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(54) Title: PROCESS FOR PREPARATION OF GLYCOPYRROLATE INTERMEDIATE

(57) Abstract: The present invention discloses an improved process for preparation of highly pure cyclopentyl mandelic acid derivative of formula (I), an intermediate of glycopyrrolate, without using hazardous chemicals.

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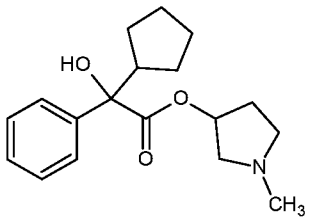
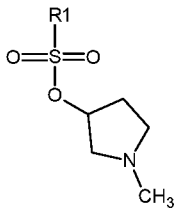
"PROCESS FOR PREPARATION OF GLYCOPYRROLATE INTERMEDIATE"

Technical Field:

The present invention relates to a novel process for preparation of highly pure cyclopentyl mandelic acid derivative of formula (I), an intermediate of glycopyrrolate, from cyclopentyl mandelic acid and sulfonyl compound of formula (II).



Formula (I)



Formula (II)

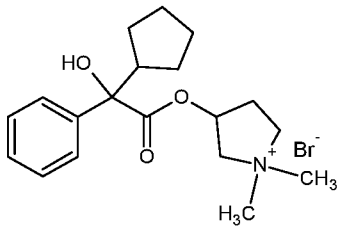
wherein R1 is alkyl containing 1 to 12 carbon atoms, aryl or substituted aryl.

Background and Prior art:

3-((Cyclopentylhydroxyphenylacetyl)oxy)-1,1-dimethylpyrrolidinium bromide also known as glycopyrronium bromide or glycopyrrolate, is an antimuscarinic agent. The drug is a potent anticholinergic useful in the treatment of peptic ulcer. It is useful for the treatment of sialorrhea, hyperhydrosis, and overactive bladder and for pre-surgery treatment. In anesthesia, glycopyrronium injection can be used before surgery in order to reduce salivary, tracheobronchial, and pharyngeal secretions, as well as decreasing the acidity of gastric secretion. It has been used topically and orally to treat hyperhidrosis, in particular, gustatory hyperhidrosis. In inhalable form it is used to treat chronic obstructive pulmonary disease (COPD). The drug is effective at extremely low concentration.

Glycopyrrolate is a quaternary ammonium compound which prevents its passage through lipid membrane and therefore does not induce undesirable side effects such as dizziness, restlessness, irritability, disorientation, depression etc.

Glycopyrrolate was disclosed for the first time in the U.S. patent number 2956062 and hasthe following chemical structure:

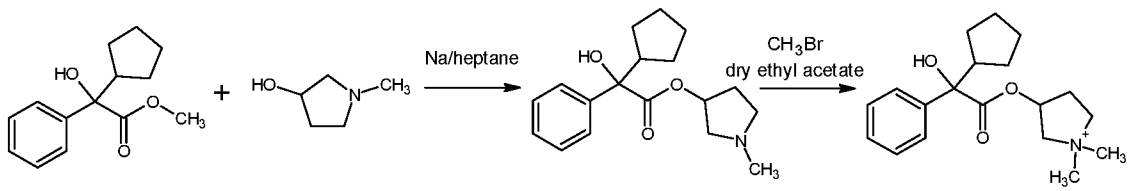


As seen in the above structure, Glycopyrrolate molecule has two chiral centres and can have four stereo isomers, i.e. two enantiomeric pairs of diastereoisomers. Glycopyrrolate is a racemic mixture containing only one pair of enantiomers. Commercially available Glycopyrrolate contains both the (R,S)-Glycopyrrolate and (S,R)-Glycopyrrolate isomers.

The above structure indicates that Glycopyrrolate is a quaternary ammonium compound. It is an ester of cyclopentyl mandelic acid which is a hydroxy acid. Being a hydroxyacid, usual activation of cyclopentyl mandelic acid, as acid chlorides, is not possible.

Following the original procedure disclosed in the U.S. patent number 2956062, Glycopyrrolate is prepared by transesterification of methyl ester of cyclopentyl mandelic acid with 1-methyl pyrolidin-3-ol; followed by quaternization of the resulting ester.

The patent describes the synthesis of glycopyrrolate as follows:



Transesterification of methyl ester of cyclopentyl mandelic acid with 1-methyl pyrolidin-3-ol is carried out under the influence of metallic sodium to obtain cyclopentyl mandelic acid ester which is the key intermediate for the synthesis of glycopyrrolate. As a tertiary amine, the cyclopentylmandelic acid ester can be purified by extraction of its salt into water to remove impurities followed by back extraction into an organic solvent.

The final step of the synthesis is N-methylation of the ester using methyl bromide to form the solid quaternary ammonium salt. As the reactants are applied as racemates, glycopyrrolate is formed as a mixture of two pairs of diastereomers which are separated by final repeated recrystallization to get the desired higher melting RS/SR-diastereomers.

Although the synthesis is easy from a chemical point of view, the scale up in the pilot and production facilities bears some drawbacks. The transesterification using metallic sodium represents a severe safety problem. Furthermore, the handling of the intermediate, cyclopentylmandelic acid ester needs special attention as it is known to cause reversible exogenous psychosis when exposed to man, and the loading of numerous vessels and tanks with solutions containing ester or its salt is potentially more hazardous.

The process also requires an additional step of preparing methyl ester of cyclopentylmandelic acid, the starting material.

The patent application number WO2010115937 discloses direct esterification of cyclopentyl mandelic acid with 1-methyl-pyrolidin-3-ol using carbonyl diimidazole (CDI) as a coupling reagent. The process requires more than 18 hours to provide the ester and results into imidazole compounds as byproducts. This process is time consuming and requires highly expensive reagents with very poor yields thus making the process industrially uneconomical.

The Indian patent application number 2236/CHE/2006 discloses a process for preparation of glycopyrrolate comprising transesterification of methyl ester of cyclopentyl mandelic acid with 1-methylpyrolidin-3-olusing sodium methoxide in an inert solvent. However, the reaction results into a mixture of cyclopentyl mandelic acid ester and cyclopentenyl mandelic acid ester byproduct. The mixture is hydrogenated using a catalyst in an organic solvent to provide cyclopentyl mandelic acid which is finally quaternized to obtain Glycopyrrolate. Thus, the process requires an additional step of hydrogenation of the mixture of cyclopentylmandelic acid ester and cyclopentenylmandelic acid ester prior to the quarternization step.

Using conventional Mitsunobu reaction, transesterification of methyl ester of cyclopentyl mandelic acid with 1-methylpyrolidin-3-ol can be carried out in presence of diisopropyl azodicarboxylate and triphenyl phosphine. However, the process results into formation of triphenylphosphine oxide in large quantity, which is hazardous for the environment and thus necessitates additional precautions as a part of safety measure.

The Korean patent number KR101317924 discloses improved conditions for Mitsunobu reaction where transesterification of methyl ester of cyclopentyl mandelic acid with 1-methylpyrolidin-3-ol is carried out using (cyanomethylene)tributylphosphorane (CMBP). Though the process is simple and provides improved conditions for Mitsunobu reaction, the reagent CMBP is expensive making the process industrially uneconomical.

The Chinese patent application number CN102627596 discloses a method for preparation of Glycopyrrolate where transesterification of methyl ester of cyclopentyl mandelic acid with 1-methylpyrolidin-3-ol is carried out using 4-chloro-2,6-dimethoxytriazine (CDMT) as a condensing agent. This process is not suitable for industrial application as CDMT is hazardous as well as expensive reagent which is not easily available. Use of CDMT causes irritation to eyes,

respiratory system and skin. It is found that the products obtained by using triazene reagents are not colourless but has bluish to grey colour and need column chromatography to get colourless products.

Needless to say it is advantageous to develop a short, high yielding and industrially viable process for preparation of highly pure glycopyrrolate which eliminates use of hazardousand expensive reagentsthat is simple and easier to scale for industrial production.

Object of the invention:

It is therefore an object of the invention is to overcome or ameliorate atleast one disadvantage of the prior art or to provide a useful alternative.

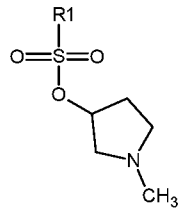
Another object of the invention is to provide novel, high yielding processes for preparation of highly pure ester of cyclopentyl mandelic acidderivative, an intermediate of glycopyrrolate, using easily available starting material; and under mild conditions avoiding need of hazardous chemicals, tedious work-up and purification process.

Yet another object of the invention is to provide a concise, commercially viable and industrially applicable process for preparation of highly pure glycopyrrolate having desirable pharmacological activity, broad safety margins, without toxicity or unfavorable side effects.

Summary of the invention:

In accordance with the above objectives, the present invention provides an economic, industrially feasible and high yielding process for the preparation of highly pure glycopyrrolate intermediate under mild conditions.

According to one aspect, the present invention provides a process for preparation of pure cyclopentyl mandelic acid ester comprising reacting cyclopentyl mandelic acid with sulfonyl compound of formula (II) in presence of a base and a solvent.



Formula (II)

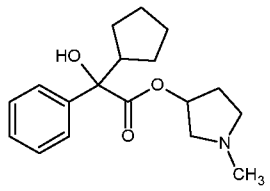
wherein R1 is alkyl containing 1 to 12 carbon atoms, aryl or substituted aryl.

Detailed description of the invention:

Unless specified otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any methods and material or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described. To describe the invention, certain terms are defined herein specified as follows:

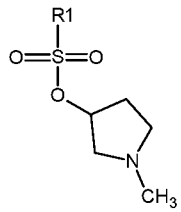
Unless stated to the contrary, any of the words 'having', 'including', 'includes', 'comprising' and 'comprises' mean 'including without limitations' and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose illustration rather than limitation of the invention as set forth the appended claims.

Accordingly, the present invention provides a process preparation of highly pure cyclopentyl mandelic acid derivative of formula (I)



Formula (I)

Comprising reacting cyclopentyl mandelic acid with sulfonyl compound of formula (II)



Formula (II)

wherein R1 is alkyl containing 1 to 12 carbon atoms, aryl or substituted aryl, in presence of a

base and a solvent.

In a preferred embodiment R1 is methyl, phenyl or 4-methylphenyl.

The reaction is carried in presence of abase which is organic or inorganic. Examples of organic base include tertiary amines such as trialkyl amine. Examples ofinorganic base include alkali metal carbonate, alkaline earth metalcarbonate, alkali metalbicarbonate, alkaline earth metal bicarbonate, alkali metal hydroxide, alkaline earth metalhydroxide and mixture thereof. Examples of alkali metal carbonate includesodium carbonateand potassium carbonate. Examples of alkali metal bicarbonate includesodium bicarbonate andpotassium bicarbonate. Examples of alkaline earth metal carbonateinclude calcium carbonateand magnesium carbonate. Examples of alkaline earth metalbicarbonate include calciumbicarbonate and magnesium bicarbonate. Examples of alkalimetal hydroxide include potassium hydroxide and sodium hydroxide.

The base is conveniently used in an amount, relative to cyclopentyl mandelic acid, preferably in a range between 1 to 12 equivalents, more preferably 3 to 10 equivalents.

The suitable solvent used in the reaction is aprotic solvent selected from acetone, acetonitrile, carbon tetrachloride, dimethylsulfoxide, and dimethylformamide.

The process avoids the use of hazardous chemicals (e.g. metallic sodium) which have been used in the literature thus avoiding accidents.

The process of the present invention may be carried out at suitable temperature. To minimize the decomposition of products and impurity formation the reaction is carried out at 50 to 130°C, more preferably at 60 to 110°C. The most preferred temperature is 70 to 100°C.

The process of manufacture of cyclopentyl mandelic acid ester via reaction of cyclopentyl mandelic acid and sulfonyl compound of formula (II) is short and thus reduces cost and atom economy.

The resultingcyclopentyl mandelic acid ester is isolated in high yield and purity without need of further purification and can directly be subjected to quaternization to obtain glycopyrrolate by methods known in the art.

The pure glycopyrrolate obtained by the process of the invention may be formulated into a dosage form by combining with one or more pharmaceutically acceptable excipients using known techniques. Further the dosage form may be formulated as immediate release or extended release dosage form.

Further details of the process of the present invention will be apparent from the examples presented below. Examples presented are purely illustrative and are not

limited to the particular embodiments illustrated herein but include the permutations, which are obvious as set forth in the description.

Examples

Example 1

Preparation of N-Methyl-3-pyrrolidinyl cyclopentylmandelate

A mixture of cyclopentyl mandelic acid (25 gm), acetonitirle (300 ml), sodium carbonate (48.16 gm) and N-methyl-3-methylsulphonyloxypyrrolidine (30.15 gm) was heated to 75 - 80°C and maintained at same temperature till completion of the reaction. The reaction was monitored on HPLC. The reaction mixture was cooled to 25 to 30°C, filtered and the solid was washed with acetonitrile (50 ml). The filtrate was concentrated under vacuum get N-Methyl-3-pyrrolidinyl cyclopentylmandelate(oil, 30 gm, 96%HPLC purity).

Example 2

Preparation of N-Methyl-3-pyrrolidinyl cyclopentylmandelate

Preparation of N-Methyl-3-pyrrolidinyl cyclopentylmandelate was carried out according to the example 1 by reacting a mixture of cyclopentylmandelic acid (10 gm), acetonitirle (120 ml), sodium carbonate (19.2 gm) using N-methyl-3-(p-toluenesulphonyloxy)pyrrolidine(17.36 gm) instead of N-methyl-3-methylsulphonyloxypyrrolidine. (Yield 11.5 gm, 95.6% HPLC purity).

Example 3

Preparation of N-methyl-3-methylsulphonyloxypyrrolidine

A mixture ofdichloromethane (500 ml), N-methyl-3-pyrrolidinol (100 gm) and 20% sodium hydroxide was cooled to 0°C. Methanesulphonyl chloride (206 gm) was added to the reaction mixture at 0°C. After completion of the reaction layers were separated. The organic layer was washed thoroughly with water and concentrated under vacuum to get N-methyl-3-methylsulphonyloxypyrrolidine (yield 124 gm, GC purity 95%).

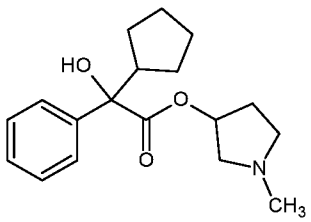
Example 4

Preparation of N-methyl-3-(p-toluenesulphonyloxy)pyrrolidine

Preparation of N-methyl-3-(p-toluenesulphonyloxy)pyrrolidine was carried out according to the example 3 using p-toluenesulphonyl chloride (67.95 gms) instead of methanesulphonychloride. (yield 150 gm, GC purity 94%).

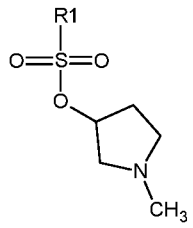
We claim,

1. A process for preparation of cyclopentylmandelic acid ester of formula (I)



Formula (I)

comprising, reacting cyclopentyl mandelic acid with sulfonyl compound of formula (II)



Formula (II)

wherein R1 is alkyl containing 1 to 12 carbon atoms, aryl or substituted aryl in presence of a base and solvent.

2. The process as claimed in claim 1, wherein R1 is methyl, phenyl or 4-methylphenyl.

3. The process as claimed in claim 1, wherein the base is organic or inorganic.

4. The process as claimed in claim 3, wherein the base is selected from tertiary amines, alkali metal carbonate, alkaline earth metal carbonate, alkali metal bicarbonate or alkaline earth metal bicarbonate.

5. The process as claimed in claim 4, wherein the base is selected from triethyl amine, N-methylmorpholine, diisopropylethyl amine, N-methylpiperidine, sodiumcarbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, calcium carbonate, magnesium carbonate, calcium bicarbonate, magnesium bicarbonate, potassium hydroxide andsodium hydroxide.

6. The process as claimed in claim 4, wherein the base is used in an amount, relative to cyclopentylmandelic acid, in a range of 1 to 12 equivalents.

7. The process as claimed in claim 1, wherein the solvent is selected fromacetone, acetonitrile, carbon tetrachloride, dimethylsulfoxide, dimethylformamide, methanol and isopropanol.

8. The process as claimed in claim 1, wherein the reaction is carried out at a temperature range of 50 to 130°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2020/050036

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/40 Version=2020.01

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)

A61K

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2010115937A1 (ALLMENDINGER THOMAS [CH]; NOVARTIS AG [CH]) 14 October 2010 scheme, page 17	1-8
Y	Yangxin Wang et al., Green Chem., 17, 3910-3915, 18 May 2015 page 1, Introduction: line 4	1-8

☐ 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
"D" document cited by the applicant in the international application
"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)
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"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
05-06-2020	05-06-2020
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Abhas Kumar Bhoi Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2020/050036

Citation	Pub.Date	Family	Pub.Date
WO 2010115937 A1	14-10-2010	US 2012022127 A1	26-01-2012
		EP 2417106 A1	15-02-2012
		JP 5902612 B2	13-06-2016
		CN 102388021 A	21-03-2012
		KR 101290893 B1	29-07-2013