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(54) Title: ZOLPIDEM, METHOD OF PREPARATION AND AN INTERMEDIATE THEREIN

(57) Abstract: The present disclosure relates to a novel intermediate for the preparation of Zolpidem. The present disclosure also provides a process for the preparation of Zolpidem using the novel intermediate. A process using inexpensive, readily available and non-toxic reagents for the preparation of Zolpidem is also disclosed in the present disclosure.

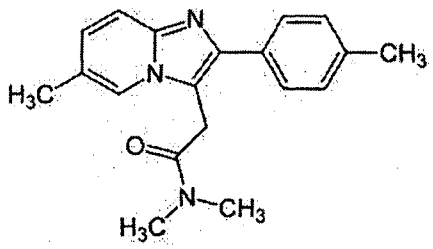
ZOLPIDEM, METHOD OF PREPARATION AND AN INTERMEDIATE THEREIN

FIELD

The present disclosure relates to a method of preparation of Zolpidem, particularly to a method of preparation of Zolpidem using a novel intermediate.

BACKGROUND

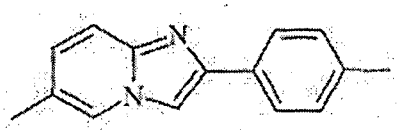
Zolpidem, an imidazo pyridine represented by Formula 6, is one of the most commonly prescribed hypnotics for the treatment of insomnia and other brain disorders such as convulsions and anxiety.



Formula 6

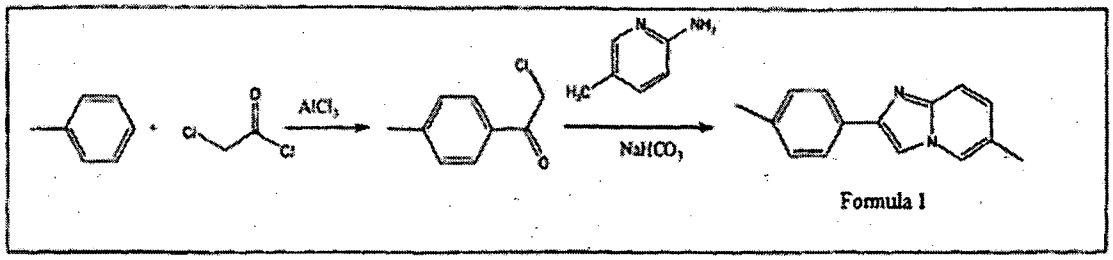
Zolpidem has a short half-life and is a non-benzodiazepine, fast-acting hypnotic that binds selectively to the $GABA_A$ receptor subtypes, the usual onset of action being within 15 minutes of administration.

6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine, a compound represented by Formula 1, is the basic starting material for the preparation of Zolpidem.



Formula 1

The Tschitschibabin reaction, represented by Scheme 1, is a method conventionally followed for the preparation of the compound of Formula 1.

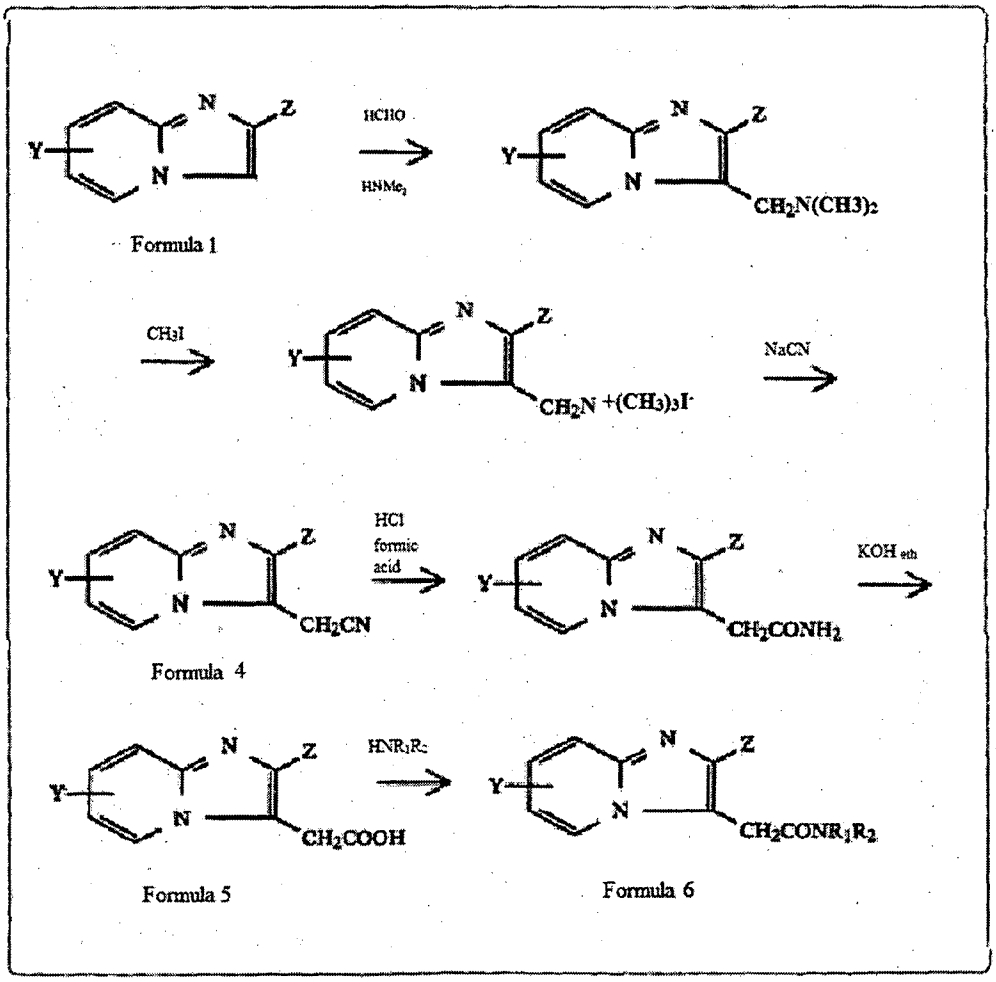


Formula 1

Scheme 1

In the Tschitschibabin reaction, toluene is reacted with chloroacetylchloride under Friedel-Crafts acylation conditions followed by condensation with 2-amino-5-methylpyridine to provide the compound of Formula 1.

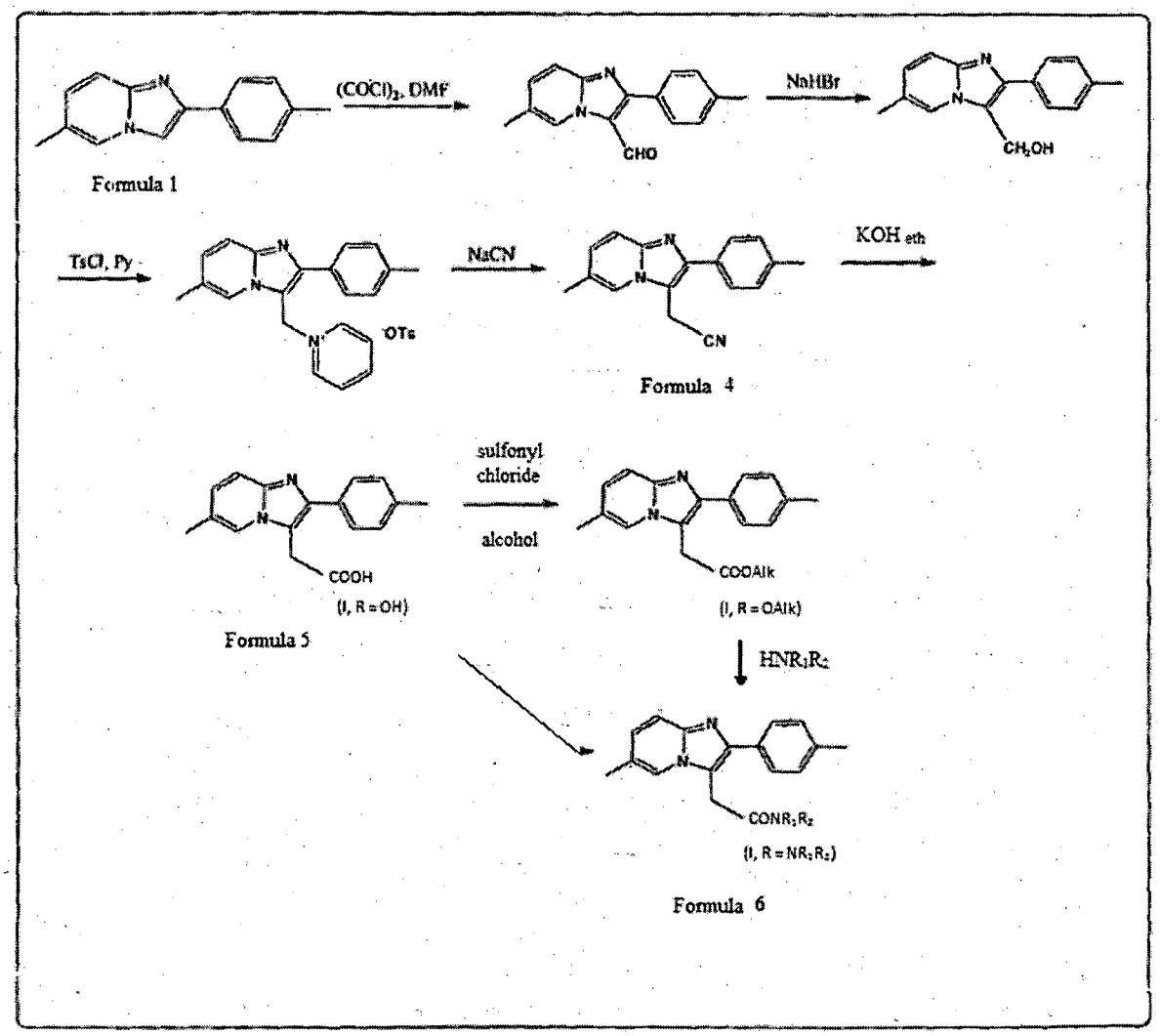
EP0050563 suggests a process for the preparation of Zolpidem as schematically represented in Scheme 2.



Scheme 2

The process of EP0050563 uses low boiling, highly expensive and toxic reagents such as methyl iodide that makes the process cost-inefficient and non-amenable to large scale.

US4492695 suggests a process for the preparation of Zolpidem as schematically represented in Scheme 3.

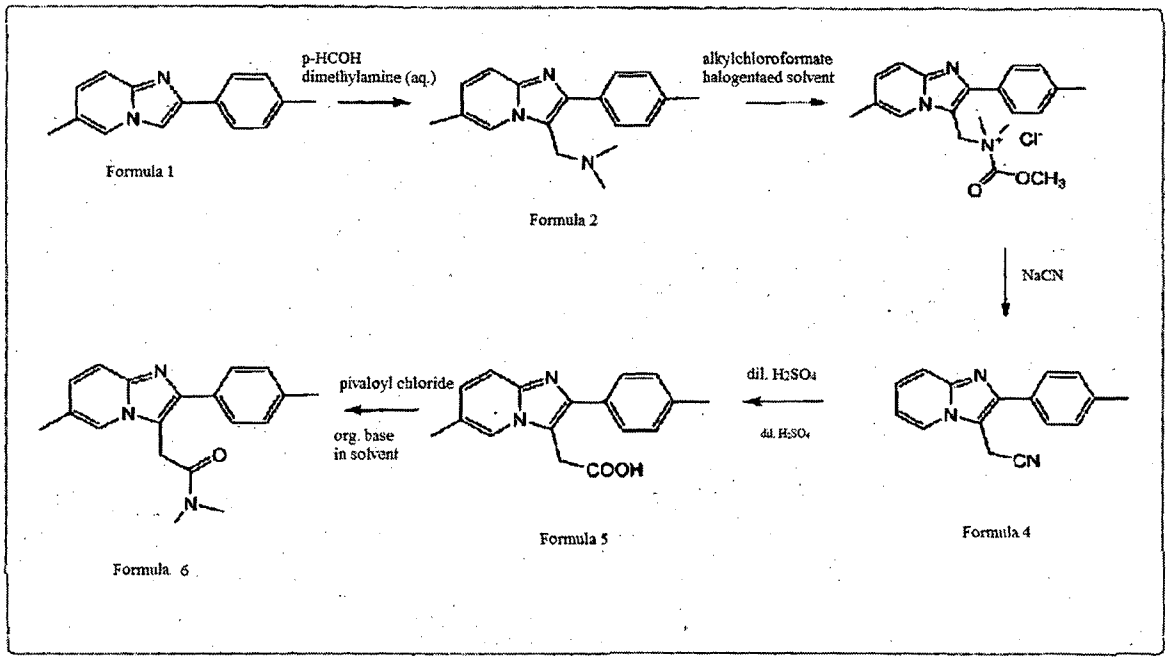


Scheme 3

The process of US 4492695 avoids the use of expensive and toxic reagent i.e., methyl iodide; however it involves a relatively more number of steps. Further, the reaction time of some of the steps of US4492695 is relatively long, thereby making the process

energy inefficient. Still further, the yield of Zolpidem is relatively low and the workup procedure to isolate Zolpidem is complex.

WO2009007995 suggests a process represented in Scheme 4 for the preparation of Zolpidem.



Scheme 4

The process of WO2009007995 uses alkyl chloroformates which are as toxic as methyl iodide. Further, the alkyl chloroformates are difficult to handle due to their low vapor pressure and lachrymatic properties. Even further, the process suffers from tedious work-up method which is undesirable for commercial production.

These suggested processes for the preparation of Zolpidem are associated with disadvantages such as use of expensive, toxic and difficult to handle reagents.

The inventors of the present disclosure, thus, provide a process for the preparation of Zolpidem that can be readily scaled up, does not require special purification steps and which employs inexpensive, readily available, easy to handle and non-toxic reagents.

OBJECTS

Some of the objects of the present disclosure which at least one embodiment is adapted to provide, are described herein below:

It is an object of the present disclosure to provide a novel intermediate useful in the preparation of Zolpidem.

It is another object of the present disclosure to provide a process for the preparation of the novel intermediate.

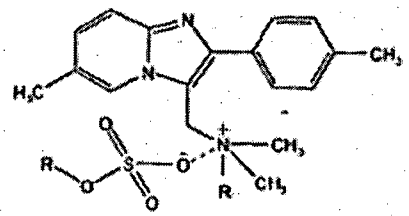
It is yet another object of the present disclosure to provide a process for the preparation of Zolpidem using a novel intermediate.

It is still another object of the present disclosure to provide a process for the preparation of Zolpidem which involves the use of economical, readily available and easy to handle reagents.

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.

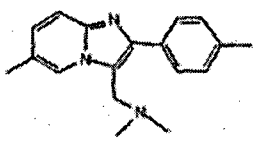
SUMMARY

In accordance with the present disclosure there is provided an intermediate for the preparation of Zolpidem, said intermediate having a structure of Formula 3, wherein R is selected from the group comprising ethyl, methyl, propyl, butyl, isopropyl, isobutyl and tertiary butyl group.

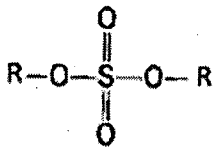


Formula 3

In accordance with another aspect of the present disclosure there is provided a process for the preparation of an intermediate of Formula 3 by alkylating a compound of Formula 2, said process comprising the following steps: first, a solution comprising Formula 2 and a first solvent is prepared; then a compound of Formula 7 is added to the prepared solution at a temperature ranging from -5 °C to 15 °C to obtain a reaction mixture; the reaction mixture is refluxed at a temperature ranging from 35 °C to the boiling point of the first solvent to obtain a compound of Formula 3.



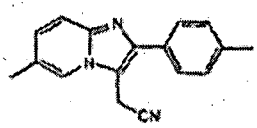
Formula 2



Formula 7

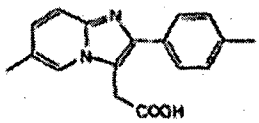
In accordance with still another aspect of the present disclosure there is provided a process for preparing Zolpidem using the novel intermediate of Formula 3, said process comprising the following steps:

- the compound of Formula 3 prepared in accordance with the present disclosure is cyanated using an aqueous solution of sodium cyanide to obtain a compound of Formula 4;



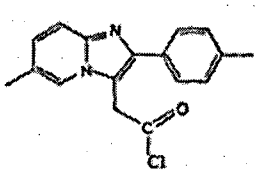
Formula 4

- then, the compound of Formula 4 is hydrolyzed said using an aqueous solution of at least one base and at least one second solvent to obtain a compound of Formula 5; and

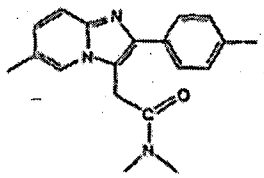


Formula 5

- the compound of Formula 5 is reacted with an acyl halide forming agent to obtain a compound of Formula 8; and finally amidating said compound of Formula 8 using dimethyl amine to obtain Zolpidem having a structure of Formula 6.



Formula 8



Formula 6

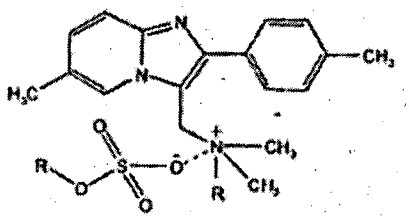
DETAILED DESCRIPTION

Zolpidem, an imidazo pyridine is one of the most commonly prescribed hypnotics for the treatment of insomnia and other brain disorders such as convulsions and anxiety. Zolpidem has a short half-life and is a non-benzodiazepine, fast-acting hypnotic that binds selectively to the $GABA_A$ receptor subtypes, the usual onset of action being within 15 minutes of administration.

Conventionally, the basic starting material for preparation of Zolpidem is 6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine (compound of Formula 1). There are many methods developed for the preparation of Zolpidem. However, these methods make use of expensive and toxic reagents like methyl iodide. Also, these methods involve more number of steps and hence, have a longer reaction time. Also, the by-products generated during the reaction contaminate the Zolpidem produced and necessitate additional purification steps.

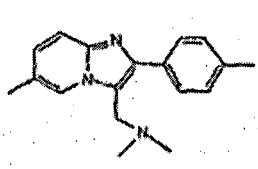
The present disclosure therefore, provides a process for preparation of Zolpidem that can be easily scaled up, does not require additional purification steps and employs inexpensive, readily available, easy to handle and non-toxic reagents.

The present disclosure provides a novel intermediate having a structure of compound of formula 3, for the preparation of Zolpidem and a process for preparing the novel intermediate.

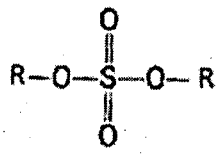


Formula 3

In the first step, a compound of Formula 7 i.e., dialkyl sulfate is added at a temperature ranging from -5 °C to 15 °C to the solution of compound of Formula 2 i.e., (2-(4-methylphenyl)-6-methyl-3-dimethylaminomethyl imidazo [1,2-a]pyridine) and solvent/s to obtain a reaction mixture. The reaction mixture is then heated to a boiling point of the solvent being used in the first step to obtain a compound of Formula 3 (a quaternary ammonium salt of Mannich base of the compound of Formula 2) after heating the reaction mixture for a time period of 15 to 480 minutes.



Formula 2



Formula 7

The R group in the compound of Formula 7 is selected from a group comprising ethyl, methyl, propyl, butyl, isopropyl, isobutyl and tertiary butyl group.

As the reaction is slightly exothermic, the addition of compound of Formula 7 to the solution of compound of Formula 2 i.e., (2-(4-methylphenyl)-6-methyl-3-

dimethylaminomethyl imidazo [1,2-a]pyridine) and solvent/s is carried out slowly in a drop-wise or batch-wise manner.

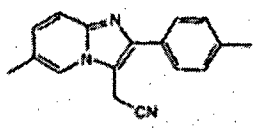
To obtain an optimum yield of the compound of Formula 3, the molar ratio of the compound of Formula 2 to the compound of Formula 7 is optimized in the range of 1:0.5 to 1:3.

Particularly, the optimized molar ratio of the compound of Formula 2 to the compound of Formula 7 ranges from 1:1 to 1:1.5.

Solvents that can be used in the present disclosure include halogenated solvent, alcohol solvent and ketone solvent. Non-limiting examples of the solvent include dichloromethane, dichloroethane, chloroform, acetone, methanol, ethanol, ethyl acetate and the like.

Non-limiting examples of the dialkyl sulfate represented by Formula 7 include diethyl sulfate, dipropyl sulfate, dibutyl sulfate, di-isopropyl sulfate, di-isobutyl sulfate, dimethyl sulfate and the like.
In an exemplary embodiment of the present disclosure the dialkyl sulfate is dimethyl sulfate.

In accordance with another aspect of the present disclosure there is provided a process for the preparation of Zolpidem using the intermediate of Formula 3.The compound of Formula 3 prepared in accordance with the process of the present disclosure is subjected to cyanation reaction using an aqueous solution of sodium cyanide to obtain a nitrile derivative represented by Formula 4 (6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetonitrile). The cyanation reaction is carried out at a temperature ranging from 10 °C to 100 °C for a time period of 1 to 6 hours.



Formula 4

In an embodiment of the present disclosure, the compound of Formula 3 is isolated from the solvent prior to cyanation with sodium cyanide.

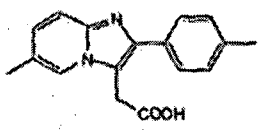
In another embodiment of the present disclosure, the compound of Formula 3 is reacted as such, *in-situ*, for cyanation with sodium cyanide.

It is observed that yield of nitrile derivative represented by Formula IV is acceptable when the molar ratio of the compound of Formula 3 to sodium cyanide is in the range of 1:1 to 1:2.

Optionally, the compound of Formula 3 is dissolved in water and the pH is adjusted in the range of 6.0 to 10.0 using a pH adjusting agent before subjecting it to the cyanation reaction.

Non-limiting examples of pH adjusting agent include potassium carbonate, sodium bicarbonate, sodium hydride and sodium hydroxide.

The compound of Formula 4 prepared in accordance with the present disclosure is further hydrolyzed using an aqueous solution of a base and at least one solvent to obtain an acid represented by the Formula 5 (6-methyl-2-(4-methylphenyl)imidazo[l,2-a]pyridine-3- acetic acid).

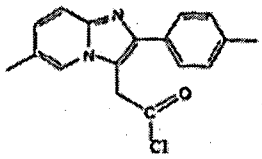


Formula 5

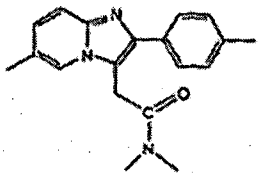
Non-limiting examples of the base include potassium hydroxide, sodium hydroxide, barium hydroxide, sodium carbonate and ammonia.

Non-limiting examples of the solvent include methanol, ethanol and acetone.

The compound of Formula 5 prepared in accordance with the present disclosure is initially reacted with an acyl halide forming agent to obtain an acyl halide derivative represented by formula 8. The compound of Formula 8 is moisture sensitive and therefore not isolated, though it can be, and is further reacted with dimethyl amine to obtain Zolpidem having the structure of Formula 6 (6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-N,N-dimethylacetamide).



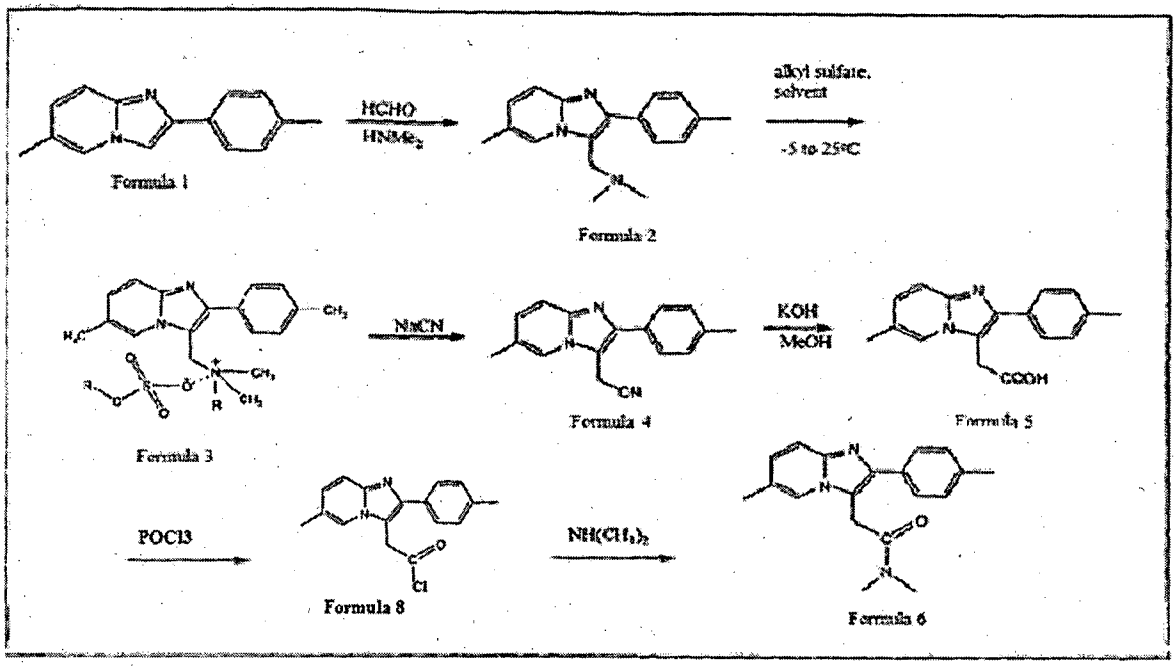
Formula 8



Formula 6

The acyl halide forming agent in accordance with the present disclosure is phosphorus oxychloride, phosphorus penta chloride, phosphorus trichloride, thionyl chloride and combinations thereof.

The process of the present disclosure prepares the compound of Formula 5 (6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetic acid) without isolation and purification of intermediate products thereby saving the time and increasing the productivity. The overall progression of the reaction for the preparation of Zolpidem in accordance with the present disclosure is represented in Scheme 5.



Scheme 5

The present disclosure is further described in light of the following non-limiting examples which are set forth for illustration purpose only and not to be construed for limiting the scope of the disclosure.

Example 1

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetonitrile (compound of Formula 4)

900 ml of acetone and 175 g of 2-(4-methylphenyl)-6-methyl-3-dimethylaminomethyl imidazo [1,2-a]pyridine (compound of Formula 2) (0.626 mol) was taken into a reactor and cooled to -5 °C. Then 120 g (0.951 mol) of dimethyl sulfate was slowly added to the above reactor at a temperature ranging from -5°C to 0 °C in a 3 hour time interval. After completion of addition, the reaction mixture was heated to reflux for 4 hours and then about 450 ml of acetone was distilled out. The reaction mass was cooled to 10 °C, the product was filtered and taken in a reactor containing 1200 ml of 6.25%sodium cyanide solution. The resultant reaction mass was heated and then maintained at 85 °C for 4 hours and then cooled to about 25 °C, filtered and washed

thoroughly with water to remove excess sodium cyanide. The filtered compound was dried at 100 °C to yield 133 g of title compound, 6-methyl-2-(4-methylphenyl)imidazo[l,2-a]pyridine-3-acetonitrile. The High Performance Liquid Chromatography (HPLC) purity of compound of Formula 4 was 91%.

Example 2

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetonitrile (compound of Formula 4)

600 ml of methanol and 180 g of 2-(4-methyl phenyl)-6-methyl-3-dimethylaminomethyl imidazo[1,2-a]pyridine (compound of Formula 2) (0.644 mol) was taken in a reactor and cooled to 0 °C. 105 g (0.832 gmol) of dimethyl sulfate was then slowly added to the above reactor at a temperature ranging between 0 and 10 °C over a time period ranging between 3 to 4 hours. After the completion of the addition, the reaction mixture was stirred at 5-10 ^{O}C for 1 hour. The above reaction mass was added into a reactor containing1200 ml of 4.83% sodium cyanide solution. The reaction mass was then heated slowly to 80-85 °C and maintained for 2 hours to distill out methanol. The reaction mass was cooled to about 25 °C, filtered and washed thoroughly with water to remove excess sodium cyanide. The filtered compound was dried at 100 °C to yield 95 g of the compound of Formula 4. HPLC purity of the compound was found to be 87%.

Example 3

Preparation of 6-methyl-2-(4-methylphenyl)imidazo[l,2-a]pyridine-3- acetic acid (compound of Formula 5).

The compound prepared in Example 1, was taken into a reactor containing 600 ml of methanol and 600 ml of water along with 100 g of potassium hydroxide. The reaction mixture was refluxed for 15 hours till the completion of the reaction and was followed by distillation with methanol (600-700 ml of methanol-water). The aqueous reaction mass was cooled to about 25 °C and washed thrice with methylene chloride. The aqueous layer was then acidified with acetic acid to precipitate the product. The white solid material obtained was filtered and washed with water. 121 g (0.432 mol) of 6-

methyl-2-(4-methylphenyl)imidazo[l,2-a]pyridine-3- acetic acid was the yield obtained having 99.70%HPLC purity.

Example 4

Process of preparation of 6-methyl-2-(4-methylphenyl)imidazo[l,2-a]pyridine-3-N,N-dimethylacetamide/ Zolpidem(compound of Formula 6).

120 g (0.428 mol) of 6-methyl-2-(4-methylphenyl)imidazo[l,2-a]pyridine-3-acetic acid (compound of Formula 5 as prepared in Example 3) was initially mixed in 1 liter ethyl acetate to prepare a suspension. The suspension was heated to 50 °C after which 131 g (0.85 mol) of phosphorus oxychloride was added over a time period of about 1 hour. The temperature was maintained at 50-55 °C during the addition. The temperature of the reaction was then raised to 70-85 °C for refluxing and the reaction mass was maintained at reflux for 4 hours. The reaction mass was then cooled to 10 °C and dimethylamine gas was purged into the reaction mass at 10-15 °C, till the pH ranged between 9 and 10. The reaction mass was further heated to 50 °C and maintained for 1 hour. Subsequently, the reaction mass was cooled to 25 °C and a solution of sodium bicarbonate (12 g in 240 ml water) was added to the reaction mass. The reaction mass was maintained at 25-30 °C for 2 hours and further cooled to 5-10 °C and maintained at this temperature for 4 hours. The reaction mass was filtered and washed with 1 liter of hot water and further with 100 ml of chilled ethyl acetate. The filtered material was dried under vacuum at 75 °C until constant weight was reached. Dry weight of the resultant compound (Zolpidem) was found to be 120.0 grams.

Yield: 91%.

Purity: 99.5%.

Melting Range: 196 to 197 °C

The embodiments herein and the various features and advantageous details thereof are explained with reference to the non-limiting embodiments in the 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 will 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.

TECHNICAL ADVANTAGES AND ECONOMIC SIGNIFICANCE

-The process of present disclosure provides a novel intermediate compound for the preparation of Zolpidem.

-The process of present disclosure also provides a process for the preparation of Zolpidem in less number of steps which reduces time and increases the productivity.

-The process of present disclosure provides a process for preparation of Zolpidem using inexpensive, readily available and non-toxic reagents.

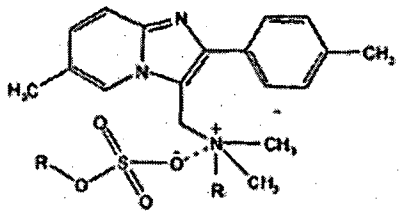
Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, 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.
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 and the claims unless there is a statement in the specification to the contrary.

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 in the process or compound or formulation or combination 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 accompanying claims and their equivalents are intended to cover such forms or modifications as would fall within the scope and spirit of the invention.

CLAIMS:

1. A compound of Formula 3:

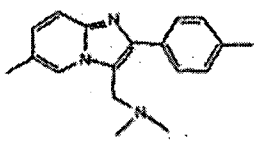


Formula 3

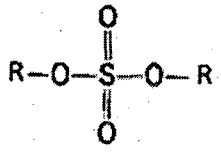
wherein R is selected from the group comprising ethyl, methyl, propyl, butyl, isopropyl, isobutyl and tertiary butyl group.

2. A process for preparing a compound of Formula 3, said process comprising a step of alkylating a compound of Formula 2 by adding a compound of Formula 7 into a solution of compound of Formula 2 and at least one first solvent at a temperature ranging from -5°C to 15 °C to obtain a reaction mixture; and refluxing said reaction mixture at a temperature ranging from 35 °C to a boiling point of said first solvent to obtain said compound of Formula 3:

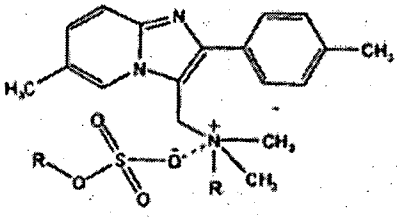
wherein R of compound of Formula 3 and compound of Formula 7 is selected from the group comprising ethyl, methyl, propyl, butyl, isopropyl, isobutyl and tertiary butyl group;



Formula 2



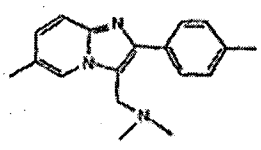
Formula 7



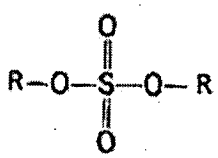
Formula 3

3. The process of claim 2, wherein said compound of Formula 7 is at least one selected from the group comprising diethyl sulfate, dipropyl sulfate, dibutyl sulfate, di-isopropyl sulfate, di-isobutyl sulfate and dimethyl sulfate.
4. The process of claim 2, wherein said compound of Formula 7 is dimethyl sulfate.
5. The process of claim 2, wherein the molar ratio of said compound of Formula 2 to said compound of Formula 7 ranges from 1:0.5 to 1:3, preferably the molar ratio range from 1:1 to 1:1.5.
6. The process of claim 2, wherein said first solvent is at least one selected from the group comprising dichloromethane, dichloroethane, chloroform, acetone, methanol, ethanol and ethyl acetate.
7. A process for preparing Zolpidem having a structure of Formula 6, said process comprising the following steps:
   a. alkylating a compound of Formula 2 by adding a compound of Formula 7 into a solution of compound of Formula 2 and at least one first solvent at a temperature ranging from -5°C to 15 °C to obtain a reaction mixture; and refluxing said reaction mixture at a temperature ranging from 35 °C to a boiling point of said first solvent to obtain said compound of Formula 3:

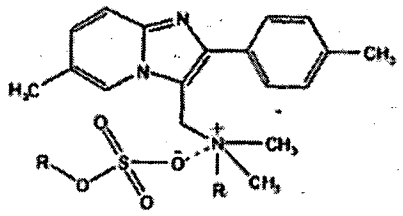
      wherein R of compound of Formula 3 and compound of Formula 7 is selected from the group comprising ethyl, methyl, propyl, butyl, isopropyl, isobutyl and tertiary butyl group;



Formula 2

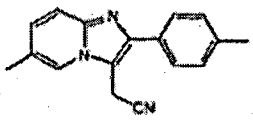


Formula 7



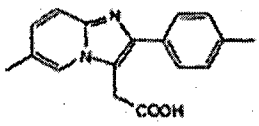
Formula 3

b. cyanating said compound of Formula 3 using an aqueous solution of sodium cyanide to obtain a compound of Formula 4;



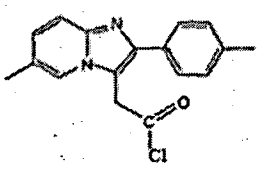
Formula 4

c. hydrolyzing said compound of Formula 4 using an aqueous solution of at least one base and at least one second solvent to obtain a compound of Formula 5; and

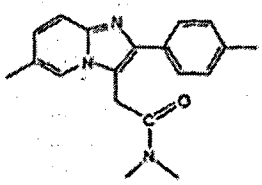


Formula 5

d. reacting said compound of Formula 5 and an acyl halide forming agent to obtain a compound of Formula 8; and amidating said compound of Formula 8 using dimethyl amine to obtain Zolpidem having a structure of Formula 6.



Formula 8



Formula 6

8. The process of claim 7, wherein step (b) is carried out at a temperature ranging from 10 to 100 °C for a time period of 1 to 6 hours.
9. The process of claim 7, wherein the molar ratio of said compound of Formula 3 to said sodium cyanide ranges from 1:1 to 1:2.
10. The process of claim 7, wherein said base is at least one compound selected from the group comprising potassium hydroxide, sodium hydroxide, barium hydroxide, sodium carbonate and ammonia.
11. The process of claim 7, wherein said second solvent is at least one selected from the group comprising methanol, ethanol and acetone.
12. The process of claim 7, wherein said acyl halide forming agent is selected from the group comprising phosphorus oxychloride phosphorus penta chloride, phosphorus trichloride, and thionyl chloride.
13. The process of claim 7, wherein the method step (a) further comprises dissolving said compound of Formula 3 in water to obtain a solution and adjusting the pH of said solution with a pH adjusting agent at a pH ranging from 6.0 to 10.0.
14. The process of claim 13, wherein the pH adjusting are selected from a group comprising potassium carbonate, sodium bicarbonate, sodium hydride and sodium hydroxide.
15. A Zolpidem having a structure of Formula 6, prepared by the process of claim 7.