Abstract:

Title: PROCESS FOR PREPARATION OF 3,4-DIHYDROXY-2-METHYL BENZOIC ACID ALKYLESTER

The present invention relates to a simple economical process for the preparation of 3,4- dihydroxy-2-methyl benzoic acid C1-4 alkyl ester and novel intermediates for use in the process.
PROCESS FOR PREPARATION OF 3,4-DIHYDROXY-2-METHYL BENZOIC ACID ALKYLESTER

The present invention relates to a simple economical process for the preparation of 3,4-dihydroxy-2-methyl benzoic acid \( \text{C}i_{-4} \) alkylester and novel intermediates for use in the process.

BACKGROUND OF THE INVENTION

A compound of Formula I and salts thereof,

\[
\text{HO} \quad \text{CH}_3 \quad \text{COOR} \\
\text{HO} \quad \text{Formula I}
\]

wherein \( R \) is selected from hydrogen and \( \text{C}i_{-4} \) alkyl is a useful intermediate for the preparation of pharmaceuticals and other chemicals.

Various processes for the preparation of compounds of Formula I are known in the literature. For instance Bulletin of the Korean Chemical Society Volume 32 Issue 5 page 1725-1728 year 2011, WIPO application WO2004072254 and WIPO application WO201125967 disclose processes for the preparation of compounds of Formula I. The processes disclosed involve either the use of toxic reagents like methyl iodide or the use of reagents like n-butyl lithium which are hazardous and not preferred for commercial manufacturing. Moreover, the use of n-butyl lithium and methyl iodide may result in the formation of positional isomers of Formula I

\[
\text{HO} \quad \text{COOR} \\
\text{HO} \quad \text{Formula I'}
\]

wherein \( R \) is selected from hydrogen and \( \text{C}1_{-4} \) alkyl.

Such isomers are difficult to remove from the compound of Formula I due to similarity in the chemical structure and hence the chemical and physical properties.
SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of 3,4-dihydroxy-2-methyl benzoic acid C_{1-4}alkyl ester or its acid derivative, a compound of Formula I, or salts thereof.

![Formula I](image)

wherein R is hydrogen or C_{1-4} alkyl, the process comprising:

a) reacting 3-hydroxy-4-methoxy benzoic acid C_{1-4} alkyl ester, a compound of Formula III, with formaldehyde and dimethyl amine to obtain 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C_{1-4} alkyl ester, a compound of Formula II,

![Formula III](image) → ![Formula II](image)

b) reducing 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C_{1-4} alkyl ester, a compound of Formula II, to obtain 3-hydroxy-4-methoxy-2-methyl benzoic acid C_{1-4} alkyl ester, a compound of Formula IV,

![Formula II](image) → ![Formula IV](image)

and

c) dealkylating the 3-hydroxy-4-methoxy-2-methyl benzoic acid C_{1-4} alkyl ester, a compound of Formula IV, and isolating 3,4-dihydroxy-2-methyl benzoic acid C_{1-4} alkyl ester, a compound of Formula I,
d) optionally, hydrolyzing the 3,4-dihydroxy-2-methyl benzoic acid C₁₋₄ alkyl ester, to get 3,4-dihydroxy-2-methyl benzoic acid, a compound of Formula I wherein R is hydrogen and,

e) optionally, converting the product of step d into its salt.

The present invention also provides compounds of Formula II or salts thereof

![Chemical structure of Formula II](image)

wherein R is selected from hydrogen and C₁₋₄ alkyl, and a process for its preparation.

10 BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1: HPLC chromatogram of 3,4-dihydroxy-2-methyl benzoic acid methyl ester (RT: 7.05 min).

Figure 2: HPLC chromatogram for 3,4-dihydroxy-2-methyl benzoic acid methyl ester (RT: 7.04 min) spiked with impurity compound of Formula I’ (RT: 8.54 min; RRT: 1.21).

DETAILED DESCRIPTION OF THE INVENTION:

In one aspect the present invention provides a process for the preparation of 3,4-dihydroxy-2-methyl benzoic acid C₁₋₄ alkyl ester or its acid derivative, a compound of Formula I, or salts thereof
wherein R is hydrogen or C$_{1-4}$ alkyl, the process comprising:

a) reacting 3-hydroxy-4-methoxy benzoic acid C$_{1-4}$ alkyl ester, a compound of Formula III with formaldehyde and dimethyl amine to obtain 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C$_{1-4}$ alkyl ester, a compound of Formula II,

b) reducing 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C$_{1-4}$ alkyl ester, a compound of Formula II, to obtain 3-hydroxy-4-methoxy-2-methyl benzoic acid C$_{1-4}$ alkyl ester, a compound of Formula IV,

c) dealkylating the 3-hydroxy-4-methoxy-2-methyl benzoic acid C$_{1-4}$ alkyl ester, a compound of Formula IV, and isolating 3,4-dihydroxy-2-methyl benzoic acid C$_{1-4}$ alkyl ester, a compound of Formula I,
d) optionally, hydrolyzing the 3,4-dihydroxy-2-methyl benzoic acid \( \text{C}_n \text{alkyl} \) ester, to get 3,4-dihydroxy-2-methyl benzoic acid, a compound of Formula I wherein R is hydrogen and,

e) optionally, converting the product of step c or step d into its salt.

The acid derivative of compound of Formula I as referred herein is the compound of Formula I wherein R is hydrogen.

In step a), a solution of 3-hydroxy-4-methoxy benzoic acid \( \text{C}_n \text{alkyl ester} \) (Formula III), which can be obtained commercially or prepared by esterifying 3-hydroxy-4-methoxy benzoic acid with \( \text{C}_n \text{alkyl alcohol} \), in a solvent is treated with formaldehyde and dimethylamine in presence of an acid. Suitable solvent for the reaction can be selected from tetrahydrofuran, dioxane, diethyl ether and the like. Formaldehyde can be obtained from formaldehyde aqueous solution or paraformaldehyde. Suitable acid for the reaction can be acetic acid or hydrochloric acid. The reaction may be carried out at temperature ranging from 25 °C to the reflux temperature of the solvent used for a time sufficient for completion of reaction like 2-10h. Upon completion reaction is worked-up to isolate the product by concentrating the reaction mass under reduced pressure and adding hydrochloric acid solution to the residue. Aqueous solution is washed with water immiscible solvent like ethyl acetate. Aqueous layer is basified with sodium bicarbonate up to a pH of 9 and extracted with an organic solvent like dichloromethane. Organic layer is concentrated to afford 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid \( \text{C}_n \text{alkyl ester} \) (Formula II) which can be used for the next step without further purification.

In step b), 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid \( \text{C}_n \text{alkyl ester} \) (Formula II) is treated with palladium on charcoal in presence of hydrogen gas under pressure of about 5-6 kg/cm². Reaction can be carried out in presence of a solvent like methanol. The reaction can be heated at 50-90 °C for a period sufficient for completion of reaction like 3-10h. Work-up of the reaction can be done by filtering the reaction mass and concentrating the filtrate under reduced pressure, dissolving the residue in a solvent like ethyl acetate and washing the solution with an acid like hydrochloric acid. The organic layer can be concentrated to furnish 3-hydroxy-4-methoxy-2-methyl benzoic acid \( \text{C}_n \text{alkyl ester} \) (Formula IV) which can be used directly for the next step without further purification.
In step c), 3-hydroxy-4-methoxy-2-methyl benzoic acid C_{1-4} alkyl ester (Formula IV) is subjected to dealkylation using a suitable reagent. Suitable reagent for the reaction can be anhydrous aluminium chloride. Reaction can be conveniently carried out in presence of a solvent like toluene, benzene, dichloromethane, tetrahydrofuran, dioxane and like. Preferred solvent for the reaction is toluene. Reaction mass can be heated to temperature from 50-100 °C for a suitable time required for completion of reaction like 1-5h. Upon completion the reaction can be worked-up by quenching the reaction mass in ice cold hydrochloric acid solution and extraction in an organic solvent like ethyl acetate. Organic layer can be concentrated to afford residue which may be further purified by treating it with solvent like hexane to afford 3,4-dihydroxy-2-methylbenzoic acid C_{1-4} alkylester (Formula I).

The complete process can be depicted as in Scheme 1:

![Scheme 1](image)

In some embodiments, the product obtained by the process of the present invention is substantially pure. The term 'substantially pure' as used herein refers to a product having an HPLC purity of at least about 99.5 %, e.g., containing less than 0.5 % of total impurities. In some examples, the product obtained by the process of the present disclosure contains less than about 2%, less than about 1%, less than about 0.5 %, less than about 0.3%, less than about 0.1% of the positional isomer of Formula Γ.

Exemplary HPLC methods useful for determining HPLC purity are described herein. It was surprisingly found that the positional isomer, the compound of Formula Γ, was absent or its content was below the level of detection in the product obtained by the
process of the present invention, e.g., in those processes in which R is methyl. Thus, in other embodiments, the compound of Formula I is substantially free of compounds of Formula Γ. 'Substantially free' refers to less than about 1%, less than about 0.8%, less than about 0.6%, less than about 0.4%, less than about 0.2%, less than about 0.1%, or less than about 0.05%. In some embodiments, 'substantially free' refers to a product of Formula I, in which the concentration of compounds of Formula Γ are below the level of detection. e.g., when using the HPLC method given in Table 1 herein below.

The present invention also provides 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C₁-₄ alkylester or its acid derivative, a compound of Formula II, and salts thereof.

![Formula II](image)

wherein R is selected from hydrogen and C₁-₄ alkyl.

In another aspect of the present invention the compound of Formula II or 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C₁-₄ alkylester is prepared by a process comprising reacting 3-hydroxy-4-methoxy benzoic acid C₁-₄ alkylester with formaldehyde and dimethyl amine and isolating the compound of Formula II. The product of the reaction can be hydrolyzed to afford the respective free acid derivative having R as hydrogen. The compound of Formula II can be prepared by the process described above.

The compound of Formula I is an important intermediate for the preparation of pharmaceutical compounds. For instance, WIPO application WO2015141616 discloses preparation of 1,3-benzodioxazoles of Formula A₂ starting from a compound of Formula A₀ (corresponds to compound of Formula I of the present invention) wherein R₄ is C₆ alkyl. The compound of Formula A₂ is further converted to compound of Formula A₄ which has EZH1 and EZH2 inhibitory activity and is useful for the treatment of cancers.
Chinese application 105130808 discloses the preparation of 2,5-dimethyl-3,4-di-
hydroxybenzoate, an important pharmaceutical intermediate, from a compound of
Formula I.

United States patent number 9145425 discloses the use of compounds of Formula I
(referred as formula ii-38b in the '425 patent) for the preparation of compounds exhibiting
antibacterial activity against a wide range of bacteria.

The use of compounds of Formula I with high purity as an intermediate results in the
formation of pharmaceuticals with high purity and yield.

The present invention is further illustrated in detail with reference to the following
example. It is desired that the example be considered in all respect as illustrative and are
not intended to limit the scope of the claimed invention.

EXAMPLES

High pressure liquid chromatography (HPLC) method for purity:

An exemplary method for determining the HPLC purity for compounds of Formula I is
provided herein. An exemplary compound of Formula I, wherein R is methyl was
analyzed using the method outlined in Table 1. Modifications of the analytical method
which may be required for compounds of Formula I wherein R is other than methyl, are
well within the capabilities of a person of ordinary skill in the art. The modifications may
include parameters like choice of the diluent depending upon the solubility of the
compound or the gradient program depending upon the elution of the compound which in
turn depend upon the changing polarity with changing definition of the R group. It may be
noted that any other column equivalent to Aquity UPLC™BEH (C-18) having
octadecylsilane chemically bonded to porous or non-porous silica or ceramic micro-
particles, 1.5 to 10 µm indiameter, or a monolithic rod as packing material may be used for
determining the HPLC purity.

Table 1

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<tr>
<th>Column</th>
<th>Aquity UPLC™, BEH C-18, (2.1mm x100 mm x 1.7 µm) or equivalent thereof</th>
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<td>Mobile phase</td>
<td>Buffer : Dissolve 1.36gm KH₂PO₄ in 1000ml water. Adjust pH 3.0 with orthophosphoric acid. Filter through 0.22µm filter Mobile phase-A : Buffer:Acetonitrile(980:20) Mobile phase-B : Buffer:Acetonitrile(300:700)</td>
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<td>Gradient programming</td>
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<td>Sample preparation</td>
<td>about 2.5 mg of sample was weighed accurately and dissolved in 5.0 mL diluent.</td>
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<tr>
<td>Calculation</td>
<td>By area normalization</td>
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</table>

Example 1: Preparation of 3-hydroxy-4-methoxy benzoic acid methyl ester

10 Concentrated sulfuric acid (1.5 mL) wasadded to a stirred solution of 3-hydroxy-4-
methoxy benzoic acid (10.0 g, 0.06 mol) in methanol (100 mL) at room temperature and then heated to reflux at 85°C for total 6 h. Reaction mixture wasconcentrated under reduced pressure at 50 °C, residue is dissolved in ethyl acetate (150mL). Ethyl acetate layer waswas washed with saturated sodium bicarbonate solution followed by water and brine solution. Organic layer wasdried over anhydrous sodium sulphate and concentrated under
Example 2: Preparation of 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid methyl ester

Aqueous formaldehyde (37% solution, 9.53 mL, 0.12 mol) was added to a stirred solution of 3-hydroxy-4-methoxy benzoic acid methyl ester (10.7 g, 0.06 mol) in 1,4-dioxane (107 mL) at room temperature. Glacial acetic acid (1 mL) followed by aqueous dimethyl amine solution (40% solution, 13.2 mL, 0.12 mol) were added to the reaction mixture and heated at 110°C for 5 h. Reaction mixture was concentrated under reduced pressure at 50°C, 2N HCl solution was added to the residue and washed with ethyl acetate. The aqueous layer was basified with sodium bicarbonate (pH~9), saturated with sodium chloride and extracted with dichloromethane. Combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to get 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid methyl ester (9.8 g, 70.0%), which was used for the next step without further purification.

Example 3: Preparation of 3-hydroxy-4-methoxy-2-methyl benzoic acid methyl ester

5% Palladium on charcoal (9.34 g, 50% wet) was added to a stirred solution of 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid methyl ester (9.86 g, 0.041 mol) in methanol (99 mL) at room temperature. Reaction mixture was hydrogenated at 85°C for 7 h under 5-6 kg/cm² pressure of hydrogen gas in an autoclave apparatus. Reaction
mixture was filtered through celite and washed with methanol. Combined filtrate was concentrated under reduced pressure at 50 °C; residue was dissolved in ethyl acetate and washed with 2N HCl solution followed by water and brine solution. Organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure at 50 °C to furnish 3-hydroxy-4-methoxy-2-methyl benzoic acid methyl ester (7.0 g, 86.6 %), which was used directly for the next step without further purification.

Example 4: Preparation of 3,4-dihydroxy-2-methyl benzoic acid methyl ester

\[ \text{Anhydrous aluminium chloride (16.6 g, 0.12 mol) was added slowly to a stirred solution of 3-hydroxy-4-methoxy-2-methyl benzoic acid methyl ester (7.0 g, 0.036 mol) in toluene (70 mL) at room temperature and then heated at 75 °C for 2 and half hours. Reaction mixture was cooled to 0-5 °C, 2N HCl solution (70 mL) was added slowly and then extracted with ethyl acetate. Combined organic layer was washed with water followed by brine solution and dried over anhydrous sodium sulphate. Activated charcoal (1.4 g) was added to the ethyl acetate layer and stirred at 55 °C for 1 h. Solution was then filtered through celite and washed with ethyl acetate. Combined organic layer was concentrated under reduced pressure at 50 °C. The product was isolated, e.g., by adding n-hexane to the residue and stirred at room temperature for 1 h. Solid thus obtained was filtered, washed with n-hexane and dried under vacuum to furnish crude 3,4-dihydroxy-2-methyl benzoic acid methyl ester which was further purified by recrystallization from methanol and water to give the title compound. HPLC purity: 99.93 %; positional isomer, compound of Formula I (R = methyl): Not detected. The HPLC purity of the compound of Formula I (R = methyl) was determined by the HPLC method described in Table 1 above. Under those conditions, the peak for the compound of Formula I (R = methyl) had a retention time (RT) of 7.05 min. An exemplary chromatogram is shown in Figure 1.}

A sample of the positional isomer, the compound of Formula I'(R = methyl), was also analyzed by the same method for which the peak appeared at 8.54 min. Relative retention
time 1.21 with respect to the peak for compound of Formula I. An exemplary chromatogram is shown in Figure 2.
Claims:

1. A process for preparation of 3,4-dihydroxy-2-methyl benzoic acid alkyl ester or its acid derivative, a compound of Formula I or salts thereof,

   \[
   \text{Formula I}
   \]

   wherein R is selected from hydrogen and C\(_1\)-4 alkyl, the process comprising:

   a) reacting 3-hydroxy-4-methoxy benzoic acid C\(_1\)-4 alkyl ester, a compound of Formula III with formaldehyde and dimethyl amine to obtain 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C\(_1\)-4 alkyl ester, a compound of Formula II,

   \[
   \text{Formula III} \quad \xrightarrow{\text{reaction}} \quad \text{Formula II}
   \]

   b) reducing 2-dimethylaminomethyl-3-hydroxy-4-methoxy benzoic acid C\(_1\)-4 alkyl ester, a compound of Formula II, to obtain 3-hydroxy-4-methoxy-2-methyl benzoic acid C\(_1\)-4 alkyl ester, a compound of Formula IV,

   \[
   \text{Formula II} \quad \xrightarrow{\text{reduction}} \quad \text{Formula IV}
   \]

   and

   c) demethylating the 3-hydroxy-4-methoxy-2-methyl benzoic acid C\(_1\)-4 alkyl ester, a compound of Formula IV, and isolating 3,4-dihydroxy-2-methyl benzoic acid C\(_1\)-4 alkylester, a compound of Formula I,
d) optionally, hydrolyzing the 3,4-dihydroxy-2-methyl benzoic acid C₁-₄ alkyl ester, to get 3,4-dihydroxy-2-methyl benzoic acid, a compound of Formula I wherein R is hydrogen and,

e) optionally, converting the product of c) or d) into its salt.

2. The process as in claim 1, wherein the compound of Formula I is substantially pure.

3. The process as in claim 1 wherein the 3,4-dihydroxy-2-methyl benzoic acid C₁-₄ alkyl ester, the compound of Formula I, has a HPLC purity of at least about 99.5%.

4. The process as in claim 3 wherein the 3,4-dihydroxy-2-methyl benzoic acid C₁-₄ alkyl ester, the compound of Formula I, has a HPLC purity of at least about 99.9%.

5. The process as in any of the preceding claims, wherein the compound of Formula I is substantially free of compounds of Formula I':

6. The process as in any of the preceding claims, wherein R in compound of Formula I, II, III and IV is methyl.

7. A compound of Formula II or salts thereof.
wherein R is selected from H and C\textsubscript{1-4} alkyl.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C67/317 C07C227/10 C07C229/38 C07C51/09 C07C69/84

ADD.

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)

- EPO-Internal
- CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>A</td>
<td>CN 105 130 808 A (SHANGHAI RAINBOW CHEMISTRY CO LTD) 9 December 2015 (2015-12-09) cited in the application on figure 1</td>
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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
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- "P" document published prior to the international filing date but later than the priority date claimed

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"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

"A" document member of the same patent family

Date of the actual completion of the international search: 23 August 2017

Date of mailing of the international search report: 19/09/2017

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer:

Del anghe, Patrick
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