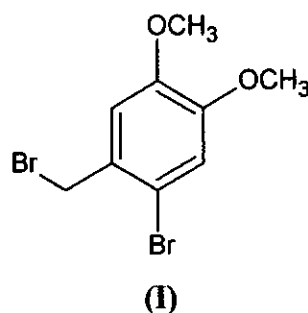


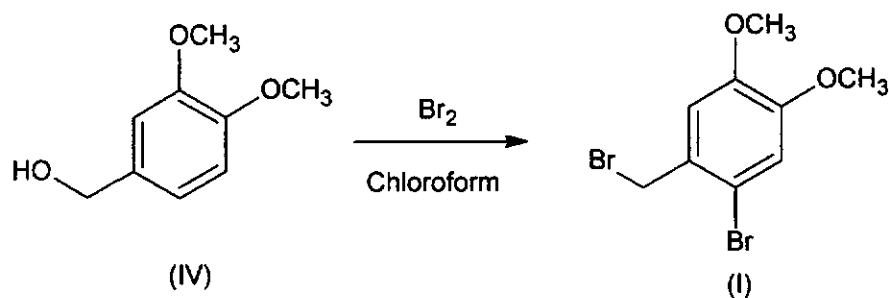
Field of the invention:

The present invention relates to novel process for the preparation of (2-bromo-4,5-dimethoxyphenyl) methyl bromide of formula (I). (2-bromo-4,5-dimethoxyphenyl) methyl bromide, which is an intermediate for the preparation of many pharmaceutical compounds. The invention also relates to the use of (2-bromo-4,5-dimethoxyphenyl) methyl bromide (I) for the preparation of pinaverium bromide.

**Background of the invention:**

Pinaverium bromide is a locally acting spasmolytic agent of the digestive tract. Its mechanism of action relies upon inhibition of calcium ion entrance into smooth muscle cells (calcium-antagonist effect). In humans pinaverium facilitates gastric emptying and decreases intestinal transit time in patients with constipation. Pinaverium is very effective in improving symptoms of irritable bowel syndrome (abdominal pain, gas, diarrhea or constipation).

(2-bromo-4,5-dimethoxyphenyl) methyl bromide of formula (I) is a key intermediate for the preparation of many pharmaceutical compounds including, mainly pinverium bromide. The synthesis of (2-bromo-4,5-dimethoxyphenyl) methyl bromide of formula (I) is reported in reference, Journal of Organic Chemistry, 1987, 52(4), 704-706, which involves bromination of (3,4-dimethoxyphenyl) methanol of formula (IV) with bromine in chloroform to afford (2-bromo-3,4-dimethoxyphenyl) methyl bromide. However, usage of chloroform at commercial scale should be avoided.



WO 2005/028434 discloses the process for preparation of (2-bromo-4,5-dimethoxyphenyl) methyl bromide (I) by reaction of (3,4-dimethoxyphenyl) methanol (II) is treated with bromine in methanol/THF and acetate buffer to afford 2-bromo-4,5-dimethoxy-phenyl)-methyl bromide.

WO 2008/1444483 discloses the process for preparation of (2-bromo-4,5-dimethoxyphenyl) methyl bromide (I), which involves bromination of (3,4-dimethoxyphenyl) methanol (IV) with bromine in acetic acid.

CN102060807 discloses the process for preparation of pinaverium bromide, which involves the reaction of (3,4-dimethoxyphenyl) methanol (IV) with bromine in acetic acid to obtain key intermediate (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide.

Organic Process Research and Development, 1999, 3(6), 451-455 also discloses the process.

However, there is need to have a simple, commercially advantageous process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide. Inventors of the present invention has found an improved process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide.

Object of the Invention:

The object of the present invention is to provide a novel process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

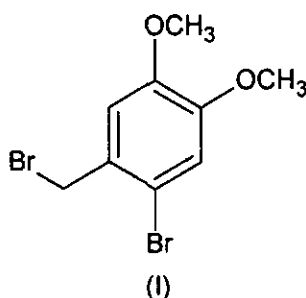
Another object of the present invention is to provide a novel process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I), which is a key intermediate for the preparation of pinaverium bromide.

Yet another object of the present invention is to provide the one-pot process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) from veratrole.

Another object of the present invention is to use (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) for the preparation of pinaverium bromide prepared in accordance with invention.

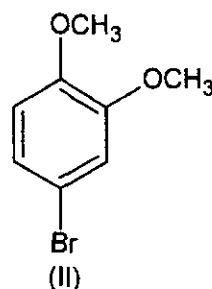
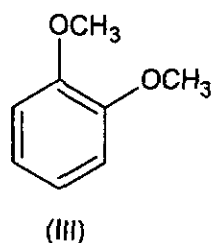
Detailed Description of the invention:

The present invention provides a novel process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I)



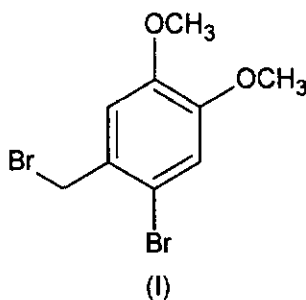
which comprise;

(a) reacting a veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide a 4-bromo-veratrole of formula (II);



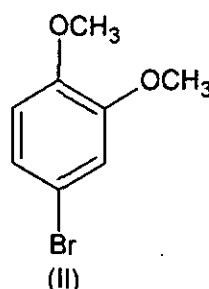
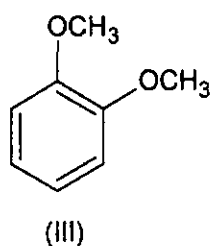
(b) reacting the 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

According to the present invention, there is provided a one-pot process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I)



which comprise;

(a) reacting a veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide a 4-bromo-veratrole of formula (II);



(b) reacting *insitu* 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I)

According to the present invention, the process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide involves reaction of veratrole of formula (III) with brominating agent in presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II).

The brominating agent can be selected from the group comprising of bromine, hydrogen bromide, N-bromosuccinamide. The preferred brominating agent is hydrogen bromide.

The suitable solvent comprises one or more solvent selected from halogenated solvent, hydrocarbon solvent, ester, ether or a polar solvent. Preferably, the suitable solvent can be selected from the group comprising of methylene dichloride, chlorobenzene, toluene, xylene, ethyl acetate, butyl acetate, isopropyl acetate, diethyl ether, isopropyl ether, diisopropyl ether, methyl *tert*-butyl ether or mixtures thereof. The preferred solvent is methylene dichloride.

The bromination reaction of veratrol can be carried out in the presence of hydrogen peroxide.

The bromination reaction of veratrol can be carried out at about 5°C to 50°C; preferably the reaction is carried out at 10° to 20°C.

Thus obtained, 4-bromo-veratrol of formula (II) is further reacted with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

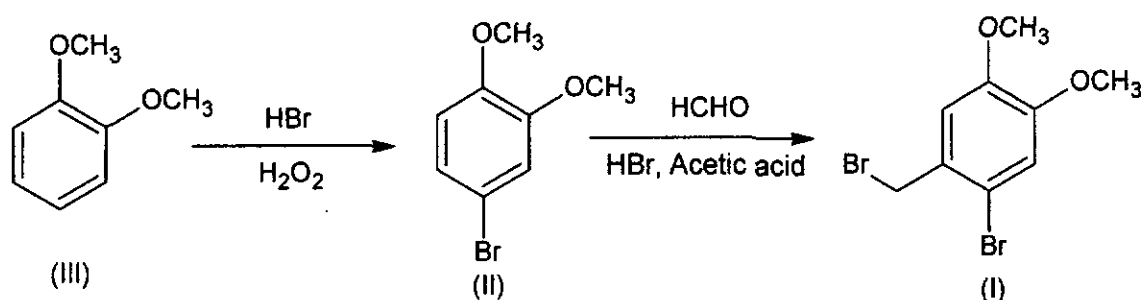
The brominating agent can be selected from the group comprising of bromine, hydrogen bromide, N-bromosuccinamide. The preferred brominating agent is hydrobromic acid solution in acetic acid.

The suitable solvent can be selected from one or more solvent selected from acetic acid, halogenated solvent or mixtures thereof. The preferred solvent is acetic acid.

According to the another aspect of the invention, there is provided a one-pot process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I), which comprise reacting veratrole of formula (III) with brominating agent, preferably hydrogen bromine in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II) and further reacting *insitu* 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

In the preferred embodiment of the present invention, veratrole is reacted with hydrogen bromide in methylene chloride in the presence of hydrogen peroxide solution at about 10 to 25°C to obtain 2-bromo veratole. The obtained reaction mass containing 2-bromo veratole is evaporated and acetic acid is added to the reaction mass. Further, formaldehyde was added at about 15 to 50°C to the reaction mass. The hydrogen bromide solution in acetic acid is added drop wise to the reaction mass at about 15 to 50°C to obtain (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I). The reaction mass was dumped in water followed by extracted with organic solvent selected from toluene, xylene, methylene dichloride. The organic layer was separated and evaporated to dryness to isolate (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide.

The process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide may be illustrated by following scheme-1.



Scheme-1

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification.

The process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide and its intermediate described in the present invention is demonstrated in examples illustrated below. This example is provided as illustration only and therefore should not be construed as limitation of the scope of invention.

Example: Preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide

138g (1.0 mole) of veratrole was added in 500ml of methylene dichloride in round bottom flask under stirring. 181g (1.07mole) of hydrobromic acid was added drop wise to the reaction mass followed by addition of 80g of 50% hydrogen peroxide (1.176mole) and stirred at 15 to 20°C for about 2-4 hours. The organic layer was extracted and evaporated to provide the reaction mass containing 4-bromo veratrole. The 250ml of acetic acid was added to reaction

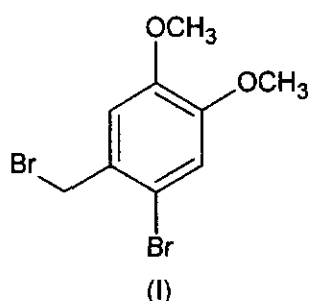
mass at 25 to 35°C. 220ml of hydrobromic acid in acetic acid was added to the reaction mass and maintained at about 25°C till the completion of the reaction. The water was added to the reaction mass after completion of reaction followed by extraction with toluene to isolate the organic layer. The organic layer was evaporated to obtain crude (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide.

Purification:

The crude (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide dissolved in cyclohexane at about 60°C and gradually cooled to about 10 to 15°C and stirred to crystallize (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide, which was isolated by filtration and dried to provide pure (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide. Yield: 80%, MP: 80 to 85°C, Purity: more than 97% by GC.

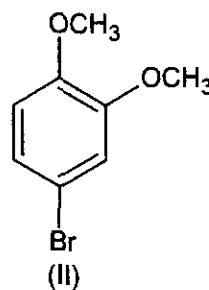
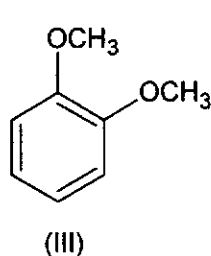
We claim:

1. A process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I)



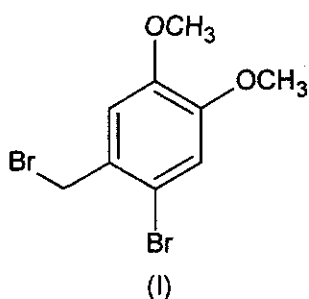
which comprise;

(a) reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II);



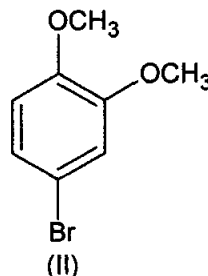
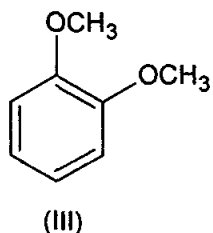
(b) reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

2. A one pot process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I)



which comprise;

(a) reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II);



(b) reacting *in situ* 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

3. The process as claimed claim 1 or 2, wherein the brominating agent is selected from the group comprising of bromine, hydrogen bromide or N-bromosuccinamide.

4. The process as claimed in claim 3, wherein the brominating agent is hydrogen bromide.

5. The process as claimed in claim 1 or 2, where in the suitable solvent in step (a) is selected from the group comprising of methylene dichloride, chlorobenzene, toluene, xylene, ethyl acetate, butyl acetate, isopropyl acetate, diethyl ether, isopropyl ether, diisopropyl ether, methyl *tert*-butyl ether.

6. The process as claimed in claim 5, wherein the suitable solvent is methylene dichloride.

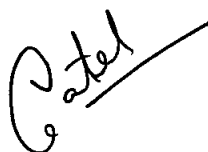
7. The process as claimed in claim 1 or 2, wherein the suitable solvent in step (b) is selected from acetic acid, halogenated solvent or mixtures thereof.

8. The process as claimed in claim 7, wherein the suitable solvent is acetic acid.

9. A process for preparing (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) such as herein described in accordance with accompanying text, description and examples thereof.

Dated this 1st day of January, 2013

Signature:



VITAL MAFATLAL PATEL

MANAGING DIRECTOR, VIHITA CHEM PVT. LTD.