br or I, and

R2 is independently selected from the group consisting of C1-6 alkyl.

2. The process of claim 1, wherein the compound of formula IIa has a bio-based carbon content in the range of 75%-100%, preferably 80%-100%, more preferably 90%-100%, more preferably 98%-100%, and more preferably 99%-100%.

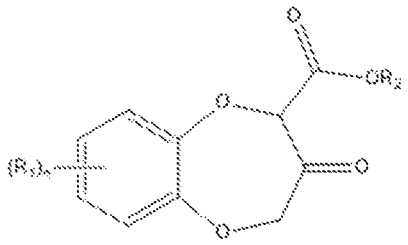
3. The process of claim 1, wherein the acidic heterogeneous catalyst is selected from the list comprising acidic zeolite, aluminophosphate (AlPO) and silicoaluminophosphate (SAPO).

4. The process of claim 1, wherein the step (i) is carried out under an inert gas atmosphere at a temperature of at least 200 °C and a pressure of at least 20 bar.

5. The process of any of claims 1-4, further comprising after step (ii):

(iii) reacting the compound of formula I with a basic reagent, which is selected from sodamide, sodium alkoxide and potassium alkoxide wherein the alkoxide has

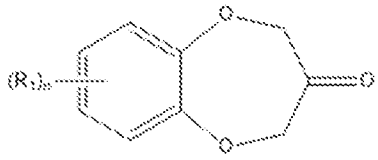
from 1 to 4 carbon atoms, trialkylamine wherein the alkyl has from 1 to 4 carbon atoms and sodium hydride, to produce a compound of formula Ia



Ia

, and

(iv) reacting the compound of formula Ia with an aqueous mineral acid to produce a compound of formula Ib



Ib

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6. The process of any of claims 1-5, wherein the step ii is carried out by:

(ii)(a) reacting the substituted or unsubstituted catechol of formula II with the haloacetate of formula III in the presence of a base in a first solvent;

(ii)(b) mixing the reaction mixture from step (a) with a second solvent to precipitate the compound of formula I, and

(ii)(c) collecting the compound of formula I.

7. The process of claim 6, wherein in step (ii)(a), the base is added in batches into the mixture of the substituted or unsubstituted catechol of formula II, the haloacetate of formula III and first solvent.

8. The process of claim 6, wherein in step (ii)(a), the substituted or unsubstituted catechol of formula II, and the haloacetate of formula III are reacted at a temperature between 25°C and the reflux temperature of the first solvent.

9. The process of claim 6, wherein the base is selected from the group consisting of hydrides, hydroxides and alkoxides of alkali metals and alkali earth metals.

10. The process of claim 6, wherein the base has a formula of M-OR2, wherein M represents an alkali metal.

11. The process of claim 6, wherein the first solvent is selected from the group consisting of alcohols such as methanol, ethanol, propanol, isopropanol, 1-butanol and tert-butanol.

12. The process of claim 6, wherein the second solvent is a mixture of the first solvent and water.

13. The process of claim 12, wherein, m1/m2 is in the range of 10-50wt%, preferably 30-45wt%, in which m1 means the total weight of the first solvent in the reaction mixture from step (ii)(b), and m2 means the total weight of the first solvent and water in the reaction mixture from step (ii)(b).

14. The process of claim 12, wherein m3/m2 is in the range of 1:3 to 1:20, preferably 1:4 to 1:5, by weight, in which m3 means the theoretical weight of the product compound of formula I, and m2 means the total weight of the first solvent and water in the reaction mixture from step (ii)(b).

15. The process of claim 5, wherein step (iii) is conducted in an anhydrous organic solvent selected from the group consisting of dimethylformamide, tetrahydrofuran, dimethylsulfoxide and ethylene glycol dimethyl ether.

16. The process of claim 15, wherein step (iii) is conducted at a temperature of from about 25 °C to the boiling point of the anhydrous organic solvent.

17. The process of claim 5, wherein step (iv) is conducted under reflux of a water-miscible organic solvent selected from the group consisting of ethanol and diethyl ether.

18. The process of claim 5, wherein the aqueous mineral acid is 5% aqueous hydrochloric acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2021/110307

A. CLASSIFICATION OF SUBJECT MATTER

C07D 321/10(2006.01)i; C07C 69/712(2006.01)i; C07C 67/31(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,CNPAT,CNKI,CAPLUS (STN), REGISTRY (STN): calone, benzodioxepinones, odorants, ignin, catechol, HZSM, pyrolysis, dimethoxytoluene, guaiacol, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KRAFT, Philip et al. "Conception, Characterization and Correlation of New Marine Odorants" *Eur. J. Org. Chem.*, No. 19, 31 December 2003 (2003-12-31), pages 3735-3743	1-18
Y	JEENPADIPHAT, Sirima et al. "Catechol production from lignin by Al-doped mesoporous silica catalytic cracking" *Journal of Analytical and Applied Pyrolysis*, Vol. 121, 12 August 2016 (2016-08-12), pages 318-328	1-18
Y	US 3799892 A (PFIZER) 26 March 1974 (1974-03-26) Examples I, II, III, IV and V	1-18
Y	US 3517031 A (PFIZER & CO., Inc.) 23 June 1970 (1970-06-23) Examples I, II, III, IV and V	1-18
Y	CN 101962378 A (CHONGQING UNIVERSITY) 02 February 2011 (2011-02-02) Examples 1-5	1-18

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2022	**29 April 2022**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing** **100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **WANG,Chao** Telephone No. **86-(10)-53962337**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2021/110307

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
US 3799892 A	26 March 1974	None	
US 3517031 A	23 June 1970	None	
CN 101962378 A	02 February 2011	None	