AN IMPROVED PROCESS FOR THE PREPARATION OF ARIPIPRAZOLE

Abstract: The present invention relates to an improved process for the preparation of Arpiprazole of formula (I), which is useful in the treatment of Schizophrenia. More particularly, the present invention relates to an improved process for the preparation of 7-(4-chlorophenyl)-3,4-dihydrocarboxyl of formula (III) by reacting 7-hydroxy-3,4-dihydrocarboxyl of formula (II) with 1,4-dichlorobutane, in presence of inorganic bases and solvent dimethylacetamide.
AN IMPROVED PROCESS FOR THE PREPARATION OF ARIPIPRAZOLE

Field of the invention

The present invention relates to an improved process for the preparation of Aripiprazole of formula (I), which is useful in the treatment of Schizophrenia. More particularly, the present invention relates to an improved process for the preparation of 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril of formula (III) by reacting 7-hydroxy-3,4-dihydrocarbostyril of formula (II) with 1,4-dichlorobutane, in presence of an inorganic base and solvent dimethylacetamide.

![Chemical structures](image)

Background of the invention

Aripiprazole, which is chemically known as 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydrocarbostyril having formula (I) is a dopamine D₂ and serotonin 5HT₁ partial agonist and a serotonin 5HT₂ antagonist. It is useful for treating Schizophrenia, which is the most common type of psychosis caused by an excessive neurotransmission activity of the dopaminergic nervous system in the central nervous system. Aripiprazole is marketed by Bristol Myers Squibb under brand name Abilify®.
Aripiprazole and salts thereof are known from US Patent No. 5,006,528 (henceforth '528), which describes its preparation in two steps. In the first step the solution of 7-hydroxy-3,4-dihydrocarbostyril in water and 1,4-dibromobutane is refluxed and the reaction mixture is extracted with dichloromethane, dried and purified by means of silica gel column chromatography to obtain 7-(4-bromobutoxy)-3,4-dihydrocarbostyril. In the second step the obtained 7-(4-bromobutoxy)-3,4-dihydrocarbostyril is refluxed with sodium iodide using acetonitrile as solvent. The obtained suspension is refluxed with 1-(2,3-dichlorophenyl)piperazine in the presence of triethylamine to obtain 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

The drawback of the process mentioned in '528 is that it involves multiple solvent systems, which are cumbersome to recover and reuse. Moreover the process according to '528 involves column chromatography for purification of the carbostyril derivative, which is very difficult at industrial scale and thus resulting in the lower yield.

US Patent Publication 2006 / 0258869 A1 (henceforth '869) claims a process for the preparation of Aripiprazole having dimer impurity less than 0.15%, comprising the steps of, (a) reacting 7-hydroxy-tetrahydroquinolinone with 1-bromo-4-chlorobutane in the presence of a base in a solvent to obtain 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril having dimer impurity less than 0.5% (b) condensing 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril having dimer impurity less than 0.5% with 1-(2,3-dichlorophenyl)piperazine or salt thereof, in the presence of a base, a phase transfer catalyst and sodium iodide in a solvent.
'869 patent discloses in the example (2) that 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril was isolated by extraction using ethylacetate as an additional solvent while in the present invention extraction using any additional solvent(s) is avoided, moreover as per the step (b) of claim 4 of '869, phase transfer catalyst is employed for the preparation of Aripiprazole, whereas in the present invention phase transfer catalyst is not used.

Hence we focused our research to simplify the process for the preparation of compound of formula (III) by avoiding column chromatography, additional solvent(s), extraction (s) and the use of phase transfer catalyst during the preparation of a compound of formula (I), to make it more cost effective with higher yield and greater purity.

Object of the invention

The main object of the present invention is to provide an improved process for the preparation of a compound of formula (I) in good yield and high purity.

Another object of the present invention is to provide a process for the preparation of a compound of formula (III), wherein solvent dimethylacetamide may be recovered and used in subsequent batches to make the process more simple, economical and commercially viable.

Summary of the invention

The present invention provides a process for the preparation of Aripiprazole of formula (I), comprising the steps of,

(a) reacting 7-hydroxy-3, 4-dihydrocarbostyril of formula (II),
with 1,4-dichlorobutane in the presence of a base and solvent dimethylacetamide to obtain 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril of formula (III);

(b) concentrating the reaction mass;
(c) adding an alkali solution to the concentrated mass obtained in the step (b);
(d) isolating the compound of formula (III);
(e) reacting 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril of formula (III) with 1-(2,3-dichlorophenyl)piperazine of formula (IV) or its salt in the presence of a base and alkali iodide in solvent dimethylacetamide.

Detailed description of the invention

In an embodiment of the present invention, the step (a) and (e) is performed by using an inorganic base, which is selected from the group comprising sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and the like, most preferably potassium carbonate.
In another embodiment of the present invention, the step (e) is performed by using alkali iodide such as sodium iodide, potassium iodide and the like, preferably sodium iodide.

In yet another embodiment of the present invention, the step (c) is performed by using an alkali solution, which is selected from the group comprising sodium hydroxide solution, potassium hydroxide solution, sodium carbonate solution, potassium carbonate solution, sodium hydrogen carbonate solution and the like, most preferably sodium hydroxide solution.

In still another embodiment of the present invention step (a) and (e) is performed at the temperature in the range of 20°C to 100°C, most preferred temperature range for step (a) is 90°C to 95°C and for step (e) is 90°C to 97°C.

The invention is further illustrated by the following examples, which should not be construed to limit the scope of the invention in anyway.

**Examples**

**Preparation of Stage 1**

A mixture of dimethylacetamide (16.8L), 7-hydroxy-3,4-dihydrocarbostyril (2.4Kg), 1,4-dichlorobutane (16.8Kg) and potassium carbonate (2.04Kg) were heated to 90°C to 95°C under stirring for 15 to 16 hrs. On completion of the reaction, the reaction mass was cooled, filtered and the residue was washed with 2 x 2.4 L of dimethyl acetamide. The filtrate was distilled to 3 to 4 Vol under reduced pressure (wherein temperature should be less than 110 °C). The reaction mass was cooled to 60°C to 70 °C and 10 L (10 Vol) of sodium hydroxide (0.5%) solution was charged portion wise. The reaction mass was further cooled to 25°C to 30 °C and was stirred for 1 to 2 hrs. The solid product formed was filtered, washed with water up to neutral pH (~ 7) and dried at 45°C to 50°C under vacuum for 10 to 16 hours to obtain 2.9 – 3.6Kg of 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril. (Yield = 75- 95 % and HPLC Purity > 90 %).
**Preparation of Stage 2**

A mixture of 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril (50g) obtained from stage I, 1-(2,3-dichlorophenyl)piperazine hydrochloride (50.1g), potassium carbonate (54.45g) and sodium iodide (32.48g,) in dimethyl acetamide (500 mL) were heated to 90°C to 97°C under stirring for 1 to 2 hrs. On completion of the reaction, the reaction mixture was cooled to room temperature and was diluted with 1.2L of dichloromethane. The organic layer was washed with 3 x 500mL of 0.5 % sodium hydroxide solution. The organic layer was evaporated to 5 Vol under reduced pressure. The reaction mixture was cooled to 0°C to 5°C and was stirred for 2hrs. The solid obtained was filtered and was washed with 2 x 100mL of ethyl acetate. The crude product thus obtained was recrystallized from ethanol to obtain Arpiprazole (50–70 g) in pure form (Yield = 56-80 % and HPLC Purity > 99 %).

**Advantages**

(1) Simple method of isolation of compound of formula (III) without using any additional solvent (s) for extraction (s).

(2) Use of 1,4-dichlorobutane is cost effective and comparatively less hazardous and less irritant as compared to 1,4-dibromobutane and 1-bromo-4-chlorobutane.

(3) The recovered dimethylacetamide solvent, which contained 1,4 dichlorobutane can be recycled and used in subsequent batches.

(4) 1,4 dichlorobutane is selected as a reactant for the preparation of a compound of formula (III), since its boiling point is relatively close to that of dimethylacetamide and can be co-distilled and reused.
We claim:

(1) A process for the preparation of Aripiprazole of formula (I) comprising the steps of,

\[
\begin{align*}
\text{(I)} & \\
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\end{align*}
\]

5  (a) reacting 7-hydroxy-3, 4-dihydrocarbostyril of formula (II);

\[
\begin{align*}
\text{(II)} & \\
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{HO}
\end{array}
\end{align*}
\]

with 1,4-dichlorobutane in the presence of a base and solvent dimethylacetamide to obtain

10  7-(4-chlorobutoxy)-3,4-dihydrocarbostyril of formula (III);

\[
\begin{align*}
\text{(III)} & \\
\begin{array}{c}
\text{Cl}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\end{align*}
\]

(b) concentrating the reaction mass;

(c) adding an alkali solution to the concentrated mass obtained in the step (b);

15  (d) isolating the compound of formula (III);

(e) reacting 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril of formula (III) with 1-(2,3-dichlorophenyl)piperazine of formula (IV) or its salt in the presence of a base and alkali iodide in solvent dimethylacetamide.

\[
\begin{align*}
\text{(IV)} & \\
\begin{array}{c}
\text{Cl}
\end{array}
\begin{array}{c}
\text{Cl}
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\end{align*}
\]

(2) A process according to claim 1 wherein, the said base is inorganic and is selected from the group comprising sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and the like.
(3) A process according to claim 2 wherein, the said base for step (a) and step (e) is potassium carbonate.

(4) A process according to claim 1 wherein, the said alkali iodide is selected from the group comprising sodium iodide, potassium iodide and the like, most preferably sodium iodide.

(5) A process according to claim 1 wherein, the said alkali solution is selected from the group comprising sodium hydroxide solution, potassium hydroxide solution, sodium carbonate solution, potassium carbonate solution, sodium hydrogen carbonate solution and the like, most preferably sodium hydroxide solution.

(6) A process according to claim 1 wherein, step (a) and (e) are performed at a temperature in the range of 20°C to 100°C.

(7) A process according to claim 6 wherein most preferred temperature range for step (a) is 90°C to 95°C and for step (e) is 90°C to 97°C.