Title: PROCESS FOR THE PREPARATION OF 1-METHYL-3-CARBOMETHOXY-4-(4'-FLUOROPHENYL)-PIPERIDINE

Abstract: A compound of formula (2) is prepared by treating a dispersion of crystalline arecoline hydrobromide in an organic solvent with an anhydrous strongly basic reagent to generate a solution of arecoline free base, which is reacted directly with an organometallic compound of formula (5) in which M is a Group II metal and Y a halogen or the group (1). The compound of formula (5) is typically a Grignard reagent in which M is Mg and Y is Cl or Br. The piperidine ester of structure (2) is reduced to a piperidine carbinol, coupled with sesamol, then deprotected, to give paroxetine. The process avoids the direct handling of the irritant alkaloid oil arecoline.
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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PROCESS FOR THE PREPARATION OF 1-METHYL-3-CARBOMETHOXY-4-\((4'-\text{FLUOROPHENYL})\)-PIPERIDINE

The present invention relates to a new process for preparing pharmaceutically active compounds and intermediates therefor. In particular the present invention relates to a new process for the preparation of paroxetine.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US 3,912,743 and US 4,007,196. An especially important compound among those disclosed is paroxetine, the (-) trans isomer of 4-(4'-fluorophenyl)-3- (3",4")-methylenedioxyphenoxy-methyl)piperidine. This compound is used in therapy as the hydrochloride salt to treat inter alia depression, obsessive compulsive disorder (OCD) and panic.

Various processes have been described for the preparation of paroxetine, for example in US 4,007,196 and Acta Chemica Scandinavica (1996) volume 50 page 164. A particularly useful starting material employed in processes described therein is the alkaloid arecoline (1)

![Chemical Structure](image-url)

In the process described in Acta Chemica Scandinavica (1996) volume 50 page 164, arecoline base, which is not commercially available, is liberated from the hydrobromide salt and reacted with a Grignard reagent such as 4-fluorophenyl magnesium bromide to give a piperidine ester of structure (2). This piperidine ester is reduced to a piperidine carbinol of structure (3), which is coupled with sesamol, then deprotected, to give paroxetine (4).
The prior art processes require the liberation of arecoline base by addition of aqueous potassium carbonate to arecoline hydrobromide, extraction into benzene and evaporation to an oil. We have found that this process is inefficient, particularly on a large scale. There are significant losses of arecoline in the aqueous phase, and a wet solution is obtained, which must be rigorously dried before use in the subsequent Grignard reaction. We have also found that the oily arecoline base generated by this procedure has very poor storage properties, is hygroscopic, and readily oxidises in the air to generate undesirable impurities which persist throughout subsequent synthetic steps. An additional problem is the hazardous nature of arecoline base, which is extremely irritant and is a known carcinogen.

The improved process of this invention is based on the finding that a mixture of crystalline arecoline hydrobromide in a suitable organic solvent may treated with a suitable anhydrous strongly basic reagent to generate a solution which may be reacted directly with the Grignard reagent. This process is higher yielding than the prior art process, has fewer processing steps, and exposure of operators to the toxic arecoline base is avoided. By comparison with arecoline base, the hazards associated with handling arecoline hydrobromide, which is a non-volatile crystalline solid and freely soluble in water, are greatly reduced. The process of this invention is therefore particularly suitable for large scale manufacture.

Accordingly the present invention provides a process for the preparation of a compound of formula (2)
in which a dispersion of crystalline arecoline hydrobromide in an effective organic solvent is treated with an effective anhydrous strongly basic reagent to generate a solution of arecoline free base, which is reacted directly with an organometallic compound of formula (5)

in which M is a Group II metal and Y is a halogen or the group

The compound of formula (5) may a Grignard reagent in which, for example, M is Mg and Y is Cl or Br. The compound of formula (5) may also be a symmetric molecule in which, for example, M is Zn and Y is the group

Suitable effective anhydrous strongly basic reagents are those which react with hydrogen bromide of the arecoline salt to form one or more volatile, inert, or insoluble by-products, and which do not generate water.

The process of this invention may be carried out in a number of ways. In one aspect sodium hydride or a similar reagent is added to arecoline hydrobromide in a suitable organic solvent and the resulting anhydrous solution of arecoline base is used directly in
the organometallic or Grignard reaction. In this process the hydrogen bromide is efficiently removed as inert sodium bromide and volatile hydrogen gas.

Analogously, the addition of butyl lithium or a similar reagent as strong base results in the removal of hydrogen bromide by conversion to inert lithium bromide and volatile butane.

Alternatively, an inorganic salt such as anhydrous sodium or potassium carbonate may be used. This generates insoluble bromide salts which, together with excess basic reagent may be removed, for example by centrifugation or filtration, to give an anhydrous solution of arecoline free base suitable for reaction with an organometallic compound or Grignard reagent such as 4-fluorophenyl magnesium bromide.

In a further embodiment, excess Grignard reagent is used as the strong base, for example by reacting arecoline hydrobromide directly with 4-fluorophenyl magnesium bromide firstly to generate the free base, and then to carry out the coupling reaction. This generates inert by-products which do not interfere with the Grignard reaction.

Suitably effective solvents are those which are compatible with the organometallic or Grignard coupling reaction, such as toluene or dichloromethane. A preferred solvent is toluene.

Addition of the strongly basic reagent is preferably carried out under an inert atmosphere at ambient or less than ambient temperature.

Arecoline hydrobromide is a commercially available compound. The organometallic compounds may be prepared by conventional procedures for such reagents.

Compounds of structure (1) may be converted to the active compound paroxetine using conventional procedures disclosed in US-A-3912743 or US-A-4007196, whereby the piperidine ester of structure (2) is reduced to a piperidine carbinol of structure (3), which is coupled with sesamol, then deprotected, to give paroxetine (4).
Where appropriate or necessary, compounds of structure (1) may be resolved to obtain the \((-\)trans\) isomer using conventional reagents such as a nitro tetracil acid, as described in EP-A-0223334 - see Example 5

The present invention includes within its scope the compound paroxetine, and paroxetine salts such as paroxetine hydrochloride, especially as an anhydride or the hemihydrate, when obtained via any aspect of this invention, and any novel intermediates resulting from the described procedures.

The resultant paroxetine is preferably obtained as or converted to a pharmaceutically acceptable derivative such as a salt, more especially the methanesulphonate salt or the hydrochloride salt and most preferably the hemihydrate of that salt, as described in EP-A-0223403. Paroxetine free base may be converted to paroxetine methanesulphonate by treatment with methanesulphonic acid or a labile derivative thereof, for example a soluble salt such as ammonium methanesulphonate. Paroxetine hydrochloride may be prepared by treatment of paroxetine free base with a source of hydrogen chloride, for example gaseous hydrogen chloride, or a solution thereof, or aqueous hydrochloric acid.

Paroxetine and its salts obtained using this invention may be formulated for therapy in the dosage forms described in EP-A-0223403 or WO96/24595, either as solid formulations or as solutions for oral or parenteral use.

Therapeutic uses of paroxetine, especially paroxetine hydrochloride, obtained using this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the Disorders".

Accordingly, the present invention also provides:
a pharmaceutical composition for treatment or prophylaxis of the Disorders comprising paroxetine or paroxetine salt obtained using the process of this invention and a pharmaceutically acceptable carrier;

the use of paroxetine or paroxetine salt obtained using the process of this invention to manufacture a medicament for the treatment or prophylaxis of the Disorders; and

a method of treating the Disorders which comprises administering an effective or prophylactic amount of paroxetine or paroxetine salt obtained using the process of this invention to a person suffering from one or more of the Disorders.

Pharmaceutical compositions using active compounds prepared in accordance with this invention are usually adapted for oral administration, but formulations for dissolution for parental administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100 mg, for example 10 to 50 mg such as 10, 12.5, 15, 20, 25, 30 or 40 mg by a human patient. Most preferably unit doses contain 20 mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules, including formulations adapted for controlled or delayed release.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing. Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.
This invention is illustrated by the following Examples.

Example 1

5 Preparation of cis/trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine using sodium hydride

A 60% dispersion of sodium hydride in mineral oil (2.0 g) was added carefully to a suspension of arecoline hydrobromide (11.8 g) in toluene and the mixture cooled to about -10°C. A solution of 4-fluorophenylmagnesium bromide in diethyl ether (2.0M, 50 ml) was added slowly with stirring under argon, maintaining the temperature at about -10°C, and the mixture stirred at this temperature for 3 hours.

The reaction was quenched by adding 2M hydrochloric acid (250 ml). The aqueous layer was washed with toluene (100 ml) then covered with fresh toluene (100 ml) and adjusted to pH 9-10 by the cautious addition of anhydrous potassium carbonate. The precipitated solids were removed by filtration, the phases were separated and the aqueous phase was extracted twice more with toluene (100 ml). The combined toluene layers were washed with saturated aqueous sodium chloride (100 ml) then evaporated under reduced pressure to give the product as an oil.

Yield 10.10g (80.5%).

Example 2

25 Preparation of cis/trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine using butyl lithium

A solution of butyl lithium in hexanes (1.6M, 6.25 ml) was added dropwise to a suspension of arecoline hydrobromide (2.36 g) in toluene (50 ml) with stirring and cooling under argon. A solution of 4-fluorophenylmagnesium bromide in diethyl ether (2.0M, 7.5 ml) was added slowly at about -10°C, and the mixture stirred at this temperature for about 3 hours.
The reaction was quenched by the addition of ice-cold water (50 ml) and concentrated hydrochloric acid (5 ml). The aqueous layer was washed with toluene (50 ml) then covered with fresh toluene (50 ml) and adjusted to pH 9-10 by the cautious addition of anhydrous potassium carbonate. The precipitated solids were removed by filtration, the phases were separated and the aqueous phase was extracted twice more with toluene (50 ml). The combined toluene layers were evaporated under reduced pressure to give the product as an oil.

Yield 1.62 g

Example 3
Preparation of cis/trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine using sodium carbonate

Sodium carbonate (1.05 g) was added to a suspension of arecoline hydrobromide (2.36 g) in toluene (50 ml) and the mixture stirred at ambient temperature for ~ 18 hours. The solids were removed by filtration and the filtrate transferred to a reaction flask under argon and cooled to about -10°C. A solution of 4-fluorophenylmagnesium bromide in diethyl ether (2.0M, 10 ml) was added and the mixture stirred at about -10°C for 2 hours.

The reaction was quenched cautiously with 2M hydrochloric acid (50 ml). The aqueous layer was washed with toluene (50 ml) then covered with fresh toluene (50 ml) and adjusted to pH 9-10 by the cautious addition of anhydrous potassium carbonate. The precipitated solids were removed by filtration, the phases were separated and the aqueous phase was extracted twice more with toluene (50 ml). The combined toluene layers were washed with saturated aqueous sodium chloride (100 ml) then evaporated under reduced pressure to give the product as an oil.

Yield 0.83 g (33%).

Example 4
Preparation of cis/trans 1-methyl-3-carbomethoxy-4-(4'-fluorophenyl)-piperidine using excess Grignard reagent
4-fluorophenylmagnesium bromide in diethyl ether (2.0M, 17.5 ml) was added slowly to a suspension of arecoline hydrobromide (2.36 g) in toluene (100 ml), with stirring under argon at about -10°C. The mixture was stirred at this temperature for 3 hours.

The reaction was quenched cautiously with 2M hydrochloric acid (50 ml). The aqueous layer was washed with toluene (100 ml) then covered with fresh toluene and adjusted to pH 9-10 by the cautious addition of anhydrous potassium carbonate. The precipitated solids were removed by filtration, the phases were separated and the aqueous phase was extracted twice more with toluene (50 ml). The combined toluene layers were washed with saturated brine (50 ml) then evaporated under reduced pressure to give the product as an oil.

Yield 1.65 g (65%)
CLAIMS

1. A process for the preparation of a compound of formula (2)

\[
\begin{array}{c}
\text{F} \\
\text{N-CH}_3 \\
\end{array}
\]

(2)

in which a dispersion of crystalline arecoline hydrobromide in an effective organic solvent is treated with an effective anhydrous strongly basic reagent to generate a solution of arecoline free base, which is reacted directly with an organometallic compound of formula (5)

\[
\begin{array}{c}
\text{F} \\
\text{M-Y} \\
\end{array}
\]

(5)

in which M is a Group II metal and Y a halogen or the group

\[
\begin{array}{c}
\text{F} \\
\end{array}
\]

2. A process according to claim 1 in which the compound of formula (5) is a Grignard reagent.

3. A process according to claim 2 in which M is Mg and Y is Cl or Br.

4. A process according to claim 1 in which M is Zn and Y is the group

\[
\begin{array}{c}
\text{F} \\
\end{array}
\]
5. A process according to any one of the preceding claims in which the strong base is a metal hydride, an alkyl lithium or a metal carbonate.

6. A process according to any one of claims 1 to 4 in which the strong base is provided by using an excess of a Grignard reagent.

7. A process according to any preceding claim in which the piperidine ester of structure (2) is reduced to a piperidine carbinol of structure (3), which is coupled with sesamol, then deprotected, to give paroxetine of structure (4).

8. A process according to claim 7 in which paroxetine is obtained as or converted to a pharmaceutically acceptable salt.

9. A method of treating the Disorders which comprises administering an effective or prophylactic amount of paroxetine or paroxetine salt obtained using the process of this invention to a person suffering from one or more of the Disorders.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C07D211/60

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEMABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>Y</td>
<td>WO 99 07680 A (BRANTFORD CHEMICALS INC ; REY ALLAN W (CA); MURTHY K S KESHAVA (CA)) 18 February 1999 (1999-02-18) the whole document</td>
<td>1-8</td>
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<td>Y</td>
<td>US 2 546 652 A (J.T. PLATI ET AL.) 27 March 1951 (1951-03-27) example 1</td>
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**X** Further documents are listed in the continuation of box C.  
**X** Patent family members are listed in annex.

* Special categories of cited documents:
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