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(54) Title: PROCESS FOR PRODUCTION OF CARBOXYLATED PHENOL DERIVATIVES

(57) Abstract: Disclosed is a new process for the production of carboxylated phenol derivatives comprising at least a step of carboxylation of a mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i) / (ii) is comprised between 0.8 and 1.2, in presence of CO₂. A process for the production of said mixture of (i) phenol derivative and (ii) phenolate derivative is also disclosed.



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PROCESS FOR PRODUCTION OF CARBOXYLATED PHENOL DERIVATIVES

The present invention concerns a new process for the production of carboxylated phenol derivatives comprising at least a step of carboxylation of a mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2, in presence of CO₂. The invention also concerns a process for the production of said mixture of (i) phenol derivative and (ii) phenolate derivative.

PRIOR ART

The following discussion of the prior art is provided to place the invention in an appropriate technical context and enable the advantages of it to be more fully understood. It should be appreciated, however, that any discussion of the prior art throughout the specification should not be considered as an express or implied admission that such prior art is widely known or forms part of common general knowledge in the field.

Carboxylated phenol derivatives, also called phenolic acids or phenolcarboxylic acids, such as vanillic acid (4-hydroxy-3-methoxybenzoic acid), may be used as flavoring agents or chemical intermediate in the production of pharmaceuticals and other fine chemicals or in polymers as additives or co-monomers.

WO9626176 discloses a process for production of vanillic acid comprising:

- heat treatment of a blend comprising guaiacol and a base in order to obtain a phenolate (also called metal phenate), in presence of a solvent such as toluene,
- carboxylation of phenolate in N-methyl-2-pyrrolidone (NMP) at a temperature of 100°C and a pressure of 20 bar; and
- purification of vanillic acid.

However it appears that the conversion and selectivity of the reaction is low and said process involves solvents having a negative effect on humans and the environment, such as toluene.

INVENTION

The present invention relates now to a process for the production of carboxylated phenol derivatives, such as vanillic acid, with a high conversion

and selectivity from a phenol derivative, such as guaiacol, in comparison with processes of the prior art; without the involvement of solvents having a negative effects on humans and the environment, such as toluene for instance. Moreover, it appears that the addition of a phenol derivative during the process after an initial heat treatment permits to increase production of carboxylated phenol derivatives, notably its conversion and selectivity.

The present invention concerns then a process for the production of a carboxylated phenol derivative, comprising at least the following steps:

- a) proceeding with heat treatment of a mixture comprising at least a phenol derivative and a base in presence of water, in order to obtain a phenolate derivative;
- b) adding an aprotic organic solvent to the mixture treated in step a) and optionally a phenol derivative;
- c) removing of water and aprotic organic solvent to obtain a mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2;
- d) proceeding with carboxylation of the mixture obtained in step c) in presence of CO₂; in order to obtain a salt of carboxylated phenol derivative; and
- e) converting the salt of carboxylated phenol derivative to the corresponding carboxylated phenol derivative.

The invention also relates to a process for the production of a mixture of (i) phenol derivative and (ii) phenolate derivative, comprising at least the following steps:

- a) proceeding with heat treatment of a mixture comprising at least a phenol derivative and a base in presence of water, in order to obtain a phenolate derivative;
- b) adding an aprotic organic solvent to the mixture treated in step a) and optionally a phenol derivative; and
- c) removing of water and aprotic organic solvent to obtain the mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2.

The invention also concerns a process for the production of a salt of carboxylated phenol derivative comprising at least a step of carboxylation of a mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2, in presence of CO₂.

The present invention also concerns a mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2, notably comprising an aprotic organic solvent.

Other characteristics, details and advantages of the invention will emerge even more fully upon reading the description which follows.

DEFINITIONS

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.

Should the disclosure of any patents, patent applications, and publications which are incorporated herein by reference conflict with the description of the present application to the extent that it may render a term unclear, the present description shall take precedence.

As used herein, the term "hydrocarbon group" refers to a group consisting of carbon atoms and hydrogen atoms, which group may be saturated or unsaturated, linear, branched or cyclic, aliphatic or aromatic. Hydrocarbon groups of the present invention may be alkyl groups, alkenyl groups, alkynyl groups, aryl groups, alkylaryl groups, aryalkyl groups, heterocyclic groups, and/or alkylheterocyclic groups.

As used herein, the terminology " (C_n-C_m) " in reference to an organic group, wherein n and m are each integers, indicates that the group may contain from n carbon atoms to m carbon atoms per group.

As used herein, "alkyl" groups include saturated hydrocarbons having one or more carbon atoms, including straight-chain alkyl groups, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclic alkyl groups (or "cycloalkyl" or "alicyclic" or "carbocyclic" groups), such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, branched-chain alkyl groups, such as isopropyl, tert-butyl, sec-butyl, and isobutyl, and alkyl-substituted alkyl groups, such as alkyl-substituted cycloalkyl groups and cycloalkyl-substituted alkyl groups. The term "aliphatic group" includes organic moieties characterized by straight or branched-chains, typically having between 1 and 22 carbon atoms. In complex structures, the chains may be branched, bridged, or cross-linked. Aliphatic groups include alkyl groups, alkenyl groups, and alkynyl groups.

As used herein, "alkenyl" or "alkenyl group" refers to an aliphatic hydrocarbon radical which can be straight or branched, containing at least one carbon-carbon double bond. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, decenyl, and the like. The term "alkynyl" refers to straight or branched chain hydrocarbon groups having at least one triple carbon to carbon bond, such as ethynyl.

The term "aryl group" includes unsaturated and aromatic cyclic hydrocarbons as well as unsaturated and aromatic heterocycles containing one or more rings. Aryl groups may also be fused or bridged with alicyclic or heterocyclic rings that are not aromatic so as to form a polycycle, such as tetralin. An "arylene" group is a divalent analog of an aryl group.

The term "heterocyclic group" includes closed ring structures analogous to carbocyclic groups in which one or more of the carbon atoms in the ring is an element other than carbon, for example, nitrogen, sulfur, or oxygen. Heterocyclic groups may be saturated or unsaturated. Additionally, heterocyclic groups, such as pyrrolyl, pyridyl, isoquinolyl, quinolyl, purinyl, and furyl, may have aromatic character, in which case they may be referred to as "heteroaryl" or "heteroaromatic" groups.

Aryl and heterocyclic including heteroaryl groups may also be substituted at one or more constituent atoms. Examples of heteroaromatic and heteroalicyclic groups may have 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O, or S heteroatoms. In general, the term "heteroatom" includes atoms of any element other than carbon or hydrogen, preferred examples of which include nitrogen, oxygen, sulfur, and phosphorus. Heterocyclic groups may be saturated or unsaturated or aromatic.

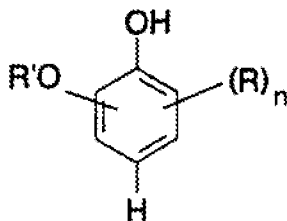
As used herein, the term "aralkyl" or "arylalkyl" means an alkyl group substituted with one or more aryl groups, such as, for example, phenylmethyl, phenylethyl, triphenylmethyl. The term "alkylaryl" means an alkyl moiety bound to an aryl moiety.

It should be noted that a chemical moiety that forms part of a larger compound may be described herein using a name commonly accorded it when it exists as a single molecule or a name commonly accorded its radical. For example, the terms "pyridine" and "pyridyl" are accorded the same meaning when used to describe a moiety attached to other chemical moieties.

DETAILS OF THE INVENTION

Various phenol derivatives may be used according to the present invention, notably those ones that can be carboxylated in the condition of the reaction.

Preferably, the phenol derivative is an ether phenol of formula (I)



(I)

wherein:

- n is a number comprised between 0 and 3, preferably 0, 1, 2 or 3,
- R' represents hydrogen or a linear or branched alkyl group comprising from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl or phenyl,
- R is chosen in the group consisting of:
 - H atom,
 - linear or branched alkyl group comprising from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl or phenyl,
 - linear or branched alkoxy group comprising from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy,
 - halogen atom, such as F, Cl, Br, and
 - trifluoromethyl radical.

More preferably, phenol derivatives of the invention will be carboxylated in para position of the hydroxyle function and will then carry no groupment or function in para position of the hydroxyle function.

Phenol derivatives are preferably chosen in the group consisting of: guaiacol, catechol, 3-methoxyphenol, guetol, 3-ethoxyphenol, 2-isopropoxyphenol, 3-isopropoxyphenol, 2-methoxy-6-methylphenol, 2-methoxy-6-tertbutylphenol, 3-chloro-5-methoxyphenol, and 2-methoxy-1-naphthol.

An alkoxide is the conjugate base of an alcohol and therefore consists of an organic group bonded to a negatively charged oxygen atom. They can be written as $R-O^-$, where R is the organic substituent. Phenoxides are close relatives of the alkoxides, in which the alkyl group is replaced by a derivative of benzene, and

are also called phenate. A phenolate derivative is a salt of phenoxide derivative, such as sodium phenolate for instance.

Phenolate derivative of the invention preferably relates to phenolate corresponding compounds of phenol derivatives of formula (I).

5 Phenolate derivatives are preferably salts of alkali metals, such as sodium or potassium.

Phenolate derivatives of the present invention are preferably chosen in the group consisting of: potassium 2-hydroxyphenolate, potassium 2-methoxyphenolate, potassium 3-methoxyphenolate, potassium 2-ethoxyphenolate, potassium 3-ethoxyphenolate, potassium 2-isopropoxyphenolate, potassium 3-isopropoxyphenolate, potassium 2-methoxy-6-methylphenolate, potassium 2-(tert-butyl)-6-methoxyphenolate, potassium 3-chloro-5-methoxyphenolate, sodium 2-hydroxyphenolate, sodium 2-methoxyphenolate, sodium 3-methoxyphenolate, sodium 2-ethoxyphenolate, sodium 3-ethoxyphenolate, sodium 2-isopropoxyphenolate, sodium 3-isopropoxyphenolate, sodium 2-methoxy-6-methylphenolate, sodium 2-(tert-butyl)-6-methoxyphenolate, and sodium 3-chloro-5-methoxyphenolate.

A carboxylated phenol derivative is a phenol derivative compound comprising at least one carboxylic acid function, for instance one carboxylic acid function or two carboxylic functions. There are also called phenolic acids or phenolcarboxylic acids that are containing a phenolic ring and an organic carboxylic acid function.

Carboxylated phenol derivatives of the invention are preferably chosen in the group consisting of: para vanillic acid (ie. vanillic acid), ortho vanillic acid, meta vanillic acid, 3,4-dihydroxybenzoic acid, 2-methoxy-4-hydroxybenzoic acid, 3-ethoxy-4-hydroxybenzoic acid, 2-ethoxy-4-hydroxybenzoic acid, 2-isopropoxy-4-hydroxybenzoic acid, and 3-isopropoxy-4-hydroxybenzoic acid.

Bases used in the present invention may be an organic base or an inorganic base. Inorganic bases are preferably chosen in the group consisting of: alkali metal carbonate, alkali metal bicarbonate, alkaline-earth metal hydroxide or alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide. Organic bases are preferably chosen in the group consisting of: ammonia, alkylamine, trialkylamine, ammonium hydroxide, and alkylammonium hydroxide, aniline, aminophenol, and alkali metal tert-butoxide, such as potassium tert-butoxide or sodium tert-butoxide.

Heat treatment is preferably carried out at a temperature comprised between 50 and 200°C, more preferably between 100 and 160°C. Such a heat treatment may be preferably carried out at atmospheric pressure.

During the reaction of after the reaction, the water content in the medium
5 may be partially or totally removed, notably by distillation.

Heat treatment of step a) allows production of phenolate derivative from phenol derivative, preferably with a conversion comprised from 80% to 100% of phenol derivative reactant.

Mixture of phenol derivative and base is preferably carried out as follows:

- 10
- phenol derivative is charged into a recipient and heated at a temperature comprised between 50 and 200°C;
 - base is charged slowly in reactor, usually in 2-3 hours;
 - temperature is kept between 50 and 200°C, in order to distill out all the introduced water and generated water; and
 - 15 - phenolate derivative is obtained.

Preferably the molar ratio between the phenol derivative and the base is comprised between 0.4 and 2.2, more preferably between 0.8 and 2.1, more preferably between 0.95 and 2.05, in the mixture. The molar ratio between the phenol derivative and the base may also be comprised between 0.8 and 1.2.

20 Preferably, the mass concentration of base, preferably in water, may be for instance comprised between 30 and 50 % by weight, more preferably comprised between 35 and 45 % by weight.

Mixture as obtained at the end of step a) may comprise a phenolate derivative and a phenol derivative, depending on the amount of phenol derivative
25 and base added at the start of the reaction. In case the molar ratio between phenol derivative and phenolate derivative is below 0.9, fresh phenol derivative may be charged into the mixture in order to ensure the molar ratio between phenol derivative and phenolate derivative is between 0.9 and 1.1, more preferably between 0.95 to 1.05.

30 Phenol derivatives as optionally used in step b) may be similar or different with respect to phenol derivative as used in step a). Preferably, phenol derivative used in step a) and b) is the same chemical compound.

The aprotic organic solvent is preferably chosen in the group consisting of: tetrahydrofuran, ethyl acetate, acetone, 2-butanone, dimethylformamide,
35 acetonitrile, dimethyl sulfoxide, N-methyl-2-pyrrolidone (NMP), hexane, perfluorohexane, pyridine, N,N-dimethylacetamide, N,N-diethylacetamide, and

hexamethylphosphoric triamide. The aprotic organic solvent may dissolve both phenol derivatives and phenolate derivatives. NMP is preferably used for its toxicological and ecological properties, notably as a low toxicity alternative solvent towards toluene.

5 Addition of a phenol derivative in an aprotic organic solvent to the mixture treated in step a) may be made at room temperature with usual appropriated device.

Weight ratio of aprotic organic solvent added to the mixture with respect to phenolate derivative present in the mixture may be comprised between 1 and 10,
10 preferably 2 and 6, more preferably 3 and 5.

Preferably molar amount of phenol derivative added in step b) is between 0.8 and 1.2 equivalent with respect to molar amount of phenol derivative used in step a), more preferably between 0.9 and 1.1 equivalent, particularly between 0.95 and 1.05 equivalent, specifically about 1 equivalent.

15 Removing of water and aprotic organic solvent from the reaction medium in step c) may be carried out by various means and device, such as distillation, for instance classical distillation or vacuum distillation. It has to be noticed that removal of aprotic organic solvent may be partial and that the obtained mixture may also comprise then a part of the aprotic organic solvent.

20 Preferably, the mixture is heated at a temperature comprised between 90 and 110°C under a pressure comprised between 10 and 180 mbar with a further distillation. The vacuum varies according to the boiling point of the solvent.

Carboxylation step d) of phenolate derivatives is well known in the prior art. The reaction mixture is usually charged into a reactor in which CO₂ is
25 introduced at a pressure comprised between 5 and 50 barg, preferably 18 and 22 barg and usually heated at a temperature comprised between 90 and 150°C, preferably 110 and 125°C, for a duration usually comprised between 1 and 10 hours, preferably 1.5 and 3 hours.

Cool down of the reaction temperature may occur between 80 and 90 °C.

30 It is notably possible to follow conversion of reactant by High Performance Liquid Chromatography (HPLC).

Carboxylation of the mixture obtain in step c) may be obtained by using CO₂ or a compound able to generate CO₂ during the reaction. CO₂ may be used pure or diluted, preferably pure.

35 An isolation of the salt of carboxylated phenol derivative may be made at the end of step d). Such an isolation may be carried out by several methods

usually known in the technical field, such as for instance centrifugation or filtration, notably vacuum filtration or pressure filtration, and distillation. For instance the salt of carboxylated phenol derivative may be isolated by filtration followed by a vacuum distillation, at a temperature comprised between 100 and 200°C and at a pressure comprised between 50 and 300 mbar.

It is notably possible to recycle the phenol derivative and the aprotic organic solvent to step b). The phenol derivative and the aprotic organic solvent present at the end of step d), notably after isolation of the salt of carboxylated phenol derivative, are preferably recycled to step b). For instance it is possible to recycle the filtrate comprising notably NMP and guaiacol to step b).

It is also possible to treat the unreacted phenolate derivative with an acid to convert it to a phenol derivative. For instance, recycle of the phenol derivative, the aprotic organic solvent, and possibly the phenolate derivative, may be mixed with an acid before proceeding to a distillation.

Recycle ratio of phenol derivative may be comprised from 70 to 99%, preferably from 80 to 99%, more preferably from 90 to 99%. Recycle ratio of aprotic organic solvent may be comprised from 50 to 99%, preferably from 80 to 99%.

Step e) refers to conversion of the salt of carboxylated phenol derivative to the corresponding carboxylated phenol derivative, notably its carboxylic acid form. It may be notably made by adding an acid to the carboxylated phenol derivative. It is notably possible to first dissolve in water a solid obtained by filtration at the end of step d) and adjust pH from 1 to 5, notably 2 to 3, for instance by adding an acid, such as for instance sulfuric acid, hydrochloric acid, phosphoric acid or nitric acid, with a subsequent filtration to isolate the carboxylic phenol derivative. Isolated carboxylated phenol derivative may be further washed with water and dried at a temperature comprised between 60 and 120°C.

Various carboxylated phenol derivatives may be obtained in accordance with the process of the present invention such as ortho, meta and/or para carboxylated phenol derivatives with respect to the position of the hydroxyl function. It is also possible that carboxylated phenol derivatives comprise one or two carboxylic acid functions.

For instance wherein phenol derivative is guaiacol, carboxylated phenol derivatives may comprises 2-hydroxy-3-methoxybenzoic acid (ortho-vanillic acid), 4-hydroxy-3-methoxybenzoic acid (vanillic acid), 4-hydroxy-5-

methoxyisophthalic acid (di-vanillic acid) and dimers of vanillic acid like for instance 5,5'-dihydroxy-4,4'-dimethoxy-[1,1'-biphenyl]-2,2'-dicarboxylic acid.

Para/Ortho selectivity of carboxylated phenol derivative may be comprised from 70/30 to 99/1, for instance from 70/30 to 90/10.

5 It is notably possible to recycle carboxylated phenol derivatives after filtration expressed at the end of step d). It is for instance possible to recycle para carboxylated phenol derivatives and/or ortho carboxylated phenol derivatives, notably in mixture, after filtration expressed at the end of step d).

Specific carboxylated phenol derivatives of interest, such as para
10 carboxylated phenol derivatives, may be further isolated at the end of step e). In order to further isolate para carboxylated phenol derivatives it's notably possible to proceed to a recrystallization or distillation of para/ortho mixture. For instance recrystallization can be carried out by adding water or alcohol to the para/ortho mixture and proceed with a subsequent heat treatment and slow cooling to
15 recrystallize the para carboxylated phenol derivative. Isolation of para carboxylated phenol derivatives by distillation may be carried out with a conventional distillation column.

Carboxylated phenol derivatives of the invention may be used in various applications such as for instance as food additive, use as a building block for
20 production of ingredients in pharma, agro and fragrance, use as a building block for production of epoxyresins, use as a food preservative or use as a biocide booster in industrial applications. Dihydroxybenzoic acid derivatives, such as vanillic acid, may be used as a flavoring agent or intermediates in the production of vanillin. Vanillic acid has been associated with a variety of pharmacologic
25 activities such as inhibiting snake venom activity, carcinogenesis, apoptosis, inflammation and it has become most popular for its pleasant creamy odour that is widely used in fragrances and licensed as a food additive.

Aqueous effluents made during the process of the present invention, notably waters obtained in step a), step b) and/or step e), can be further processed
30 according to state of the art techniques to achieve compliant effluents with relevant regulations.

The following examples are included to illustrate embodiments of the invention. Needless to say, the invention is not limited to described examples.

EXPERIMENTAL PART

Example 1:

To a 1L reaction flask equipped with a stirrer, thermometer, Dean-Stark trap and a condenser was charged 120 g of guaiacol and heated to 120°C, 139g of
5 KOH (38.96% in water, 1eq to guaiacol) was added into the mixture at 120°C over 2 h while removing water by distillation. Distillation is carried out until no water was distilled out.

Molar ratio of guaiacol to KOH was 1 at the start of the reaction.

480g of N-methyl-pyrrolidone (NMP) with 120g of guaiacol was charged
10 into the flask. Water is removed by distillation under vacuum (< 180 mbar). Further distillation to remove NMP under < 50 mbar to further remove water from NMP, total 67.5 g liquid was distilled out. The mixture was cooled down to room temperature.

The reaction mixture (674g) was charged into the pressure reactor; 20 barg
15 CO₂ was introduced and heated to 118°C, kept CO₂ pressure at 20 barg, and stirred the mixture for 2h at 118°C.

The reaction mixture has been filtered at 85°C. 250g of filtration cake was obtained and 433g of filtrate was obtained. The cake was washed with 170g of NMP and filtrated. 223g of filtration cake and 172g of filtrate were obtained.
20 Both filtrates comprising notably NMP and guaiacol have been recycled to the 1L reaction flask for a next batch.

Specifically, the 433 g filtrate, which mainly contains NMP, guaiacol and unreacted GAK (potassium guaiacolate), was mixed with 23.7 g 98% H₂SO₄, in order to convert unreacted GAK to guaiacol. Then, NMP and guaiacol was
25 distilled out at 140°C under vacuum (60-250 mbar). The collected NMP and guaiacol, which was totally 383g, including 106g of guaiacol and 277.1g of NMP determined by HPLC, would then be used in next batch by mixing with fresh guaiacol and NMP.

The 172 g filtrate, which mainly contains NMP and guaiacol was
30 distilled at 140°C under vacuum (60-250 mbar). The collected NMP and guaiacol, which was totally 161g, including 20g of guaiacol and 140g of NMP determined by HPLC, would then be used in next batch by mixing with fresh guaiacol and NMP.

The cake was dissolved into 508g of water and pH of the solution has been
35 adjusted to 2-3 with a 30% sulfuric acid solution for 30 mins and then a filtration

was carried out. 258g of filtration cake was obtained and 579g of filtrate was obtained. This filtrate has been then treated as wastewater.

The cake is then washed with 508g of water and a filtration is then carried out. 170g of filtration cake was obtained, while 592g filtrate was obtained. This
5 filtrate has been then treated as wastewater.

The cake was then dried at 90°C for 4 h in order to obtain 77.5g of white solid, which is 4-hydroxy-3-methoxybenzoic acid, i.e., para-vanillin acid.

For final product, the purity is determined by High Performance Liquid Chromatograph (HPLC), which is > 99%.

10 Yield is calculated as below: mass of real product (para-vanillin acid)/mass of theoretical para-vanillin acid is 48%.

The conversion of guaiacol, with respect to vanillic acid, ortho-vanillic acid and diacid derivative, is calculated as follows:

(1) The weight% of guaiacol, vanillic acid, ortho-vanillic acid and diacid
15 derivative was determined by HPLC with external standard reference method. In this particular case, they were 22.31%, 11.76%, 1.82%, and 0.25%, respectively. The rest of weight% was NMP and other minor impurities.

(2) This weight% was then normalized, by deducting NMP and other
20 impurities. In this particular case, the normalized weight% of guaiacol, vanillic acid, ortho-vanillic acid and diacid derivative were 61.73%, 32.54%, 5.04%, and 0.69%, respectively.

(3) Then, this normalized weight% was converted to normalized molar%,
25 in order to calculate the conversion of guaiacol. In this particular case, the molar% of guaiacol, vanillic acid, ortho-vanillic acid and diacid derivative were 68.68%, 26.73%, 4.14%, and 0.45%, respectively.

(4) The conversion of guaiacol is defined as: (1-normalized molar% of
guaiacol) *2, since there was 1 eq. extra guaiacol introduced into the
reactor with NMP. In this particular case, the conversion of guaiacol =
30 (1-68.68%)*2=62.63%

Selectivity of para to ortho = molar% of para/molar% of ortho=87/13.

Comparative example 1:

To a 1L reaction flask equipped with a stirrer, thermometer, Dean-Stark trap and a condenser was charged 62 g of guaiacol and 500 mL of toluene, 65 g of
35 30% KOH (1 eq) was added drop wise in 25 minutes, then heated to 84°C. Water is then removed by carrying out an azeotropic distillation. A slurry was formed

and hard to stir, cooled to room temperature under the protection with N₂, filtered the solid and washed with dried toluene. The filter cake is dried in an oven at 100°C, 1-2 mmHg. 68 g potassium salt of guaiacol was obtained. To a 50 mL Burton Corbelin reactor, 2.8g of potassium salt of guaiacol and 20 mL of N-methyl pyrrolidone (NMP) was added. 20 bar CO₂ was introduced to the reactor and the mixture was heated for 7h at 100°C. The mixture was cooled down to room temperature, and its pH adjusted to 2 with 5N HCl. Some solid was formed and acetonitrile was added to make a clear solution.

HPLC was used to check the conversion and selectivity as follows:

-Conversion = 37

-Para vanillic acid Selectivity = 85/15

Comparison of results

Process according to the present invention and process of comparative example 1 are then compared in Table 1:

Table 1

Parameters	Comparative example 1	Example 1
Guaiacol conversion (%)	37	63
Para/Ortho vanillic acid selectivity	85/15	87/13
Yield (%)	32	48

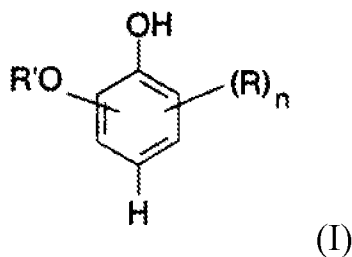
It appears then that the process for the production of vanillic acid according to the present invention permits to obtain a higher conversion of phenol derivative, in comparison with the process of the prior art.

CLAIMS

1. Process for the production of a carboxylated phenol derivative, comprising at least the following steps:

- 5 a) proceeding with heat treatment of a mixture comprising at least a phenol derivative and a base in presence of water, in order to obtain a phenolate derivative;
- b) adding an aprotic organic solvent to the mixture treated in step a) and optionally a phenol derivative;
- 10 c) removing of water and aprotic organic solvent to obtain a mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2;
- d) proceeding with carboxylation of the mixture obtained in step c) in presence of CO₂; in order to obtain a salt of carboxylated phenol derivative; and
- 15 e) converting the salt of carboxylated phenol derivative to the corresponding carboxylated phenol derivative.

2. Process according to claim 1 wherein the phenol derivative is an ether phenol of formula (I)



20 wherein:

- n is a number comprised between 0 and 3,
- R' represents hydrogen or a linear or branched alkyl group comprising from 1 to 6 carbon atoms,

- R is chosen in the group consisting of:

- H atom,

- linear or branched alkyl group comprising from 1 to 6 carbon atoms,

- linear or branched alkoxy group comprising from 1 to 6 carbon atoms,

5 - halogen atom, and

- trifluoromethyl radical.

3. Process according to claim 1 or 2 wherein the phenol derivatives is chosen in the group consisting of: guaiacol, catechol, 3-methoxyphenol, guetol, 3-ethoxyphenol, 2-isopropoxyphenol, 3-isopropoxyphenol, 2-methoxy-6-
10 methylphenol, 2-methoxy-6-tertbutylphenol, 3-chloro-5-methoxyphenol, and 2-methoxy-1-naphthol.

4. Process according to anyone of claims 1 to 3, wherein the base is an inorganic base.

5. Process according to anyone of claims 1 to 4, wherein the phenolate
15 derivative is a salt of alkali metal.

6. Process according to anyone of claims 1 to 5, wherein the phenolate derivative is chosen in the group consisting of: potassium 2-hydroxyphenolate, potassium 2-methoxyphenolate, potassium 3-methoxyphenolate, potassium 2-ethoxyphenolate, potassium 3-ethoxyphenolate, potassium 2-
20 isopropoxyphenolate, potassium 3-isopropoxyphenolate, potassium 2-methoxy-6-methylphenolate, potassium 2-(tert-butyl)-6-methoxyphenolate, potassium 3-chloro-5-methoxyphenolate, sodium 2-hydroxyphenolate, sodium 2-methoxyphenolate, sodium 3-methoxyphenolate, sodium 2-ethoxyphenolate, sodium 3-ethoxyphenolate, sodium 2-isopropoxyphenolate, sodium 3-
25 isopropoxyphenolate, sodium 2-methoxy-6-methylphenolate, sodium 2-(tert-butyl)-6-methoxyphenolate, and sodium 3-chloro-5-methoxyphenolate.

7. Process according to anyone of claims 1 to 6, wherein the carboxylated phenol derivative is chosen in the group consisting of: para vanillic acid, ortho vanillic acid, meta vanillic acid, 3,4-dihydroxybenzoic acid, 2-methoxy-4-

hydroxybenzoic acid, 3-ethoxy-4-hydroxybenzoic acid, 2-ethoxy-4-hydroxybenzoic acid, 2-isopropoxy-4-hydroxybenzoic acid, and 3-isopropoxy-4-hydroxybenzoic acid.

8. Process according to anyone of claims 1 to 7, wherein in step a) the heat
5 treatment is carried out at a temperature comprised between 50 and 200°C.

9. Process according to anyone of claims 1 to 8, wherein in step a) during the reaction of after the reaction, the water content in the medium is removed by distillation.

10. Process according to anyone of claims 1 to 9, wherein in step a) the
10 molar ratio between the phenol derivative and the base is comprised between 0.4 and 2.2, in the mixture.

11. Process according to anyone of claims 1 to 10, wherein in step b) the aprotic organic solvent is chosen in the group consisting of: tetrahydrofuran, ethyl acetate, acetone, 2-butanone, dimethylformamide, acetonitrile, dimethyl
15 sulfoxide, N-Methyl-2-pyrrolidone, hexane, perfluorohexane, pyridine, N,N-dimethylacetamide, N,N-diethylacetamide, and hexamethylphosphoric triamide.

12. Process according to anyone of claims 1 to 11, wherein the weight ratio of aprotic organic solvent added to the mixture in step b) with respect to phenolate derivative present in the mixture is comprised between 1 and 10.

20 13. Process according to anyone of claims 1 to 12, wherein the molar amount of phenol derivative added in step b) is between 0.8 and 1.2 equivalent with respect to molar amount of phenol derivative used in step a).

14. Process according to anyone of claims 1 to 13, wherein at the end of step c) the obtained mixture comprises a part of the aprotic organic solvent.

25 15. Process according to anyone of claims 1 to 14, wherein the salt of carboxylated phenol derivative is isolated at the end of step d).

16. Process according to anyone of claims 1 to 15, wherein the phenol derivative and the aprotic organic solvent present at the end of step d) are recycled to step b).

17. Process according to anyone of claims 1 to 16, wherein a specific carboxylated phenol derivative, may be further isolated at the end of step e).

18. A process for the production of a mixture of (i) phenol derivative and (ii) phenolate derivative, comprising at least the following steps:

- 5 a) proceeding with heat treatment of a mixture comprising at least a phenol derivative and a base in presence of water, in order to obtain a phenolate derivative;
- b) adding an aprotic organic solvent to the mixture treated in step a) and optionally a phenol derivative; and
- 10 c) removing of water and aprotic organic solvent to obtain the mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2.

19. A process for the production of a salt of carboxylated phenol derivative comprising at least a step of carboxylation of a mixture of (i) phenol derivative
15 and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2, in presence of CO₂.

20. A mixture of (i) phenol derivative and (ii) phenolate derivative, wherein the molar ratio of (i)/(ii) is comprised between 0.8 and 1.2.

21. Mixture according to claim 18, wherein it also comprises an aprotic
20 organic solvent

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2017/096254

A. CLASSIFICATION OF SUBJECT MATTER

C07C 51/15(2006.01)i; C07C 65/21(2006.01)i; C07C 65/05(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)

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)

CNABS, CNTXT, DWPI, VEN, CNKI, Google Scholar, STN(REGISTRY), STN(CAPLUS), carboxyla+, guaiacol, vanillic acid, phenol, phenolate, naphtholate, base, CO2, carbon dioxide.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN 103012123 A (ZHEJIANG UNIVERSITY) 03 April 2013 (2013-04-03) claim 1, paragraphs [0012], [0018] and [0027]-[0030]	1-21
Y	US 2006052632 A1 (HYOGO, RYUZO UENO ET AL.) 09 March 2006 (2006-03-09) paragraphs [0030]-[0031]	1-21
A	WO 9626176 A1 (RHONE-POULENC CHIMIE ET AL.) 29 August 1996 (1996-08-29) description, pages 4-5	1-21

☐ 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

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2017/096254

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