FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

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THE PATENTS RULES, 2003

PROVISIONAL SPECIFICATION

(See section 10 and rule 13)

1. Title of the Invention

A PROCESS FOR PREPARATION OF 4-METHYLENEPIPERIDINE HYDROCHLORIDE

2. Applicant(s)

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3. Preamble to the description

The following specification describes the invention.

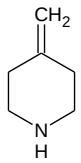
FIELD

The present disclosure relates a process for preparation of 4-methylenepiperidine hydrochloride.

BACKGROUND

4-Methylenepiperidine is used as an active intermediate for the preparation of Effinaconazole, which is an effective anti-fungal drug. 4-methylenepiperidine moiety is used as a reactant in the final step of the preparation of Effinaconazole, therefore quality of 4-methylenepiperidine will significantly impact quality of final API product.

4-Methylenepiperidine [CAS no. 144230-50-2] is represented as **Formula I**



I

Several methods are reported for synthesis of 4-methylenepiperidine. However, these methods are associated with drawbacks such as obtaining product with low yield and/ or low purity. Further, these methods involve tedious purification, thereby resulting in an expensive process.

There is, therefore, felt a need to provide a simple and economical process for the preparation of 4-methylenepiperidine.

OBJECTS

Some of the objects of the present disclosure, which at least one embodiment herein satisfies, are as follows:

It is an object of the present disclosure to ameliorate one or more problems of the prior art or to at least provide a useful alternative.

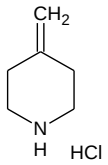
An object of the present disclosure is to provide a process for the preparation of 4-methylenepiperidine.

Another object of the present disclosure is to provide an economical and simple process for preparation of 4-methylenepiperidine.

Other objects and advantages of the present disclosure will be more apparent from the following description, which is not intended to limit the scope of the present disclosure.

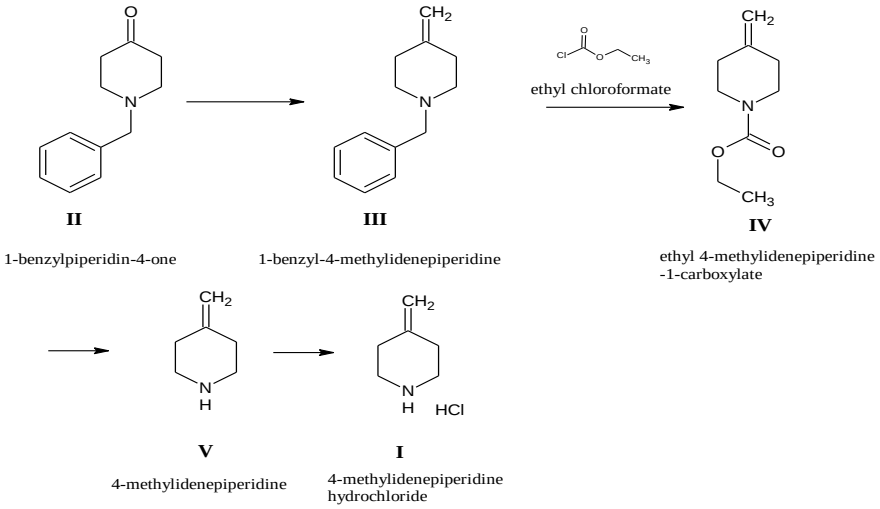
DETAILED DESCRIPTION:

4-Methylenepiperidine is used as an intermediate in the preparation of anti-fungal drug Effinaconazole. The present disclosure envisages a simple method for the preparation of 4-methylenepiperidine hydrochloride. The product is represented by **Formula I**:



I

In accordance with the present disclosure, there is provided a process for the preparation of 4-methylenepiperidine (**I**). The preparation of 4-methylenepiperidine (**I**), in accordance with the process of the present disclosure, is shown as Scheme I:

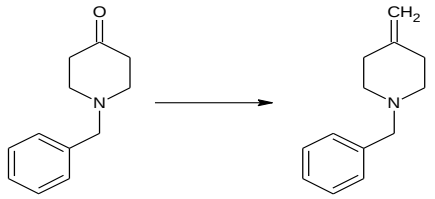


The process of the present disclosure involves a simple synthesis of 4-methylene piperidine HCl (**I**) comprises the following steps.

- Wittig reaction of 1-benzylpiperidine-4-one **(II)** to obtain 1-benzyl-4-methylidenepiperidine (**III**);
- Debenzylation of 1-benzyl-4-methylidenepiperidine (**III**) to obtain N-carbethoxy-4-methylene piperidine **(IV)**;
- Hydrolytic deprotection of N-carbethoxy-4-methylene piperidine **(IV)** to obtain 4-methylidenepiperidine **(V)**; and
- Hydrochloride salt formation of 4-methylidenepiperidine **(V)** to obtain 4-methylene piperidine HCl (**I**).

The process is described in detail herein below:

Step-I: Wittig reaction of 1-benzylpiperidine-4-one **(II)** to obtain 1-benzyl-4-methylidenepiperidine (**III**)



II 1-benzylpiperidin-4-one **III** 1-benzyl-4-methylidenepiperidine

Wittig reaction of 1-benzylpiperidine-4-one **(II)** can be carried out using methyl triphenylphosphonium bromide and an alkali in a first fluid medium to obtain 1-benzyl-4-methylidenepiperidine (**III**).

The reaction can be carried out at a temperature in the range of 50 °C to 90 °C, preferably 70 °C to 72 °C for a time period in the range of 1 hour to 10 hours, preferably 1 hour to 4 hours to obtain a first product mixture comprising 1-benzyl-4-methylidenepiperidine (**III**).

The first product mixture can be cooled. The cooled first product mixture can be diluted with water to obtain a first biphasic mixture comprising a first aqueous layer and a first organic layer. The first aqueous layer can be separated from the first biphasic mixture to obtain the first organic layer comprising 1-benzyl-4-methylidenepiperidine (**III**).

In accordance with the embodiments of the present disclosure, the first organic layer can be directly taken to the next step, without further purification.

Conventionally, the Wittig reaction is carried out at lower temperature, preferably in the range of 0 °C to 30 °C. However, in accordance with the present disclosure, the Wittig reaction is carried out at higher temperature.

In accordance with the process of present disclosure, methyl triphenylphosphonium bromide and N-benzyl piperidone (**II**) can be added to the first mixture in predetermined fashion. The addition in predetermined fashion includes adding the

methyl triphenylphosphonium bromide and N-benzyl piperidone (**II**) in parts of equal volume over a period of time in the range of 20 min to 30 min.

In accordance with the embodiments of the present disclosure, the molar ratio of 1-benzylpiperidine-4-one **(II)** and methyl triphenylphosphonium bromide can be in the range of 1: 1 to 1:5.

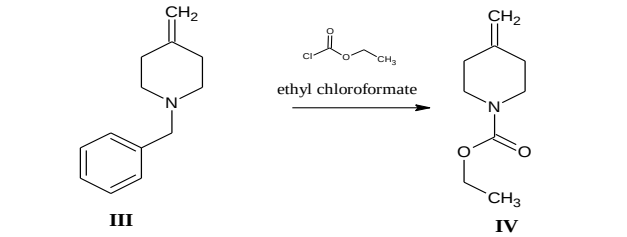
In an exemplary embodiment of the present disclosure, the molar ratio of 1-benzylpiperidine-4-one **(II)** and methyl triphenylphosphonium bromide is 1: 1.2.

The alkali can be at least one selected from group consisting of sodium methoxide, sodium ethoxide and sodium t-butoxide. In an exemplary embodiment of the present disclosure, the alkali is sodium ethoxide.

In accordance with the embodiments of the present disclosure, the molar ratio of 1-benzylpiperidine-4-one **(II)** and the alkali can be in the range of 1: 15 to 1: 25.

In accordance with the embodiments of the present disclosure, the first fluid medium can be at least one selected from group consisting of toluene, tetrahydrofuran and ether. In an exemplary embodiment of the present disclosure, the first fluid medium is toluene.

Step-II: Debenzylation of 1-benzyl-4-methylidenepiperidine (**III**) to obtain N-carbethoxy-4-methylene piperidine **(IV)**



III

1-benzyl-4-methylidenepiperidine

IV

ethyl 4-methylidenepiperidine -1-carboxylate

Debenzylation of 1-benzyl-4-methylidenepiperidine (**III**) can be carried out using ethylchloroformate in a second fluid medium.

The debenzylation of 1-benzyl-4-methylidenepiperidine (**III**) can be carried out at a temperature in the range of 0 °C to 10 °C, preferably 0 °C to 5 °C for a time period in the range of 1 hour to 5 hours to obtain a second product mixture comprising N-carbethoxy-4-methylene piperidine **(IV)**.

The so obtained second product mixture can be diluted with water to obtain a second biphasic mixture comprising a second aqueous layer and a second organic layer. The second organic layer can be separated from the biphasic mixture and the volatiles present in the second organic layer can be distilled out to obtain a first residue comprising N-carbethoxy-4-methylene piperidine (**IV**).

In accordance with the embodiments of the present disclosure, the molar ratio of 1-benzylpiperidine-4-one **(II)** and ethyl chloroformate can be in the range of 1: 5 to 1: 15.

In accordance with the embodiments of the present disclosure, the second fluid medium can be at least one selected from group consisting of toluene, tetrahydrofuran and ether.

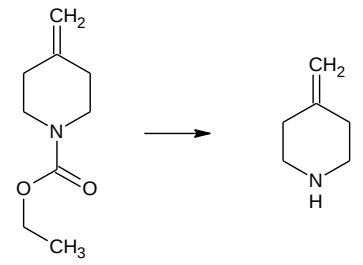
In accordance with one embodiment of the present disclosure, the second fluid medium can be same as the first fluid medium.

The first residue can be further purified with the help of a purification fluid medium. A purification fluid medium can be added to the first residue and stirred for a time period in the range of 10 min to 60 min, followed by filtration to obtain a filtrate. The volatiles present in the filtrate can be evaporated to obtain a second residue. The second residue can be further subjected to distillation under vacuum to obtain N-carbethoxy-4-methylene piperidine (**IV**).

In accordance with the embodiments of the present disclosure, the purification fluid medium can be di-iso-propylether.

N-carbethoxy-4-methylene piperidine (**IV**) obtained by the process of the present disclosure has purity greater than 95%. No further purification is required and N-carbethoxy-4-methylene piperidine (**IV**) can be directly taken to the next step.

Step-III: Hydrolytic deprotection of N-carbethoxy-4-methylene piperidine **(IV)** to obtain 4-methylidenepiperidine **(V)**:



IV

ethyl 4-methylidenepiperidine-1-carboxylate

V

4-methylidenepiperidine

Hydrolytic deprotection of N-carbethoxy-4-methylene piperidine **(IV)** can be carried out using at least one base in a third fluid medium.

The reaction can be carried out at a temperature in the range of 100 °C to 130 °C, preferably 108 °C to 110 °C, for a time period of 10 hours to 20 hours to obtain a third product mixture comprising 4-methylidenepiperidine **(V)**. The third product mixture can be directly taken to the next step, without further purification.

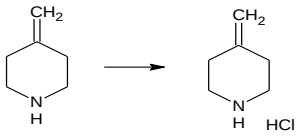
In accordance with the embodiments of the present disclosure, the third product mixture is directly taken to the next step.

In accordance with the embodiments of the present disclosure, the base can be selected from the group consisting of sodium hydroxide and potassium hydroxide.

In accordance with the embodiments of the present disclosure, the molar ratio of N-carbethoxy-4-methylene piperidine **(IV)** and a base can be in the range of 1: 1 to 1: 10.

In accordance with the embodiments of the present disclosure, the third fluid medium can be ethylene glycol.

Step-IV: Hydrochloride salt formation of 4-methylidenepiperidine to obtain 4-methylene piperidine HCl (**I**)



V 4-methylidenepiperidine

I 4-methylidenepiperidine hydrochloride

HCl salt formation of 4-methylidenepiperidine can be carried out in the fourth fluid medium using anhydrous HCl gas. Anhydrous HCl gas can be purged in the reaction mixture till the pH of the reaction mixture is acidic.

The HCl salt formation can be carried out at a temperature in the range of 5 °C to 10 °C to obtain a fourth product mixture comprising 4-methylidenepiperidine hydrochloride (**I**).

In accordance with the embodiments of the present disclosure, the fourth fluid medium can be methylene dichloride.

The so obtained 4-methylidenepiperidine hydrochloride (**I**) can be further purified with the help of a fifth fluid medium. The fifth fluid medium can be added to 4-methylidenepiperidine hydrochloride (**I**) and stirred at a temperature in the range of 0 °C to 5 °C for 1 hour to obtain slurry comprising a solid phase and a liquid phase. The solid phase can be separated from the slurry by filtration. The solid phase can be

dried under reduced pressure at a temperature in the range of 50 °C to 55 °C to obtain pure 4-methylidenepiperidine hydrochloride (**I**).

In accordance with the embodiments of the present disclosure, the fifth fluid medium can be acetone.

The process of the present disclosure is simple and employs inexpensive and easily available reagents. Thus, the process of the present application is economical. The intermediate 4-methylidenepiperidine-1-carboxylate (**IV**) is obtained with high purity and therefore can be used directly in the next step without further purification. High purity of the 4-methylidenepiperidine-1-carboxylate (**IV**) helps in obtaining high purity of 4-methylidenepiperidine hydrochloride (**I**).

The present disclosure is further described in light of the following laboratory experiments which are set forth for illustration purpose only and not to be construed for limiting the scope of the disclosure. The following laboratory scale examples can be scaled up to industrial/commercial scale.

Experiment-I: Preparation of 4-methylidenepiperidine hydrochloride (**I**)

Step I: Wittig reaction of 1-benzylpiperidine-4-one **(II)** to obtain 1-benzyl-4-methylidenepiperidine (**III**)

A reactor was charged with sodium methoxide (0.419 kg) and toluene (3.5 lit) under stirring at room temperature, followed by heating at 70 °C for 15 minutes. Methyl triphenylphosphonium bromide (163 gm) and N-benzyl piperidone (**II**) (70 gm) were added to the reactor in 10 equal mix portions over a period of 20 minutes. The resultant mixture was further heated at a temperature in the range of 70 °C for 4 hours to obtain a first product mixture.

The first product mixture was cooled to 20 °C and diluted with water (2 lit) to obtain a first biphasic mixture comprising a first aqueous layer and a first organic layer. The

first aqueous layer was separated from the first biphasic mixture to obtain the first organic layer comprising 1-benzyl-4-methylidenepiperidine (**III**). The first organic layer was directly taken to the next step without further purification.

Step II: Debenzylation of 1-benzyl-4-methylidenepiperidine (**III**) to obtain N-carbethoxy-4-methylene piperidine **(IV)**

The first organic layer obtained in **step I** was cooled to 5 °C. To the cooled organic layer, was added ethylchloroformate (0.467 kg) in drop-wise manner, followed by stirring at 5 °C for 7 hours to obtain a second product mixture.

The second product mixture was diluted with water to obtain a second biphasic mixture comprising a second aqueous layer and a second organic layer. The second aqueous layer was separated from the second biphasic mixture to obtain the second organic layer. The volatiles present in the second organic layer were distilled out to obtain a first residue comprising N-carbethoxy-4-methylene piperidine (**IV**). The first residue was further purified with the help of di-isopropyl ether.

Di-isopropyl ether (1.5 lit) was added to the first residue and stirred for 30 min, followed by filtration to obtain a first filtrate. The volatiles present in the first filtrate were evaporated to obtain a second residue. The second residue was further subjected to distillation under reduced pressure to obtain N-carbethoxy-4-methylene piperidine (**IV**) (0.35 Kg).

Step III: Hydrolytic deprotection of N-carbethoxy-4-methylene piperidine **(IV)** to obtain 4-methylidenepiperidine **(V)**

A reactor was charged with ethyl 4-methylidenepiperidine-1-carboxylate (**IV**) (100 gm), mono-ethylene glycol (200 gm) and aqueous KOH (200 gm KOH and 200 gm water), followed by heating at 108 °C to 110 °C for 15 hours to obtain a third product mixture. The reaction was monitored by thin layer chromatography (TLC). After

completion of reaction, the third product mixture was cooled to 20 °C and the cooled third product mixture was directly taken to the next step.

Step IV: Hydrochloride salt formation of 4-methylidenepiperidine **(V)** to obtain 4-methylene piperidine HCl (**I**)

The third product mixture was diluted with methylene dichloride (500 mL) and cooled to 5 °C. Anhydrous HCl gas was purged till the pH of the mixture is 2 to obtain a fourth product mixture.

After completion of reaction (monitored by TLC), the volatiles present in the fourth product mixture were removed at reduced pressure to obtain 4-methylidenepiperidine hydrochloride (**I**).

The so obtained 4-methylidenepiperidine hydrochloride (**I**) was further purified with the help of acetone. Acetone (200 mL) was added to the 4-methylidenepiperidine hydrochloride (**I**) and stirred at 5 °C for 1 hour to obtain slurry comprising a solid phase and a liquid phase. The solid fraction was separated by filtration, followed by washing and drying under reduced pressure at 50 °C to obtain pure 4-methylidenepiperidine hydrochloride (**I**) (55 gm).

Purity calculated by HPLC = 99%.

TECHNICAL ADVANCEMENTS

The present disclosure described herein above has several technical advantages including, but not limited to, the realization of:

- a simple process for the preparation of 4-methylene piperidine hydrochloride; and
- an economical process for the preparation of 4-methylene piperidine hydrochloride.

Throughout this specification the word “comprise”, or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The use of the expression “at least” or “at least one” suggests the use of one or more elements or ingredients or quantities, as the use may be in the embodiment of the invention to achieve one or more of the desired objects or results. While certain embodiments of the inventions have been described, these embodiments have been presented by way of example only, and are not intended to limit the scope of the inventions. Variations or modifications to the formulation of this invention, within the scope of the invention, may occur to those skilled in the art upon reviewing the disclosure herein. Such variations or modifications are well within the spirit of this invention.

The numerical values given for various physical parameters, dimensions and quantities are only approximate values and it is envisaged that the values higher than the numerical value assigned to the physical parameters, dimensions and quantities fall within the scope of the invention unless there is a statement in the specification to the contrary.

While considerable emphasis has been placed herein on the specific features of the preferred embodiment, it will be appreciated that many additional features can be added and that many changes can be made in the preferred embodiment without departing from the principles of the disclosure. These and other changes in the preferred embodiment of the disclosure will be apparent to those skilled in the art from the disclosure herein, whereby it is to be distinctly understood that the foregoing

descriptive matter is to be interpreted merely as illustrative of the disclosure and not as a limitation.

Dated this 30th day of March, 2018

MOHAN DEWAN

of R.K. DEWAN & COMPANY

APPLICANT'S PATENT ATTORNEY

TO,

THE CONTROLLER OF PATENTS

THE PATENT OFFICE, AT MUMBAI