(54) Title: PROCESS FOR THE PREPARATION OF A COSMETIC ACTIVE

(57) Abstract: A process for the preparation of formula (1): wherein R is alkyl or aryl, cyclic or acyclic, substituted or unsubstituted, and optionally containing one or more oxygen, nitrogen or sulphur heteroatoms; comprising reacting resorcinol with an alkanolic carboxylic acid in the presence of a Lewis acid or a Bronsted acid catalyst, wherein the mole ratio of the acid catalyst to resorcinol is at least one and the mole ratio of alkanolic acid to resorcinol is at least two.
PROCESS FOR THE PREPARATION OF A COSMETIC ACTIVE

The present invention relates to a novel process for the preparation of compounds of formula 1 in high yields and purity:

(Formula 1)

wherein R is a group chosen from alkyl or aryl, either cyclic or acyclic, either unsubstituted or substituted (branched) and may have heteroatoms (oxygen, nitrogen or sulphur).

In particular, it refers to the preparation of compound of formula 1 by reaction of resorcinol and organic carboxylic acid, particularly useful in cosmetic applications.

Resorcinol and its derivatives have a wide variety of applications. The largest consumption of resorcinol is in the tyre industry, where the preferred hardening resins are based on resorcinol. Another value-added application of resorcinol and its derivatives is in cosmetic products. Some compounds like 2, 4 - dihydroxyacetophenone have been used in sun-protective applications or compositions for providing sun protection.
Alkyl resorcinols and aromatic resorcinols are reported to possess valuable therapeutic and antiseptic properties. In particular, 4-alkyl resorcinol is reported to have skin-beautifying effect and low toxicity and irritation when applied on to human skin. Alkyl resorcinols like 4-n-butyl resorcinol have been used in skin creams and lotions which are claimed to have good bleaching and anti-microbial effect. 2-alkyl resorcinol (where the alkyl group is linear) has been reported to have skin depigmentation properties.

US2006039 [Redo Labs, 1932] describes a process for the preparation of di-substituted derivatives of resorcinol in which the two substituting groups (which may be alkyl or aralkyl) are unlike. The process steps include reaction of resorcinol with an acid, acid chloride or acid anhydride of the aliphatic or aromatic series in the presence of a condensing agent like zinc chloride to prepare a mono-ketone derivative. The mono-ketone derivative is further reacted with an acid, acid chloride or acid anhydride of the aliphatic or aromatic series, containing a radical different from the substituting radical already present in the resorcinol derivative in the presence of zinc chloride or other suitable condensing agent to form a diketone derivative.

GB793770 [Dow Chemical Co., 1958] describes a process for preparing 4,6-diacyl resorcinols by reaction of resorcinol dialkyl ether with an acyl chloride and aluminium chloride. This publication also describes that when resorcinol was employed in the above process in place of the dialkyl ether,
the resulting product consisted of 90 per cent of the 2,4-isomer and 10 per cent of the 4,6-isomer.

Current Science, Vol. 48, No.7, Pg. 300-301, 1979 and JP59065039 (Sumitomo Chem, 1984) both report a process where resorcinol is heated with acetic acid and zinc chloride for the preparation of 2,4-dihydroxyacetophenone.

US5621146 (Kuraray Co. Ltd., 1997) describes a process where resorcinol was reacted with acetic acid in the presence of a proton acid catalyst (e.g. acidic ion-exchange resin Amberlyst 15) while removing formed water for the preparation of 2,4-dihydroxyacetophenone.

A journal article in the Clean Techn. Environ Policy 4 (2002) pg. 157 - 164 also describes method to prepare 2,4-dihydroxyacetophenone from resorcinol and acetic acid in the presence of variety of solid acid catalysts like montmorillonite clay (K-10), decatungstophosphoric acid supported on K-10, sulfated zirconia and ion-exchange resins like Amberlyst-36. The catalyst concentration used in this work is very low.


Many of the above prior art publications report reaction of resorcinol with acetic acid to prepare compounds other than
those of formula 1. Some compounds of formula 1 viz. 4,6-diacetyl resorcinol have been prepared from resorcinol and acetic anhydride using zinc chloride catalyst. Acetic anhydride is very difficult to purchase in many countries due to very strict government regulations on its procurement, storage and use. There is still a need felt in the art to prepare compounds of formula 1 using more easily and economically available compounds.

The present inventors have found that resorcinol when reacted with readily available organic carboxylic acids in the presence of an acidic catalyst, with maintenance of specific catalyst:reactant ratios produce the compounds of formula 1 of high yield and purity.

It is thus an object of the present invention to be able to prepare compounds of the formula 1,

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\begin{array}{c}
\text{O} \\
\text{R} \\
\text{6} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{4} \\
\text{OH} \\
\text{R} \\
\text{CO} \\
\end{array}
\]

where R is a group chosen from alkyl or aryl, either cyclic or acyclic, either unsubstituted or substituted (branched) and may have heteroatoms (oxygen, nitrogen or sulphur).

It is a further object of the present invention to prepare compounds of formula 1 of high yields and purity in a single step reaction, thus requiring only a single reaction vessel.
It is a further object of the present invention to be able to prepare compounds of formula 1 that use chemicals/raw materials which are readily available at economical prices.

It is a yet another object of the present invention to prepare compounds of formula 1 that use chemicals/raw materials which are readily available at economical prices, and create a minimal amount of bi-products which are also easy to separate and environmentally friendly.

According to a first aspect of the invention, there is provided a process for preparation of compound of formula 1 as hereinabove described, comprising reacting resorcinol with an organic carboxylic acid chosen from an aliphatic or aromatic carboxylic acid, either straight chain or branched in the presence of an acidic catalyst such that the mole ratio of the acidic catalyst to the resorcinol used is at least one.

It is particularly preferred that the mole ratio of the carboxylic acid to the resorcinol used is at least two.

According to a further preferred aspect of the invention, there is provided a process for preparation of compound of formula 1 comprising reacting resorcinol with an alkanoic acid (straight chain or branched) with a carbon chain length of 1 to 18 in the presence of a Lewis acid catalyst such that the mole ratio of the Lewis acid catalyst to the resorcinol used is at least one, and the mole ratio of the alkanoic acid to the resorcinol used is at least two.
According to an further preferred aspect of the invention, there is provided a process for preparation of compound of formula 1 comprising the step of reacting resorcinol with an alkanoic acid with a carbon chain length of 1 to 8 in the presence of a Lewis acid catalyst selected from zinc chloride, aluminium chloride, boron trifluoride, or ferric chloride, such that the mole ratio of the Lewis acid catalyst to the resorcinol used is at least two and the mole ratio of the alkanoic acid to the resorcinol used is at least four.

According to yet another preferred aspect of the invention, there is provided a process for preparation of compound of formula 1 comprising the step of reacting resorcinol with an alkanoic acid with a carbon chain length of 1 to 8 at a temperature range of 50 to 200 °C, in the presence of a Lewis acid catalyst selected from zinc chloride or aluminium chloride, such that the mole ratio of the Lewis acid catalyst to the resorcinol used is at least two and the mole ratio of the alkanoic acid to the resorcinol used is at least four.

The present invention provides for a novel process to prepare compounds of formula 1, particularly 4,6-dialkanoyl resorcinols. The process is a single step reaction which involves reacting resorcinol with an organic carboxylic acid which is chosen from an aliphatic or aromatic acid, either straight chain or branched, using an acid catalyst such that the mole ratio of the acidic catalyst to the resorcinol used is at least one. It is preferred that the mole ratio of the carboxylic acid to the resorcinol used is at least two.
Although the raw material as per this invention is resorcinol, the process could also be carried out starting with precursors of resorcinol, from which reactions known in the art could be employed to first prepare resorcinol, following which the process of the invention could be carried out.

Suitable organic carboxylic acids which may be used for the reaction may be aliphatic or aromatic. The carboxylic acid could be straight chain or branched in configuration. The carboxylic acid could also have a heteroatom like oxygen, nitrogen or sulphur.

Preferred carboxylic acids as per the invention are aliphatic in nature, and have carbon chain lengths of 1 to 18, more preferably 1 to 8. The preferred concentration of the carboxylic acid is such that the mole ratio of the carboxylic acid to the resorcinol used is at least 2, preferably at least 4.

The reaction has to be carried out in the presence of an acidic catalyst. The acid catalyst is preferably chosen from Lewis acid or Bronsted acid catalysts. Preferably, a Lewis acid catalyst is used to carry out the reaction as per the invention. The catalysts that may be used include zinc chloride, aluminium chloride, ferric chloride, boron trifluoride, titanium tetrachloride and zirconium tetrachloride. The preferred catalysts include zinc chloride, aluminium chloride, boron trifluoride and ferric chloride, while highly preferred catalysts are zinc chloride and aluminium chloride. It is essential as per this
invention to use a concentration of the catalyst such that the mole ratio of catalyst to resorcinol reacted is at least one, and preferably at least two.

The reaction as per this invention is preferably carried out from 50 to 200°C, more preferably from 70 to 170°C.

The reaction could be quenched using acids, preferably using hydrochloric acid. However it has been found that it is preferable to use bases instead of acids to quench the reaction as per this invention. Preferred bases include alkali metal hydroxides, carbonates or bicarbonates. Highly preferred bases are alkali metal hydroxides.

The invention will now be illustrated with the help of the following non-limiting examples.

EXAMPLES

All solvents were reagent grade and were used as received. All reagents were purchased from the Aldrich or Sigma Chemical Companies, and were used as received unless otherwise noted.

Example 1

A mixture of octanoic acid (144g, 1 mole) and zinc chloride (272g, 2.0 moles) was gradually heated until all the zinc chloride had dissolved in it. To this vigorously stirred solution was added dropwise a solution of resorcinol in octanoic acid (110g i.e. 1 M of resorcinol in 432 g i.e. 3 M
of octanoic acid), and the mixture was stirred under heating at 160°C for 24 hrs. At the end of this period, the reaction mixture was cooled and then quenched with 1:1 dilute HCl (500mL) with external cooling, until completion of the quenching operation. The organic layer was separated, and excess octanoic acid was removed under reduced pressure to prepare a product of formula 1 where R is an octyl group. The product was produced at a yield of 93.0% of the theoretical yield.

The product was characterised by infra red spectrometry and by gas chromatography-mass spectrometry (GC-MS).
IR : 1661 cm\(^{-1}\) and 1590 cm\(^{-1}\)
GC-MS: Mass 418

The analytical methods used to characterize the compounds prepared are described below.

**Gas chromatography/mass spectrometry (GC-MS)**

GC-MS was performed on an Agilent 6890 Series Plus gas chromatograph in conjunction with an Agilent 5973 Network Mass Selective Detector. An Agilent HP-1 column used was.

**Gas chromatography (GC)**

GC analysis was performed using a Hewlett-Packard 5890 Series II Plus gas chromatograph with an HP 7673 injector controlled by Hewlett-Packard ChemStation software. The Hewlett-Packard HP-1 column used was 25 M x 0.22 mm with a 0.33 μm coating of cross-linked methyl silicone.
Proton magnetic resonance (NMR)

NMR spectra were recorded on a Bruker 200 mHz spectrophotometer. Chemical shifts are reported in parts per million from tetramethylsilane as an internal standard. Spin multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). The deuterated NMR solvents contain 99.0–99.8 % deuterium in the indicated position.

Infrared (IR)

IR spectra were recorded on a Nicolet Impact model 410 spectrometer using a NaCl cell. Data was processed using OMNIC software. Peak positions are listed in cm⁻¹ as vs (very strong), s (strong), m (medium), w (weak) or br (broad).

Example 2

An example as per Example 1 was carried out except that reaction mixture was cooled and then quenched with 1:1 dilute NaOH with external cooling to a neutral pH. A product of formula 1 was prepared where R is an octyl group. The product was produced at a yield of 95.0% of the theoretical yield.

The product was characterised by IR and GC-MS.
IR : 1661 cm⁻¹ and 1590 cm⁻¹
GS-MS: Mass 418
Example 3

A mixture of acetic acid (500g, 8.3M) and freshly fused zinc chloride (500g, 3.7M) was stirred under reflux until all zinc chloride dissolved in it. To this was added resorcinol (165g, 1.5M) portion-wise over a period of 30 minutes. Additional portions of acetic acid (4 moles) and fused zinc chloride (322g, 2.36M) were added during the period of 24 hours, while the reaction mixture was continuously stirred under reflux. At the end of this period, the reaction mass was cooled, and quenched carefully with 1:1 HCl solution (1500mL) over a period of 90 minutes. Precipitated solid was found to be produced in 92% yield, and the product was characterized to be one of formula 1 where R<sub>1</sub> and R<sub>2</sub> are both a methyl group. The compound was found to have the following characteristics:

Melting point 178°C.
IR spectra with peaks at 1660 cm<sup>-1</sup> and 1592 cm<sup>-1</sup>
NMR (CDCl<sub>3</sub>): ppm 6.4 (s, 1H), 8.21 (s, 1H) and 2.64 (s, 6H)
GCMS Mass: 194

Example 4

An experiment as per Example 3 was carried except that 1:1 sodium hydroxide was used instead of hydrochloric acid until the solution was neutral.

Precipitated solid was found to be produced in 95% yield, and the product was characterized to be one of formula 1 where R is a methyl group. The compound was found to have the following characteristics:
Melting point 178°C,
IR: 1660 cm⁻¹ and 1592 cm⁻¹
NMR (CDCl₃): ppm 6.4 (s, 1H), 8.21 (s, 1H) and 2.64 (s, 6H)
GCMS Mass: 194

Example 5

To a stirred mixture of acetic acid (240g, 4.0M) and freshly sublimed aluminium chloride (267g, 2M) was added with stirring resorcinol (110g, 1.0M) portion-wise over a period of 30 minutes at room temperature. Mixture was then heated to 120°C and maintained at this temperature for 8 hrs. At the end of this period, the reaction mass was cooled, and quenched carefully with 1:1 HCl solution (1500mL) over a period of 90 minutes. Precipitated solid was found to be produced in 89% yield, and the product was characterized to be one of formula 1 where R is a methyl group. The compound was found to have the following characteristics

Melting Point 179-180°C.

Example 6

An experiment as per Example 5 was conducted except that 120 grams (0.9 moles) of aluminium chloride was used. Very poor yield (20%) of compound of formula 1 was obtained.

The examples demonstrate that compounds of formula 1 can be prepared in high yield using the process as per the invention.
1. A process for the preparation of compound 1

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R
\[ \text{C} \]
\[ \text{O} \]
\[ \text{OH} \]
\[ \text{R} \]
\[ \text{OH} \]
\[ \text{R} \]
\[ \text{CO} \]
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wherein R is alkyl or aryl, cyclic or acyclic, substituted or unsubstituted, and optionally containing one or more oxygen, nitrogen or sulphur heteroatoms; comprising reacting resorcinol with an alkanic carboxylic acid in the presence of a Lewis acid or a Bronsted acid catalyst, wherein the mole ratio of the acid catalyst to resorcinol is at least one and the mole ratio of alkanic acid to resorcinol is at least two.

2. The process of claim 1 wherein the mole ratio of the acid catalyst to the resorcinol is at least two.

3. The process of claim 1 or claim 2 wherein the alkanic carboxylic acid is a straight or branched chain of length 1 to 18 carbons.

4. The process of claim 3 wherein the alkanic carboxylic acid has a chain length of 1 to 8 carbon atoms.

5. The process of any of the preceding claims wherein the catalyst is a Lewis acid catalyst.
6. The process of any of the preceding claims wherein the ratio of alkanolic acid to resorcinol is at least four.

7. The process of any of the preceding claims wherein the catalyst is a Lewis acid and is selected from zinc chloride, aluminium chloride, boron trifluoride, ferric chloride, titanium tetrachloride and zirconium tetrachloride.

8. The process of claim 6 wherein the mole ratio of the Lewis acid catalyst to the resorcinol is at least two and the ratio of the alkanolic acid to the resorcinol is at least four.

9. The process of any of the preceding claims wherein the reaction is carried out within a temperature range of 50 to 200°C.

10. The process of any of the preceding claims wherein the reaction is quenched using hydrochloric acid.

11. The process of any of claims 1 to 8 wherein the reaction is quenched using a base selected from alkali metal hydroxides, carbonates or bicarbonates.

12. The process according to any of the preceding claims wherein the resorcinol is a 4,6,-dialkanoyl resorcinol.

13. The process according to any of the preceding claims wherein the process is a single step process.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION No**

PCT/EP2004/001188

### A. CLASSIFICATION OF SUBJECT MATTER

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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)

**IPC 7 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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
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  - "E" earlier document but published on or after the International filing date
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### Date of the actual completion of the international search

7 May 2004

### Date of mailing of the international search report

18/05/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL -- 2280 HV RIJSWIJK

Tel. (+31-70) 346-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

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