The present invention relates to an improved process for the preparation of (-) trans-N-methyl paroxetine of formula (I), which is an intermediate in the synthesis of Paroxetine of formula (II). (-) Trans-N-methyl paroxetine is prepared by reacting (-) trans sulphonate compound of formula (III) with 3,4-methylenedioxyphenol (“sesamol”) of formula (IV) in the presence of base potassium carbonate using Methyl isobutyl ketone (MIBK) as solvent.
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IMPROVED PROCESS FOR THE PREPARATION OF (-) TRANS-N-METHYL PAROXETINE

Field of the Invention

The present invention relates to an improved process for the preparation of (-) Trans-N-methylparoxetine of formula (I) using methyl isobutyl ketone (MIBK) as solvent, which is a key intermediate in the synthesis of Paroxetine.

Background of the Invention

Paroxetine, trans (-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidine, is a serotonin re-uptake inhibitor, and has the following structural formula (II):

Paroxetine is an orally administered antidepressant for the treatment of depression, social anxiety disorders, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder and posttraumatic stress disorder. Paroxetine is marketed as Paxil® by GlaxoSmithKline.

U.S Patent 4,007,196 (henceforth '196) disclosed the process for the preparation of N-methylparoxetine using pyridine as solvent; the reaction scheme of the process is shown below:
The '196 patent discloses obtaining N-methylparoxetine by reacting 4-(4-fluorophenyl)-3-chloromethyl-N-methyl-piperidine, also named CIPMA of structure (V):

\[
\begin{align*}
\text{F} - \text{Ph} & \quad \text{Cl} \\
\text{C} & \quad \text{CH}_3 \\
\text{N} & \quad \text{R'} \\
\text{OH} & \quad \text{SO}_2\text{CH}_3
\end{align*}
\]

(V)

with 3,4-methylenedioxyphenol ("sesamol") of structure (IV) to obtain N-raethylparoxetine.

\[
\text{HO-Ph}
\]

(IV)

As per '196 patent CIPMA reacts with sesamol in a solution of sodium in methanol, giving N-methylparoxetine of the following structure (I) with a yield of about 25%.

\[
\begin{align*}
\text{F} - \text{Ph} & \quad \text{O-Ph} \\
\text{C} & \quad \text{O-Ph} \\
\text{N} & \quad \text{CH}_3 \\
\text{C} & \quad \text{CH}_3
\end{align*}
\]

(I)
U.S. Patent 4,585,777 (henceforth '777) is directed to the composition 4-(4-fluorophenyl)-3-((4-methoxyphenoxy)-methyl)-piperidine, which has the structure of:

![Chemical Structure](image)

[(-) trans]

In example 5 and 8 of '777 patent, first N-methyl intermediate is prepared by reacting the sulfonate esters of the enantiomers of cis-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine with p-methoxyphenol. The '777 patent does not mention the yield in example 5. In example 8, 38.5 grams of the ester were used to obtain 1.8 grams of the product as a free base, giving a yield of about 5%.

In U.S. Patent No. 3,912,743, example 1, a solution of 3-hydroxymethyl-1-methyl-4-phenyl piperidine in pyridine is reacted with methanesulphonyl chloride. The pyridine is removed and the crude resultant sulphonate ester is treated with sodium methoxide and 4-methoxyphenol in methanol under reflux. In Example 5 of EP 152273, 4-(4-fluorophenyl)-3-hydroxymethyl-1-methyl piperidine is dissolved in toluene together with triethylamine and cooled. Benzenesulphonyl chloride is added to this mixture. The resultant solution of the benzenesulphonic ester is then mixed with sodium methoxide and 4-methoxyphenol in methyl isobutyl carbinol and heated.

US 2004/0087795 publication claims the process for the preparation of N-methyl paroxetine by reacting the sulphonate ester with sesamol using toluene as a solvent.

Most of the prior art is directed to synthesis of CIPMA, related compounds and their precursors, rather than synthesis of N-methylparoxetine from CIPMA. For example, U.S. Patent No. 6,326,496, incorporated herein by reference, teaches obtaining CIPMA by reducing a precursor through the use of a metal hydride. These
patents provide little insight on how to synthesize N-methylparoxetine after obtaining CIPMA, or how to increase the yield of such synthesis.

The low yield of N-methylparoxetine produced results in lower yields of paroxetine. The low yield increases the cost of the process and requires additional purification.

None of the prior art references disclose or claim the use of solvent methyl isobutyl ketone (MIBK) for the preparation of compound of formula (I).

We focused our research to develop an improved and efficient process for the preparation of the compound of formula (I) in comparatively good yield and high purity. The process disclosed in the present invention is having advantages over the processes described in the above-mentioned prior art documents.

**Objectives of the Invention**

The main objective of the present invention is to provide an improved process for the preparation of compound of formula (I) using methyl isobutyl ketone (MIBK) as a solvent in presence of base potassium carbonate.

Another objective of the present invention is to provide a process for the preparation of compound of formula (I), which would be easy to implement on commercial scale and which can avoid the use of toxic solvents like toluene and benzene.

Another objective of the present invention is to recover methyl isobutyl ketone (MIBK) and the recovered methyl isobutyl ketone (MIBK) is used in subsequent batches to make process more economical and commercially viable.

Still another objective of the present invention is to provide a process for the preparation of compound of formula (I) in good yield and high purity.
Summary of the Invention

Accordingly, the present invention provides an improved process for the preparation of (-) Trans-N-methyl paroxetine of formula (I), which involves the reaction of sulphonate ester of formula (III) with sesamol of formula (IV) in presence of base potassium carbonate using methyl isobutyl ketone (MIBK) as solvent at a temperature of about 118-120°C.

The process is shown in the scheme given below

Description of the Invention

In an embodiment of the present invention, the reaction step is performed in a solvent. The solvent is selected from the group consisting of methyl isobutyl ketone, methyl ethyl ketone, methyl vinyl ketone, methyl isopropyl ketone, methyl propyl ketone and N-methyl pyrrolidone; the most preferred solvent for this reaction is methyl isobutyl ketone (MIBK).

In still another embodiment of the present invention the base used for the reaction is alkali carbonates selected from Sodium carbonate and Potassium carbonate preferably Potassium carbonate.
In another embodiment of the present invention, the reacting step is preferably performed at a temperature of about 45°C to about 120°C. Most preferably, the reaction step is performed at a temperature of about 118°C to about 120°C.

The starting material of this invention may be prepared according to the literature available in the prior art.

The present invention is exemplified by the following example, which is provided for illustration only and should not be construed to limit the scope of the invention.

**Example 1**

**Preparation of Compound of formula (I):**

Preparation of (-)-trans-4- (4'-fluorophenyl)-3-(3", 4"-methylenedioxyphenoxy methyl)-1-methyl piperidine [(−)-Trans-N-methyl paroxetine].

10 gm (0.033 mol) of (3E4i?)-trans-4-(4-fluorophenyl)-1-methyl-3-methylsulphonyloxy piperidine and 30 ml of methyl isobutyl ketone (MIBK) were charged to a 500 ml 4-necked RB flask at 28-30°C. The contents were stirred to dissolve the mass completely. 4.6 gm (0.033 mol) of Sesamol was charged at 28-30°C and stirred to dissolve. 6.7 gm (0.0483 mol) of dry potassium carbonate was charged to the mass under stirring at 28-30°C. The reaction mixture was refluxed and simultaneously removed water azeotropically at 118-120°C for 5 hr in order to complete the reaction. The reaction mass was diluted with distilled water (100 ml) at 60°C and stirred for 15 min at 60°C. The organic portion was separated and washed with distilled water (50 ml). The organic portion was concentrated to a thick mass under vacuum at 60-65°C. To the residue, isopropyl alcohol (IPA) (50 ml) was charged at 28-30°C and heated to 60-65°C. The mass was concentrated under vacuum to remove solvents and to get residue. To this residue, charged IPA (50 ml) and heated to 60°C to get homogeneous solution. Distilled water (60 ml) was charged under stirring at 60°C for 30 min. The slurry mass was cooled to 15°C and stirred for 60 min. The slurry was filtered at 15°C and washed the wet cake with 45 ml distilled water at 28-30°C. The
wet cake was made reslurry-using n-hexane (15 ml) at 28-30°C and stirred for 60 min. The solid was filtered and washed with n-hexane (10 ml) at 28-30°C and dried the wet material to get 7.4 gm of N-methyl paroxetine (Purity > 97.5%).
We Claim:

(I) A process for preparing (-) Trans-N-ethyl paroxetine of formula (I), which comprises: reacting the sulphonate ester of formula (III) with sesamol of formula (IV) in the presence of base potassium carbonate using methyl isobutyl ketone (MIBK) as solvent at reflux temperature.

(2) A process according to claim 1, wherein the wet cake of N-methyl paroxetine is further treated with hexane to get higher purity.

(3) A process according to claim 1, wherein (-) Trans-N-methyl paroxetine is used further for the preparation of Paroxetine.