FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

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THE PATENTS RULES, 2003

COMPLETE 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 particularly describes the invention and the manner in which it is to be performed

FIELD

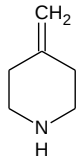
The present disclosure relates a process for preparation of 4-methylenepiperidine hydrochloride.

BACKGROUND

The background information herein below relates to the present disclosure but is not necessarily prior art.

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



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 hydrochloride.

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

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.

SUMMARY

The present disclosure relates to a simple and economical process for preparing 4-methylene piperidine hydrochloride. The process is described herein below:

Initially, 1-benzylpiperidine-4-one is alkylated using alkylating agent in the presence of an alkali and a first fluid medium to obtain 1-benzyl-4-methylidenepiperidine. In the step of alkylation, 1-benzylpiperidine-4-one and the alkylating agent are added in parts of equal volume to a mixture comprising the alkali and the first fluid medium over a period of time in the range of 20 to 40 minutes. 1-benzyl-4-ethylidenepiperidine is then subjected to debenzylation using ethyl chloroformate in the presence of a second fluid medium to obtain N-carbethoxy-4-methylene piperidine. N-carbethoxy-4-methylene piperidine so obtained is further treated with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity greater than 95%. N-carbethoxy-4-methylene piperidine is deprotected using a base in the presence of a third fluid medium to obtain 4-methylidenepiperidine. 4-

methylidenepiperidine is then treated with anhydrous hydrochloride gas in the presence of a fourth fluid medium to obtain 4-methylene piperidine hydrochloride. 4-methylene piperidine hydrochloride is further treated with acetone to obtain pure 4-methylene piperidine hydrochloride having purity greater than 95%.

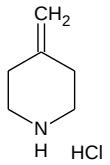
DETAILED DESCRIPTION

Embodiments are provided so as to thoroughly and fully convey the scope of the present disclosure to the person skilled in the art. Numerous details are set forth, relating to specific components, and methods, to provide a complete understanding of embodiments of the present disclosure. It will be apparent to the person skilled in the art that the details provided in the embodiments should not be construed to limit the scope of the present disclosure. In some embodiments, well-known processes, well-known apparatus structures, and well-known techniques are not described in detail.

The terminology used, in the present disclosure, is only for the purpose of explaining a particular embodiment and such terminology shall not be considered to limit the scope of the present disclosure. As used in the present disclosure, the forms "a," "an," and "the" may be intended to include the plural forms as well, unless the context clearly suggests otherwise. The terms "comprises," "comprising," "including," and "having," are open ended transitional phrases and therefore specify the presence of stated features, integers, steps, operations, elements, modules, units and/or components, but do not forbid the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. The particular order of steps disclosed in the method and process of the present disclosure is not to be construed as necessarily requiring their performance as described or illustrated. It is also to be understood that additional or alternative steps may be employed.

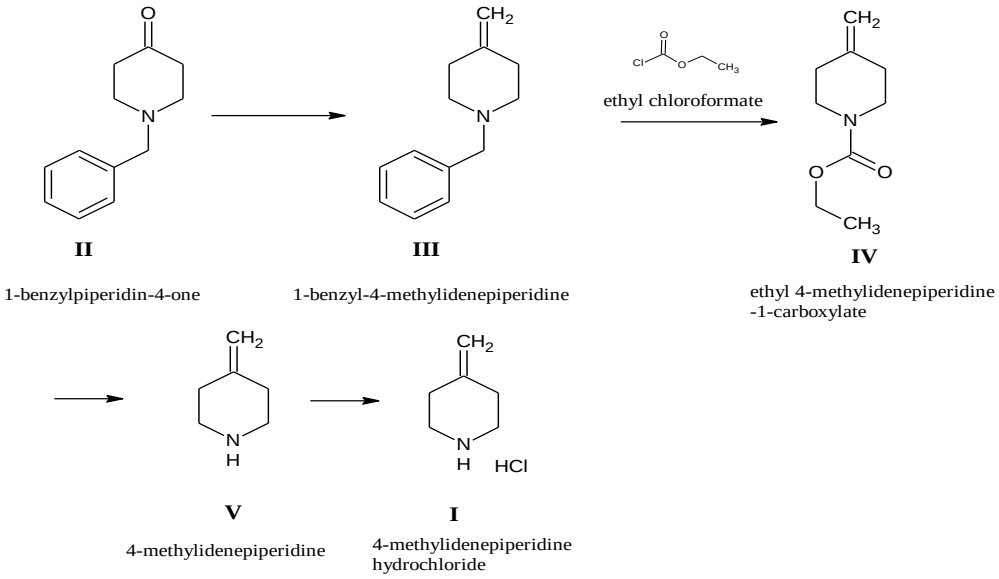
The terms first, second, third, etc., should not be construed to limit the scope of the present disclosure as the aforementioned terms may be only used to distinguish one element, component, region, layer or section from another component, region, layer or section. Terms such as first, second, third etc., when used herein do not imply a specific sequence or order unless clearly suggested by the present disclosure.

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



I

The process of the present disclosure is shown in Scheme I given below:

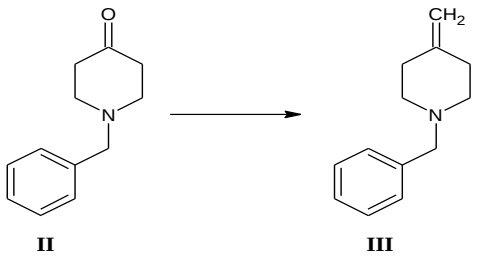


The process of the present disclosure involves synthesis of 4-methylene piperidine HCl (**I**) comprising the following steps:

- Alkylating 1-benzylpiperidine-4-one **(II)** to obtain 1-benzyl-4-methylidenepiperidine **(III)**;
- Debenzylating 1-benzyl-4-methylidenepiperidine **(III)** to obtain N-carbethoxy-4-methylene piperidine **(IV)**;
- Deprotecting N-carbethoxy-4-methylene piperidine **(IV)** to obtain 4-methylidenepiperidine **(V)**; and
- Forming a salt of 4-methylidenepiperidine **(V)** to obtain 4-methylene piperidine hydrochloride **(I)** having purity greater than 95%.

The process is described in detail herein below:

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



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

A reactor is charged with an alkali and a first fluid medium under stirring, followed by heating 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 mixture. An alkylating agent and 1-benzylpiperidine-4-one **(II)** are added to the first mixture to obtain a first resultant mixture. The so obtained resultant mixture is heated at a temperature in the range of 60 °C to 80 °C and for a time period

in the range of 2 hour to 5 hours to obtain a first product mixture comprising 1-benzyl-4-methylidenepiperidine **(III)**. The first product mixture is cooled to a temperature in the range of 15 °C to 25 °C and then diluted with water to obtain a first biphasic mixture comprising a first aqueous layer and a first organic layer. The first aqueous layer is separated from the 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 is directly taken to the next step, without further purification.

In accordance with the process of present disclosure, the alkylating agent and N-benzyl piperidone (**II**) is added to the first mixture in predetermined fashion. The addition involves adding the alkylating agent and N-benzyl piperidone (**II**) in parts of equal volume over a period of time in the range of 20 min to 30 min.

The alkylating agent is methyl triphenylphosphonium bromide and the molar ratio of 1-benzylpiperidine-4-one **(II)** and the alkylating agent is in the range of 1: 1 to 1:3. In an exemplary embodiment of the present disclosure, the molar ratio of 1-benzylpiperidine-4-one **(II)** to methyl triphenylphosphonium bromide is 1: 1.2.

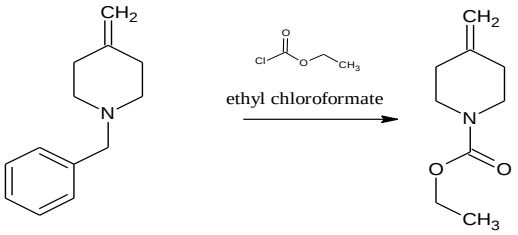
The alkali is selected from the group consisting of sodium methoxide, sodium ethoxide and sodium t-butoxide. In an exemplary embodiment of the present disclosure, the alkali is sodium ethoxide. The molar ratio of 1-benzylpiperidine-4-one **(II)** to the alkali is in the range of 1: 20 to 1: 25.

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

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 reaction is carried out at higher temperature in the range of 50 °C to 90 °C. In

accordance with the present disclosure, at lower temperatures the rate of reaction is very slow; moreover at lower temperatures, the reaction does not lead to completion.

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

The first organic layer comprising 1-benzyl-4-methylidenepiperidine (**III**) is directly used without any purification.

A second fluid medium is added to the first organic layer comprising 1-benzyl-4-methylidenepiperidine to obtain a second mixture. The second mixture is cooled to a temperature in the range of 0 °C to 10 °C, preferably 0 °C to 5 °C, followed by addition of ethylchloroformate in drop wise manner obtain a second resultant mixture. The so obtained second resultant mixture is stirred at a temperature in the range of 0 °C to 10 °C for a time period in the range of 1 to 10 hours, preferably 1 hour to 5 hours to obtain a second product mixture comprising N-carbethoxy-4-methylene piperidine. The second product mixture is further diluted with water to obtain a second biphasic mixture comprising a second aqueous layer and a second organic layer. The second aqueous layer is separated from the second biphasic mixture to obtain the second organic layer comprising N-carbethoxy-4-methylene piperidine. The volatiles present in the second organic layer are removed by distillation under reduced pressure to obtain a first residue comprising N-carbethoxy-4-methylene piperidine **(IV)**.

The so obtained first residue is further purified by treatment with diethyl ether. Diethyl ether is added to the first residue and the resultant mixture is stirred for a time period in the range of 20 to 40 min to obtain a suspension. The suspension is then filtered to obtain a filtrate comprising N-carbethoxy-4-methylene piperidine **(IV)**. The volatiles present in the filtrate are removed by distillation under reduced pressure to obtain N-carbethoxy-4-methylene piperidine **(IV)** having purity more than 95%.

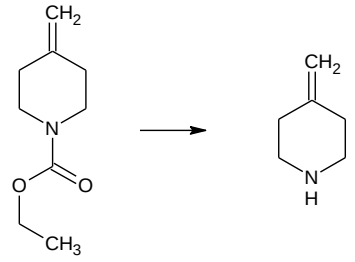
In accordance with the embodiments of the present disclosure, the molar ratio of 1-benzylpiperidine-4-one **(II)** to ethyl chloroformate is in the range of 1: 10 to 1: 15.

In accordance with the embodiments of the present disclosure, the second fluid medium is selected from the 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.

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**) is 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

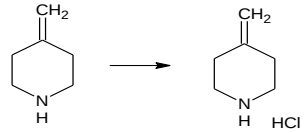
A reactor is charged with N-carbethoxy-4-methylene piperidine **(IV)** and a third fluid medium to obtain a third mixture. Aqueous solution of a base is then added to the third mixture in drop-wise manner to obtain a third resultant mixture; followed by heating the third resultant mixture at a temperature in the range of 100 °C to 120 °C, preferably 108 °C to 110 °C and for a time period in the range of 10 hours to 20 hours to obtain a third product mixture comprising 4-methylidenepiperidine **(V)**. After completion of reaction (monitored by TLC), the third product mixture is cooled to a temperature in the range of 10 °C to 20 °C.

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 is selected from sodium hydroxide and potassium hydroxide. The molar ratio of N-carbethoxy-4-methylene piperidine **(IV)** to a base is in the range of 1: 5 to 1: 10.

In accordance with the embodiments of the present disclosure, the third fluid medium is selected from ethylene glycol and diethylene glycol.

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



V 4-methylidenepiperidine

I 4-methylidenepiperidine hydrochloride

The third product mixture comprising 4-methylidenepiperidine **(V)** is diluted with a fourth fluid medium to obtain a fourth mixture; followed by cooling the fourth mixture to a temperature in the range of 0 °C to 5 °C. Anhydrous hydrochloride gas is purged through the cooled fourth mixture under stirring till pH of the resultant

mixture is in the range of 1 to 2 to obtain a fourth product mixture comprising 4-methylene piperidine hydrochloride **(I)**;

After completion of the reaction (monitored by TLC), the volatiles present in the fourth product mixture are removed by distillation under reduced pressure to obtain a second residue comprising 4-methylene piperidine hydrochloride **(I)**;

The second residue is further purified by treatment with acetone. Acetone is added to the second residue; followed by stirring at a temperature in the range of 0 °C to 5 °C for a time period in the range of 1 to 2 hours to obtain slurry comprising a solid phase and a liquid phase. The solid phase is separated from slurry by filtration, followed by washing and drying the solid phase to obtain 4-methylene piperidine hydrochloride having purity greater than 95%.

In accordance with the embodiments of the present disclosure, the fourth fluid medium is selected from the group consisting of methylene dichloride, ethylene dichloride and acetonitrile.

The process of the present disclosure is simple and employs inexpensive and easily available reagents. Thus, the process of the present application is economical. Further, the process of the present disclosure involves reacting 1-benzyl-4-methylidenepiperidine **(III)** with ethyl chloroformate to obtain methylidenepiperidine-1-carboxylate (**IV**). The intermediate 4-methylidenepiperidine-1-carboxylate (**IV**) is obtained with high purity and therefore is 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 foregoing description of the embodiments has been provided for purposes of illustration and not intended to limit the scope of the present disclosure. Individual components of a particular embodiment are generally not limited to that particular

embodiment, but, are interchangeable. Such variations are not to be regarded as a departure from the present disclosure, and all such modifications are considered to be within the scope of the present disclosure.

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

EXPERIMENTAL DETAILS

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

Step I: Alkylation 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: 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.

The embodiments herein and the various features and advantageous details thereof are explained with reference to the non-limiting embodiments in the following description. Descriptions of well-known components and processing techniques are omitted so as to not unnecessarily obscure the embodiments herein. The examples

used herein are intended merely to facilitate an understanding of ways in which the embodiments herein may be practiced and to further enable those of skill in the art to practice the embodiments herein. Accordingly, the examples should not be construed as limiting the scope of the embodiments herein.

The foregoing description of the specific embodiments so fully reveal the general nature of the embodiments herein that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. Therefore, while the embodiments herein have been described in terms of preferred embodiments, those skilled in the art will recognize that the embodiments herein can be practiced with modification within the spirit and scope of the embodiments as described herein.

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 disclosure to achieve one or more of the desired objects or results.

Any discussion of documents, acts, materials, devices, articles or the like that has been included in this specification is solely for the purpose of providing a context for the disclosure. It is not to be taken as an admission that any or all of these matters form a part of the prior art base or were common general knowledge in the field relevant to the disclosure as it existed anywhere before the priority date of this application.

The numerical values mentioned for the various physical parameters, dimensions or quantities are only approximations and it is envisaged that the values higher/lower than the numerical values assigned to the parameters, dimensions or quantities fall

within the scope of the disclosure, unless there is a statement in the specification specific to the contrary.

While considerable emphasis has been placed herein on the components and component parts of the preferred embodiments, it will be appreciated that many embodiments can be made and that many changes can be made in the preferred embodiments without departing from the principles of the disclosure. These and other changes in the preferred embodiment as well as other embodiments 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.

WE CLAIM:

1. A process for preparing 4-methylene piperidine hydrochloride comprising the following steps:

    a. alkylating 1-benzylpiperidine-4-one to obtain 1-benzyl-4-methylidenepiperidine;

    b. debenzylating 1-benzyl-4-methylidenepiperidine to obtain N-carbethoxy-4-methylene piperidine;

    c. deprotecting N-carbethoxy-4-methylene piperidine to obtain 4-methylidenepiperidine; and

    d. forming a salt of 4-methylidenepiperidine to obtain 4-methylene piperidine hydrochloride having purity greater than 95%.

2. The process as claimed in claim 1, wherein the step (a) of alkylation is carried out using methyl triphenylphosphonium bromide as an alkylating agent; in the presence of an alkali selected from the group consisting of sodium methoxide, sodium ethoxide and sodium t-butoxide; and a first fluid medium selected from the group consisting of toluene, tetrahydrofuran and ether.

3. The process as claimed in claim 1, wherein the step (a) of alkylation is carried out at a temperature in the range of 60 °C to 80 °C until completion of the alkylation.

4. The process as claimed in claim 1, wherein the step (a) of alkylation comprises the step of adding 1-benzylpiperidine-4-one and the alkylating agent in parts of equal volume to a mixture comprising the alkali and the first fluid medium over a period of time in the range of 20 to 40 minutes.

5. The process as claimed in claim 1, wherein the molar ratio of 1-benzylpiperidine-4-one and the alkali is in the range of 1: 20 to 1: 25.

6. The process as claimed in claim 1, wherein the molar ratio of 1-benzylpiperidine-4-one and the alkylating agent is in the range of 1: 1 to 1: 3.

7. The process as claimed in claim 1, wherein the step (b) of debenzylation is carried out using ethyl chloroformate in the presence of a second fluid medium selected from the group consisting of toluene, tetrahydrofuran and ether.

8. The process as claimed in claim 1, wherein the step (b) of debenzylation is carried out at a temperature in the range of 0 °C to 10 °C until completion of the debenzylation.

9. The process as claimed in claim 1, wherein the molar ratio of 1-benzyl-4-methylidenepiperidine and ethyl chloroformate can be in the range of 1: 10 to 1: 15.

10. The process as claimed in claim 1, wherein the step (b) of debenzylation further comprises treating N-carbethoxy-4-methylene piperidine with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity greater than 95%.

11. The process as claimed in claim 1, wherein the step of (c) of de-protection is carried out using a base selected from sodium hydroxide and potassium hydroxide and in the presence of a third fluid medium selected from ethylene glycol and di-ethylene glycol.

12. The process as claimed in claim 1, wherein the step of (c) of de-protection is carried out at a temperature in the range of 100 °C to 130 °C until completion of the deprotection.

13. The process as claimed in claim 1, wherein the molar ratio of N-carbethoxy-4-methylene piperidine and the base is in the range of 1: 5 to 1: 10.

14. The process as claimed in claim 1, wherein the step (d) of salt formation is carried out using anhydrous hydrochloride gas and in the presence of a fourth fluid

medium selected from the group consisting of dichloromethane, dichloroethane, and acetonitrile and at a temperature below 10 °C.

15. The process as claimed in claim 1, wherein the step (d) of salt formation further comprises treating 4-methylene piperidine hydrochloride with acetone at a temperature below 5 °C to obtain 4-methylene piperidine hydrochloride having purity greater than 95%.

16. The process as claimed in claim 1 comprising:

i. charging a first reactor with sodium methoxide and toluene under stirring, followed by heating at 70°C to obtain a first mixture; adding methyl triphenylphosphonium bromide and N-benzyl piperidone to said first mixture over a period of 20 minutes in 10 parts of equal volumes; and continuing heating at 70°C until complete consumption of N-benzyl piperidone to obtain a first product mixture comprising 1-benzyl-4-methylidenepiperidine;

ii. washing said first product mixture with water to obtain a first organic layer comprising 1-benzyl-4-methylidenepiperidine;

iii. cooling first organic layer comprising 1-benzyl-4-methylidenepiperidine to 5 °C in a second reactor; followed by addition of ethyl chloroformate in drop-wise manner and continuing stirring at 5 °C until complete consumption of 1-benzyl-4-methylidenepiperidine to obtain a second product mixture comparing N-carbethoxy-4-methylene piperidine;

iv. washing said second product mixture with water to obtain a second organic layer comprising N-carbethoxy-4-methylene piperidine; removing the volatiles present in said second organic layer under reduced pressure to obtain first residue comprising N-carbethoxy-4-methylene piperidine;

treating said first residue with diethyl ether to obtain N-carbethoxy-4-methylene piperidine having purity greater than 95%;

v. charging a third reactor with N-carbethoxy-4-methylene piperidine and mono-ethylene glycol to obtain a third mixture; adding aqueous solution of potassium hydroxide in drop-wise manner to said third mixture; followed by heating at 110 °C until complete consumption of N-carbethoxy-4-methylene piperidine to obtain a third product mixture comprising 4-methylidenepiperidine; and

vi. cooling said third product mixture comprising 4-methylidenepiperidine to 10 °C; and diluting said cooled third product mixture with methylene dichloride to obtain a fourth mixture; cooling said fourth mixture to 5 °C and purging anhydrous hydrochloride gas through said cooled fourth mixture till pH of the resultant mixture is 1 to obtain a fourth product mixture comprising 4-methylene piperidine hydrochloride;

vii. removing the volatiles present in said fourth product mixture under reduced pressure to obtain a second residue comprising 4-methylene piperidine hydrochloride; treating said second residue with acetone to obtain 4-methylene piperidine hydrochloride having purity greater than 95%.

Dated this 27th day of March, 2019

MOHAN DEWAN
of R.K. DEWAN & COMPANY
IN/PA-25
APPLICANT'S PATENT ATTORNEY

ABSTRACT

A PROCESS FOR PREPARATION OF 4-METHYLENEPIPERIDINE HYDROCHLORIDE

The present disclosure relates to a process for preparing 4-methylene piperidine hydrochloride. The process comprises alkylating 1-benzylpiperidine-4-one using an alkylating agent in the presence of an alkali and a first fluid medium to obtain 1-benzyl-4-methylidenepiperidine. In the next step, 1-benzyl-4-ethylidenepiperidine is subjected to debenzylation using ethyl chloroformate in the presence of a second fluid medium to obtain N-carbethoxy-4-methylene piperidine. N-carbethoxy-4-methylene piperidine is deprotected using a base in the presence of a third fluid medium to obtain 4-methylidenepiperidine. 4-methylidenepiperidine is then treated with anhydrous hydrochloride gas in the presence of a fourth fluid medium to obtain 4-methylene piperidine hydrochloride having purity greater than 95%.