(54) Title: PROCESS FOR PREPARATION OF β-PHENETHYLAMINE DERIVATIVE

(57) Abstract: A process for the production of Sibutramine i.e. N-1-{[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl-N, N-dimethy- lamine of formula (I) comprising the steps of: (a) reacting a nitrile, 1-(4-chlorophenyl) cyclobutyl carbonitrile of formula (III) with a Grignard reagent, namely isobutyl magnesium bromide to produce the magnesium complex of formula (IV); (b) cleaving the magnesium complex of formula (IV) under basic conditions to form an imine of formula (VIII); (c) reducing the imine of formula (VIII) by a metal hydride to obtain an amine of the formula (VII), and (d) converting the amine (VII) first to its hydrochloride and then to Sibutramine of formula (I) by Eschweiler Clarke methylation.
PROCESS FOR PREPARATION OF β-PHENETHYLAMINE DERIVATIVE

The present invention relates to a novel cost effective process for the production of Sibutramine.

Sibutramine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine of formula(1),

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{CH}_3 & \\
\text{Cl} & \quad \text{N} \\
\text{C} & \quad \text{N}
\end{align*}
\]

(1)

is a potent serotonin and noradrenaline reuptake inhibitor and has the dual action, of enhancing both satiety and metabolism and is thus marketed as the drug of choice for the management of obesity. Sibutramine is also useful in the treatment of depression, Parkinson's disease, Non Insulin Dependent Diabetes Mellitus (NIDDM) and epilepsy. (Barker et al, WO 97/20810).

As a significant proportion of the population strives to lose weight, the pharmaceutical management of obesity has gained increasing attention in new weight loss treatments. Obesity is a major healthcare problem especially in the United States and Europe and its prevalence continues to escalate. Obesity results from an imbalance between calorific intake and energy expenditure resulting in the
deposition of fat. In clinical trials Sibutramine hydrochloride monohydrate has been shown to cause marked weight reduction, and unlike other currently available drugs, remains effective over a longer period of time (> 12 months).

The original synthetic route for the production of Sibutramine involves the following steps:

a) Cycloalkylation of 4-chlorophenyl acetonitrile (II) to 1-(4-chlorophenyl) cyclobutyl carbonitrile (III) by condensation with 1, 3 dibromopropane and a base such as sodium hydride.

\[
\text{Cl-} \quad \text{CN} \quad \text{(II)} \quad \xrightarrow{1,3-	ext{Dibromopropane}} \quad \text{Cl-} \quad \text{CN} \quad \text{(III)} \\
\text{DMSO} \quad \text{NaH}
\]

\text{REACTION - 1}

b) Grignard reaction of 1-(4-chlorophenyl) cyclobutyl carbonitrile (III) with isobutyl magnesium bromide to form the magnesium complex (IV)

\[
\text{Cl-} \quad \text{CN} \quad \text{(III)} \quad \xrightarrow{\text{MgBrCH}_2} \quad \text{BrMgN} \quad \text{(IV)} \\
\text{Toluene}
\]

\text{REACTION - 2}

c) Cleavage of the intermediate magnesium complex (IV) under acidic conditions to give the Ketone (V)
(d) Leuckart reaction of Ketone (V) to give the formamide compound (VI)

(e) Acidic hydrolysis of the formamide compound (VI) to give the primary amine (VII) which is the key intermediate involved in the synthesis of Sibutramine.
(f) Eschweiler - Clarke methylation of the primary amine (VII) to yield the target compound Sibutramine.

The Reaction-2 above in step (b) gives an optimum yield of 80% for the magnesium complex (IV) when the ethereal solvent used initially for the preparation of Grignard reagent is removed by distillation and the reaction is carried out in an inert solvent like toluene or xylene, preferably toluene, and the mixture is kept under stirring at 90°C for 18 hours.

The main drawback of the above synthetic route is drastic reaction conditions like high temperature of 170°-180°C, long reaction time period of 20-24 hours required for the Leuckart reaction step (d) besides poor yield of less than 20% of the amine (VII) and use of a costly solvent namely bis(2-methoxy ethyl ether) in the Leuckart reaction.

Jeffery J.E. et al (J. Chem. Soc, Perkin Trans 1, 1996, 2583) reported a short cut route for production of the intermediate primary amine (VII) by a tandem Grignard reduction step in which the Grignard reaction product (IV) of step (b) above is treated with sodium borohydride to give the primary amine (VII) directly. However, subsequent attempts by Reddy et al to repeat the same process using
reported conditions were not successful and yielded compounds other than the said amine (VII) (Organic Process Research & Development, (1999) 3(6), 466-492.)

Reddy et al further mentioned that by innovator’s process one gets Dimer (A), the undesired product, as the only product instead of the required amine (VII). This was also the experience at our hand:

![Chemical Structure](image)

(A)

Accordingly there is a need to devise a simple cost effective and reproducible route for the production of Sibutramine which has of late gained importance as a drug for various therapies as discussed above.

The first object of the present invention is to provide a simple, cost effective and reliable process for the preparation of Sibutramine.

Another object of the invention is to provide for a simple, cost effective and reliable process for the preparation of the intermediate β-phenethyamine derivative in the production of Sibutramine.
Yet another object of the invention is to provide a process for formation of the intermediate magnesium complex (IV) wherein the reaction time is reduced with corresponding reduction in reactor occupancy and the requirement of the utilities associated with it.

Accordingly, the present invention provides a process for the production of Sibutramine of formula (I).

\[
\text{H}_2\text{C}-\text{NCH}_3
\]

\[
\text{Cl-}\begin{array}{c}
\text{CN} \\
\text{III}
\end{array}
\]

comprising the steps of:

(a) reacting one equivalent of a nitrile, 1-(4-chlorophenyl) cyclobutyl carbonitrile of formula (III)

with 2.5 to 3.5 equivalent of a Grignard reagent, namely isobutyl magnesium bromide at 90°C to produce the magnesium complex of formula (IV)

\[
\left[\begin{array}{c}
\text{Cl-} \\
\text{IV}
\end{array}\right]
\]
(b) cleaving the magnesium complex of formula (IV) with ammonium hydroxide and ammonium chloride at 0°C to 10°C to form an imine of formula (VIII)

(c) reducing the imine of formula (VIII) by a metal hydride to obtain the amine of formula (VII)

(d) converting the amine (VII) first to its hydrochloride and then to Sibutramine of formula (I) by Eschweiler Clarke methylation.

The Grignard reagent, isobutyl magnesium bromide, was freshly prepared from magnesium and isobutyl bromide in ether as solvent and iodine crystals were added to initiate the formation of the Grignard reagent.

The nitrile (III) in inert solvent was added to 2.5 to 3.5 equivalents of Grignard reagent. The ratio of Grignard reagent to nitrile (III) used is preferably 3 equivalents of the Grignard reagent to 1 equivalent of the nitrile (III). Inert
solvents such as toluene and xylene can be used. The preferred solvent used was toluene. At high temperature of 90°C, the Grignard reaction was carried out for 3 hrs to form the magnesium complex (IV). Thus, the reaction time was found to be reduced from 18 hrs as reported by Jeffery et al (J.Chem.Soc.Perkin Trans 1, 1996, 2583) to 3 hrs. for this process step with corresponding reduction in the time for the reactor occupancy, and the utilities required to maintain high temperature to make the process economical.

The magnesium complex (IV) was cleaved under basic conditions, by ammonium hydroxide and ammonium chloride at 0 to 10°C in a time period of 2 to 3 hours to give the imine (VIII)

\[
\begin{align*}
\text{[IV]} & \quad \stackrel{\text{NH}_4\text{Cl}}{\text{NH}_4\text{OH}} \quad \text{0 - 10 °C} \\
\text{[VIII]} & 
\end{align*}
\]

**REACTION - 6**

The imine was immediately reduced by using a metal hydride such as sodium borohydride, or lithium aluminum hydride, to give the amine (VII). Preferably the
reduction of imine was carried out by sodium borohydride.

**REACTION-7**

The target compound sibutramine can be prepared from 1-[1-(4-chlorophenyl)cyclobutyl]-3-methyl butylamine (VII) first by converting it to its hydrochloride followed by Eschweiler - Clarke methylation.

The total time period involved for the conversion of the magnesium complex IV to the key intermediate, the amine (VII), by the process of the instant invention is around 22 hours. This is much lower than the time period involved in the prior art process involving the Leuckart reaction wherein the time period for the Leuckart reaction alone was 20 to 24 hours.

The temperature involved in the conversion of magnesium complex (IV) to amine (VII) by the process of the instant invention is between 0°C to room temperature whereas a high temperature of 170° to 180°C is required for the Leuckart reaction of the prior art process.

Costly solvent, bis(2-methoxy ethyl ether) was used in the Leuckart reaction of prior art process whereas only toluene and methanol are used in the process of the instant invention.

A yield of less than 20% of the amine (VII) was obtained in the prior art synthetic route involving the Leuckart reaction whereas the process of the instant invention gave a significantly higher yield of 66%.
Hence, the present invention provides a reliable reproducible, high yield and economical process for the synthesis of Sibutramine.

The invention is explained in the examples given below which are provided by way of illustration alone and does not in any way restrict the scope of invention.

EXAMPLES:

PREPARATION OF 1-[1-(4-CHLOROPHENYL)CYCLOBUTYL]-3-METHYL BUTYLIMINE (VIII).

Magnesium turnings were added in a 1 l. four necked round bottom flask. To the flask 103 ml of ether and 10 mg. of iodine were also added and heated to reflux for 5 min. The solution of isobutylbromide (145.8 g) in ether (146 ml) was prepared at room temperature and 15 ml of this solution was carefully added with stirring and under reflux conditions over 15 min. to initiate the reaction and subsequently the remaining solution of isobutylbromide in ether was added carefully. A solution of 1-(4-chlorophenyl)cyclobutane carbonitrile (68.3 g) in toluene (340 ml) was added to the reaction mixture and simultaneously ether was distilled from the reaction mixture. The reaction mixture was heated and kept at 90°C for 3 hrs. and then cooled to 10°C. A solution of ammonium chloride (300 g) in water (500 ml) and commercial ammonium hydroxide solution (300 ml) was prepared and cooled to 0°C. To this solution the reaction mass was added while
maintaining the temperature at 0 to 10°C. The organic layer was separated and the aqueous layer was extracted with toluene (2 X 170 ml) at room temperature. The combined organic layers were washed with water (2 X 140 ml) and dried over anhydrous sodium sulphate to give the title compound 1-[1-(4-chlorophenyl)cyclobutyl]-3-methyl butylimine (VIII) in toluene.

PREPARATION OF 1-[1-(4-CHLOROPHENYL)CYCLOBUTYL]-3-METHYL BUTYLAMINE (VII).

In a 2l four necked round bottom flask the solution of 1-[1-(4-chlorophenyl)cyclobutyl])-3-methyl butylimine (VIII) in toluene obtained above was maintained at 0°C, under stirring, and methanol (350 ml) was added followed by the slow addition of sodium borohydride over 2 hrs. The reaction mixture was maintained at room temperature for 12 hrs. and then 350 ml of water was added over 30 min. The layers were separated and the organic layer was washed with water (2 X 130 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the title compound 1-[1-(4-chlorophenyl)cyclobutyl])-3-methyl butylimine (VII) (yield : 80g).

PREPARATION OF N-{1-[1-(4-CHLOROPHENYL)CYCLOBUTYL]-3-METHYL BUTYL}-N,N-DIMETHYLAMINE (SIBUTRAMINE)

Formic acid (460ml) was added to a stirred ice cold solution of 1-[1-(4-chlorophenyl) cyclobutyl -3-methyl butylimine VIII (152g, 0.604 mole), then aqueous formaldehyde (37-40% w/v 92ml) was added and the mixture was heated
at 90-95°C for 1 hour. Further aqueous formaldehyde (92ml) was added, and heating at 90-95°C was continued for 19 hours. Then the mixture was cooled to room temperature and added to a stirred mixture of ice (1000g) and 16M aqueous sodium hydroxide (650ml). The product was extracted into ether (4 x 500ml), and the extracts were washed with saturated brine (2 x 200ml) and water (2 x 200ml), dried over anhydrous magnesium sulphate and evaporated. The residue was distilled to give sibutramine (141.5g, 84%) as a pale yellow oil, at room temperature which solidified slowly to give a pale yellow solid, mp 51-55°C.
WE CLAIM:

1. A process for the production of Sibutramine i.e N-1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl-N,N- dimethylamine of formula (I)

\[
\begin{align*}
\text{H}_3\text{C} & \text{N} \text{CH}_3 \\
\text{Cl} & \text{N} \text{CN} \\
\text{Cl} & \text{N} \text{CN} \\
\end{align*}
\]

(1)

comprising the steps of:

(a) reacting a nitrile, 1-(4-chlorophenyl) cyclobutyl carbonitrile of formula (III)

\[
\begin{align*}
\text{Cl} & \text{CN} \\
\end{align*}
\]

(III)

with a Grignard reagent, namely isobutyl magnesium bromide to produce the magnesium complex of formula (IV);

\[
\begin{align*}
\text{Cl} & \text{BrMgN} \\
\end{align*}
\]

(IV)

(b) cleaving the magnesium complex of formula (IV) under basic conditions to form an imine of formula (VIII);
(c) reducing the imine of formula (VIII) by a metal hydride to obtain an amine of the formula (VII), and

(d) converting the amine (VII) first to its hydrochloride and then to Sibutramine of formula (I) by Eschweiler Clarke methylation.

2. The process as claimed in claim 1, wherein in step (a) the nitrile (III), taken in an inert solvent is added to 2.5 to 3.5 equivalent of Grignard reagent and the reaction is carried out for 3 hours.

3. The process as claimed in claim 2, wherein 3 equivalents of the Grignard reagent is added.

4. The process as claimed in claim 2, wherein the inert solvent is selected from the group of toluene and xylene.

5. The process as claimed in claim 4, wherein the inert solvent is toluene.
6. The process as claimed in claim 1 wherein in step (b) the magnesium complex is cleaved by ammonium hydroxide and ammonium chloride at 0°C to 10°C.

7. The process as claimed in claim 1, wherein in step (c) the reduction of imine (VIII) is carried out by metal hydride.

8. The process as claimed in claim 1, wherein in step (c) the reduction of imine (VIII) is carried out by a reducing agent selected from the group of sodium borohydride and lithium aluminium hydride.

9. The process as claimed in claim 8, wherein the reducing agent is sodium borohydride.

10. A process for producing Sibutramine i.e. N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethyl amine substantially as herein described.
(d) converting the amine (VII) first to its hydrochloride and then to Sibutramine of formula (I) by Eschweiler Clarke methylation.