A PROCESS FOR PREPARATION OF NEVIRAPINE

The present invention provides a process for the preparation of nevirapine, which comprises reaction of 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide with cyclopropyl amine in presence of a suitable reagent such as carbonates, bicarbonates, acetates of alkali metals and lanthanum oxide, followed by cyclization of the resultant product.

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A PROCESS FOR PREPARATION OF NEVIRAPINE

PRIORITY

This application claims the benefit under Indian Provisional Application No. 1913/CHE/2011, filed on June 06, 2011, the content of each of which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention generally relates to a process for the preparation of Nevirapine, and to a pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION

Nevirapine, also known as 11-cyclopropyl-4-methyl-5,1 1-dihydro-6H-dipyrido [3,2-\&;2',3'\- e][1,4]diazepin-6-one, belonging to the member of the dipyridodiazepinone chemical class of compounds, is represented by the structure of Formula I:

![Formula I](image)

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat HIV-1 infection and AIDS and is available in the market under the brand name Viramune® in the form of 200 mg and 400 mg tablets and 50mg/5ml of oral suspension.

U.S. Patent No. 5,366,972 ("the '972 patent") discloses dipyridodiazepines such as nevirapine. The '972 patent further discloses a process for the preparation of nevirapine, its anti-HIV activity and its use in pharmaceutical product. The '972 process is depicted in the following reaction scheme:
The reaction of compound (1-1) with compound (1-2) produces 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III, which is then, reacts with cyclopropylamine in a sealed reactor to give N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II, followed by cyclization in presence of sodium hydride to produce nevirapine of Formula I.

U.S. Patent No. 5,569,970 ("the '970 patent") discloses an improved process for preparation of nevirapine, which involves use of neutralizing agent such as an oxide or hydroxide of an element of the second main or second subgroup of the periodic table, with calcium oxide being particularly preferred, in the reaction of 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine.

PCT publication WO 2008/142528 ("the '528 publication") discloses a process for preparation of nevirapine by reaction of 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine in presence of a reagent such as potassium fluoride or trisodium phosphate dodecahydrate followed by cyclisation with sodium hydride.

CN publication No. 101585836 ("the '836 publication") discloses a process for preparation of nevirapine by reaction of 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine in presence of a copper catalyst and an alkali base, followed by cyclisation of the resulting N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II with sodium hydride.

The '972 patent discloses the use of large excess of cyclopropyl amine for preparing N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II results an impure product containing undesired side products, and is difficult to control and thus requires excess of sodium hydride in the subsequent cyclisation step to produce nevirapine.
The ‘836 publication discloses the use of metal catalysts such as copper metal, this leads to metal contamination of the final product and thus additional process steps required to remove, which in turn result to an increase in the manufacturing cycle time and a decrease in the product yield.

Despite all prior advances, available methods for synthesizing nevirapine remain labor intensive, time consuming and environmentally unfavorable. Thus, there remains a need for a simple, industrially feasible and scalable process for the synthesis of nevirapine that would avoid the aforementioned difficulties.

The present invention provides a process for the preparation of nevirapine by using simple and commercially available bases as neutralizing agent that are away from the aforementioned difficulties. The process of the present invention can be practiced on an industrial scale, and also can be carried out without sacrifice of overall yield.

**SUMMARY OF THE INVENTION**

The present invention encompasses a process for the preparation of nevirapine or a pharmaceutically acceptable salt thereof with high product yield and quality.

In accordance with one embodiment, the present invention provides a process for preparation of N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II,

![Formula II](image)

which comprises: reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III

![Formula III](image)

with cyclopropylamine (CPA) in presence of a suitable reagent in an organic solvent.

In accordance with a second embodiment, the present invention provides a process for preparation of N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine
carboxamide of Formula II, which comprises: reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine in presence of a suitable reagent in an organic solvent; wherein the suitable reagent is selected from the group consisting of carbonates, bicarbonates, acetates of alkali metals and lanthanum oxide.

In accordance with a third embodiment, the present invention provides a process for preparation of nevirapine of Formula I, which comprises:

![Formula I]

10 a) reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine in presence of a suitable reagent in an organic solvent to obtain N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II,

15 b) cyclizing the resultant compound of formula II to obtain nevirapine.

In accordance with a fourth embodiment, the present invention provides a process for preparation of nevirapine, which comprises:

20 a) reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine in presence of a suitable reagent in an organic solvent to obtain N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II,

25 b) cyclizing the resultant compound of formula II in presence of a base to obtain nevirapine.

wherein the suitable reagent is selected from the group consisting of carbonates, bicarbonates, acetates of alkali metals and lanthanum oxide.

In accordance with a fifth embodiment, the present invention provides pharmaceutical composition comprising nevirapine prepared by the processes of the present invention and at least one pharmaceutically acceptable excipient.

**BRIEF DESCRIPTION OF THE DRAWINGS**

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.
Figure 1 is the characteristic powder X-ray diffraction (XRD) pattern of nevirapine as obtained in Example 10.

Figure 2 is the characteristic differential scanning calorimetric (DSC) thermogram of nevirapine as obtained in Example 10.

Figure 3 is the characteristic thermo gravimetric analysis (TGA) curve of nevirapine as obtained in Example 10.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides a process for the preparation of nevirapine. In particular, the present invention provides a process to prepare nevirapine by using safe and simple reagents in the conversion of compound of Formula III into compound of Formula II.

In one embodiment, the present invention provides a process for preparing nevirapine of Formula I,

which comprises:

a) reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III

with cyclopropylamine in presence of a suitable reagent in an organic solvent to obtain N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II.
b) cyclizing the resultant compound of formula II to obtain nevirapine.

The starting material 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III is known in the art and can be prepared by any known method, for example starting compound of Formula III may be synthesized as disclosed in U.S. Patent No. 5,366,972.

The '972 patent disclose use of about 4 mole equivalents of relatively expensive cyclopropylamine for preparing N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II, this leads to formation of undesired cyclic by-products during this reaction. The inventors of the present invention surprisingly have found that use of excess of expensive cyclopropylamine may be reduced if the reaction is carried out in the presence of a suitable reagent of the present invention such as carbonates, bicarbonates, acetates of alkali metals or lanthanum oxide. The cyclopropylamine may be present in any amount of about 2 to about 3 mole equivalents to the starting compound of Formula III.

The suitable reagent in the foregoing process may be selected from the group consisting of one or more of carbonates, bicarbonates, acetates of alkali metals and lanthanum oxide, carbonates of alkali metals include, but are not limited to sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate and the like; bicarbonates of alkali metals include, but are not limited to sodium bicarbonate, potassium bicarbonate, cesium bicarbonate, lithium bicarbonate and the like; acetates of alkali metals include, but are not limited to sodium acetate, potassium acetate, cesium acetate, lithium acetate and the like. Preferably the suitable reagent is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate, potassium acetate and lanthanum oxide.

The suitable reagent may be present in any amount that will produce the compound of Formula II upon the process of the present invention. Preferably, the suitable reagent is present in an amount of about 0.5 to about 3 mole equivalents to the starting compound of Formula III.
The organic solvent includes, but is not limited to alcohols such as methanol, ethanol, isopropanol, propanol, butanol and the like and mixtures thereof; ethers such as tetrahydrofuran, 1,4-dioxane, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether and the like and mixtures thereof; aromatic hydrocarbons such as toluene, o-xylene, chlorobenzene, pyridine, anisole and the like and mixtures thereof; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, N-methyl pyrrolidinone, hexamethyl phosphoramide and the like and mixtures thereof. Preferably the organic solvent is selected from the group consisting of toluene, o-xylene, dimethyl formamide, diethylene glycol dimethyl ether; more preferably o-xylene.

The reaction temperature should be sufficient to effect conversion of compound of Formula III into compound of Formula II. Typically the reaction temperature may be from about 35°C to about 165°C, preferably about 75°C to about 150°C, more preferably about 130°C to about 150°C. The reaction may take from about 6 hours to about 48 hours depending upon the suitable reagent, solvent and temperature chosen, for example conversion of compound of Formula III into compound of Formula II in o-xylene at a temperature of about 135°C to about 145°C may complete about 12 hours.

After completion of the reaction, the resultant N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II can be further processed directly without isolation, to form nevirapine of Formula I. Alternatively, the resultant compound of Formula II may be isolated by any method known in the art, at the end of the reaction. For example distillation, evaporation, rotational drying (such as with the Buchi Rotavapor), freeze drying, fluidized bed drying, flash drying, spin flash drying, cooling the reaction mass to precipitation and the like.

Preferably, salt bi-products that are produced after completion of the reaction are separated, such as by filtration, the organic layer of the filtrate can be separated and washed with water. The resultant organic layer can be removed partially by methods known in the art, for example evaporation at atmospheric pressure, evaporation under vacuum to form the N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II.

The present invention encompasses methods of preparing nevirapine or a pharmaceutically acceptable salt thereof with high purity. The processes of the invention allow for economical synthesis, shorter reaction times, and yields of high purity.

The present invention provides nevirapine, obtained by a process comprising providing a N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II as obtained by the process described above, as a starting material or as an
intermediate, where the nevirapine may have a purity equal to or greater than about 99.5% as determined by HPLC.

Step b) of foregoing process may be carried out by adding sufficient amount of a base to the resultant product in order to cyclization to obtain nevirapine.

The base for use in the cyclization reaction may be selected from the group consisting of alkali metal hydrides such as sodium, potassium and lithium hydrides and the like; alkali metal tertiary butoxides such as sodium and potassium tertiary butoxides and the like; and lithium alkyls such as n-butyl lithium and the like and mixtures thereof; preferably the base is sodium hydride.

The cyclization may be carried out in presence of an organic solvent, wherein the organic solvent include, but is not limited to aromatic hydrocarbons such as toluene, o-xylene, anisole, chlorobenzene, pyridine and the like; ethers such as tetrahydrofuran, 1,4-dioxane, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether and the like; amides such as dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide and the like; sulfolane, and mixtures thereof. Preferably the organic solvent is selected from toluene, o-xylene, dimethyl formamide and mixtures thereof.

The reaction temperature should be sufficient to effect cyclization of compound of Formula II. Typically the reaction temperature may be from about 35°C to about 150°C, preferably about 80°C to about 135°C, more preferably about 130°C to about 135°C. The reaction may take from about 1 hour to about 12 hours depending upon the base, solvent and temperature chosen. After completion of the reaction, the resultant product nevirapine may be recovered by methods known in art.

In another embodiment of the present invention, nevirapine thus obtained may be purified by dissolving crude nevirapine in an organic solvent, wherein the organic solvent include, but is not limited to C₄₋₄ alcohols such as methanol, ethanol, isopropanol, butanol and the like; esters such as ethyl acetate, isopropyl acetate, butyl acetate and the like; hydrocarbons such as hexane, heptanes, cyclohexane, toluene, xylene, methyl cyclohexane and the like; water and mixtures thereof; Preferably methanol, ethyl acetate, hexane or their mixtures. The solvent may be heated to obtain a solution at a temperature of from about ambient temperature to about reflux temperature, preferably at about reflux temperature. The reaction solution may be cooled at a temperature from about 20°C or less such that the nevirapine can be isolated by conventional techniques. This may allow for a high purity level of the resulting nevirapine from the crude nevirapine, e.g., a purity of at least about 95% preferably at least about 98% and more preferably at least about 99.5%.
The present invention provides nevirapine obtained using the process described herein, may have a residual solvent content that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") guidelines. The guideline solvent level depends on the type of solvent but is not more than about 5000 ppm, or about 4000 ppm, or about 3000 ppm.

The present invention provides a nevirapine, obtained by the process disclosed herein, having less than about 800 parts per million (ppm) CI_4 alcohols such as methanol, ethanol, isopropanol; less than about 500 ppm of ethyl acetate; less than about 500 ppm of toluene; less than about 500 ppm of tetrahydrofuran; less than about 500 ppm of dimethyl formamide; less than about 500 ppm of xylene; less than about 500 ppm of one of n-heptane, n-hexane, methyl cyclohexane, and cyclohexane; and less than about 500 ppm of cyclopropyl amine.

In another embodiment, the present invention provides a pharmaceutical composition comprising nevirapine or a pharmaceutically acceptable salt thereof prepared by the process of the present invention and at least one pharmaceutically acceptable carrier.

The following non limiting examples illustrate specific embodiments of the present invention. They are not intended to be limiting the scope of the present invention in any way.

**EXAMPLES:**

**Example 1:** Preparation of N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide (Compound of Formula II)

To a clean 1L autoclave vessel o-xylene (600 ml), 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide (Compound of Formula III) (100 gms), potassium carbonate (73.5 gms, 1.5 mol. eq.), cyclopropyl amine (60.7 gms, 3 mol. eq.) was charged at temperature 25°C to 35°C. The reaction was heated to 135°C to 145°C and maintained for 16 hours at same temperature. After completion of the reaction by HPLC, the reaction mixture was allowed to cool to 90°C to 95°C and filtered the salts. The filtrate was taken in to a clean 3-necked 2L round bottom flask and washed with 0.1% Hydrose solution (400 ml) at temperature 90°C to 95°C and followed by washed with water (400 ml). The organic layer was taken and the solvent was removed by distillation under vacuum at below 70°C up to minimum volume present in the solution. The solution was allowed to cool to 25°C to 35°C and stirred for 1 hour and then again cooled to 5°C to 10°C and stirred for 2 hours. Filtered the product and washed with chilled o-xylene (50 ml). The wet product was dried at 70°C to 75°C under reduced pressure for 12 hours to provide the title compound.

Yield: 90 gms.
HPLC purity: 98.30%

Example 2 - 8: Preparation of N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide (Compound of Formula II)

Using a procedure analogous to that employed in Example 1, but using different reagents and conditions as described in the following table:

<table>
<thead>
<tr>
<th>Suitable reagent</th>
<th>CPA (mol. eq.)</th>
<th>Reaction Time (Hr)</th>
<th>Yield (wt/wt)</th>
<th>Purity by HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium carbonate</td>
<td>1.5</td>
<td>2.5</td>
<td>12</td>
<td>0.88</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>1.5</td>
<td>3.0</td>
<td>14</td>
<td>0.85</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>1.0</td>
<td>3.0</td>
<td>12</td>
<td>0.90</td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
<td>3.0</td>
<td>3.0</td>
<td>12</td>
<td>0.80</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>3.0</td>
<td>3.5</td>
<td>16</td>
<td>0.75</td>
</tr>
<tr>
<td>Potassium acetate</td>
<td>3.0</td>
<td>3.0</td>
<td>20</td>
<td>0.82</td>
</tr>
<tr>
<td>Lanthanum oxide</td>
<td>1.5</td>
<td>3.0</td>
<td>16</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Example 9: Preparation of Nevirapine.

To a clean 3-necked 2L round bottom flask equipped with a mechanical stirrer, thermometer socket and addition funnel was charged o-xylene (250 ml) and 65% sodium hydride (18.5 gms) under nitrogen atmosphere at temperature 25°C to 35°C. The reaction was heated to 130°C to 135°C and solution of compound of Formula II (obtained from Ex-1) (50 gms of compound of Formula II dissolved in 15 ml of dimethyl formamide and 25 ml of o-xylene) was added and stirred for 1 hour at same temperature. After completion of the reaction by HPLC, reaction was allowed to cool to 25°C to 35°C and methanol (30 ml) and then water (250 ml) was added to the reaction mass at same temperature. The reaction mass was allowed to cool to 5°C and pH was adjusted to 6.8 to 7.2 with CP HC1 (35 ml) and stirred for 2 hours. Filtered the product and washed with chilled water (100 ml). The wet product was dried at 60°C to 70°C for 12 hours to provide the title compound.
Yield: 43 gms
HPLC purity: 99.5%

Example 10: Purification of Nevirapine

To a clean 3-necked 2L round bottom flask equipped with a mechanical stirrer, thermometer socket and addition funnel was charged ethyl acetate (1400 ml) and crude nevirapine (20 gms, obtained from Ex-9) at temperature 25°C to 35°C. The reaction mixture was heated to 75°C and stirred for 30 minutes at 75°C to 80°C. Activated carbon (2 gms) was charged and stirred for 30 minutes at same temperature. Filtered the carbon and
cooled the filtrate to 0°C to 5°C and stirred for 2 hours at same temperature. Filtered the product and washed with ethyl acetate (10 ml). The wet product was dried at 90-100°C under reduced pressure for 6 hours to provide the title compound.

Yield: 19 gms
HPLC purity: 99.9%
The XRPD is set forth in Figure-1
The DSC thermogram is set forth in Figure-2
The TGA is set forth in Figure-3

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the specification appended hereto.
We Claim:

Claim 1. A process for preparation of N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II,

\[
\begin{array}{c}
\text{CH}_3 \\
\text{N} \\
\text{Cl} \\
\text{HN} \\
\text{N} \\
\end{array}
\]

(II)

which comprises: reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III

\[
\begin{array}{c}
\text{CH}_3 \\
\text{N} \\
\text{Cl} \\
\text{Cl} \\
\text{HN} \\
\text{N} \\
\end{array}
\]

(III)

with cyclopropylamine (CPA) in presence of a suitable reagent in an organic solvent; wherein the suitable reagent is selected from carbonates, bicarbonates, acetates of alkali metals or lanthanum oxide.

Claim 2. The process of claim 1, wherein the suitable reagent is selected from the group consisting of sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, cesium bicarbonate, lithium bicarbonate, sodium acetate, potassium acetate, cesium acetate, lithium acetate and lanthanum oxide.

Claim 3. The process of claim 1, wherein the ratio of suitable reagent is about 0.5 to about 3 moles to the compound of Formula III.

Claim 4: The process of claim 1, wherein the organic solvent is selected from alcohols such as methanol, ethanol, isopropanol, propanol, butanol and the like; ethers such as tetrahydrofuran, 1,4-dioxane, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether and the like; aromatic hydrocarbons such as toluene, o-xylene, chlorobenzene, pyridine, anisole and the like; amides such as dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, N-methyl pyrrolidinone, hexamethyl phosphoramide and the like; or mixtures thereof.

Claim 5. The process of claim 4, wherein the organic solvent is o-xylene.
Claim 6. The process of claim 1, wherein the reaction is carried out at a temperature of about 75°C to about 150°C.

Claim 7. The process of claim 6, wherein the reaction is carried out at a temperature of about 135°C to about 145°C.

Claim 8. A process for preparation of nevirapine of Formula I, which comprises:

Formula I

\[
\begin{align*}
\text{O} & \\
\text{N} & \\
\text{CH}_3 & \\
\end{align*}
\]

5 a) reacting 2-chloro-N-(2-chloro-4-methyl-3-pyridinyl)-3-pyridine carboxamide of Formula III with cyclopropylamine in presence of a suitable reagent in an organic solvent to obtain N-(2-chloro-4-methyl-3-pyridyl)-2-(cyclopropylamino)-3-pyridine carboxamide of Formula II,

b) cyclizing the resultant compound of formula II in presence of a base to obtain nevirapine.

wherein the suitable reagent is selected from the group consisting of carbonates, bicarbonates, acetates of alkali metals and lanthanum oxide.

Claim 9: The process of claim 8, wherein the suitable reagent is selected from the group consisting of sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, cesium bicarbonate, lithium bicarbonate, sodium acetate, potassium acetate, cesium acetate, lithium acetate and lanthanum oxide.

Claim 10. The process of claim 8, wherein the organic solvent is o-xylene.

Claim 11. The process of claim 10, wherein the organic solvent is o-xylene.
Claim 12. The process of claim 8, wherein the base is selected from sodium hydride, potassium hydride, lithium hydride, sodium tertiary butoxide, potassium tertiary butoxide, or n-butyl lithium.

Claim 13. The process of claim 12, wherein the base is sodium hydride.
Figure 1
Figure 2

LAURUS LABS PVT LTD

244.84°C
334.4°C

Temperature (°C)

250

245.91°C

300