(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
11 May 2006 (11.05.2006)

PCT

(10) **International Publication Number**
WO 2006/048720 A1

(51) **International Patent Classification:**
C07C 269/04 (2006.01) *C07C 271/44* (2006.01)
C07C 269/00 (2006.01)

(21) **International Application Number:** PCT/IB2005/003237

(22) **International Filing Date:** 29 October 2005 (29.10.2005)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
1207/MUM/2004 8 November 2004 (08.11.2004) IN

(71) **Applicant** *(for all designated States except US)*: **EMCURE PHARMACEUTICALS LIMITED** [IN/IN]; EMCURE HOUSE, T-184, MIDC, Bhosari, Pune, Maharashtra 411 018 (IN).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **GHARPURE, Milind, Moreshwar** [IN/IN]; 12/2 F-II Block, M.I.D.C., Pimpri, Pune, Maharashtra 411 018 (IN). **BHAWAL, Baburao, Manikrao** [IN/IN]; 12/2 F-II Block, M.I.D.C., Pimpri, Pune, Maharashtra 411 018 (IN). **SHAH, Viral, Bipinbhai** [IN/IN]; 12/2 F-II Block, M.I.D.C., Pimpri, Pune, Maharashtra 411 018 (IN). **ZOPE, Umesh, Rewaji** [IN/IN]; 12/2 F-II Block, M.I.D.C., Pimpri, Pune, Maharashtra 411 018 (IN). **MEHTA, Satish, Ramanlal** [IN/IN]; 12/2 F-II Block, M.I.D.C., Pimpri, Pune, Maharashtra 411 018 (IN).

(74) **Agents: HARIHARAN, Rajeshwari** et al.; K & S PARTNERS, 84-C, C6 LANE, OFF CENTRAL AVENUE, SAINIK FARMS, NEW DELHI 110 062 (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

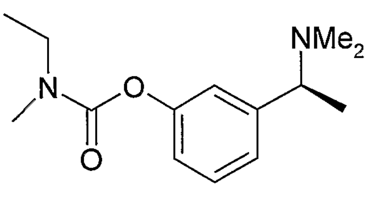
(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AN EFFICIENT METHOD FOR PREPARATION OF (S)-3-[(1-DIMETHYL AMINO)ETHYL]-PHENYL-N-ETHYL-N-METHYL-CARBAMATE



(I)

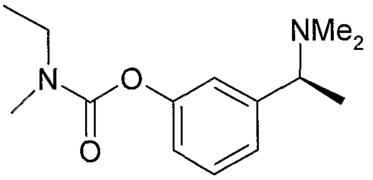
(57) **Abstract:** The present invention relates to a method for preparation of substituted phenyl carbamate and pharmaceutically acceptable salts thereof, which are of current pharmaceutical interest. The substituted phenyl carbamate and pharmaceutically acceptable salts thereof are useful to raise cholinergic activity in the central nervous system and useful in treatment of diseases such as Alzheimer's disease, Down's syndrome, Huntingdon's chorea, Friedrich's ataxia etc. (S)-3-[(1-dimethyl amino)ethyl]- phenyl-N-ethyl-N-methyl-carbamate (I) is the active ingredient of the pharmaceutical composition referred in US 5,602,176. This compound is also used to induce selective inhibition of acetylcholinesterase activity in the brain.

WO 2006/048720 A1

AN EFFICIENT METHOD FOR PREPARATION OF (S) - 3- [(1-DIMETHYL AMINO)ETHYL]- PHENYL-N-ETHYL-N-METHYL-CARBAMATE

FIELD OF THE INVENTION:

The present invention relates to a method for preparation of substituted phenyl carbamate and pharmaceutically acceptable salts thereof, which are of current pharmaceutical interest. The substituted phenyl carbamate and pharmaceutically acceptable salts thereof are useful to raise cholinergic activity in the central nervous system and useful in treatment of diseases such as Alzheimer's disease, Down's syndrome, Huntingdon's chorea, Friedrich's ataxia etc.

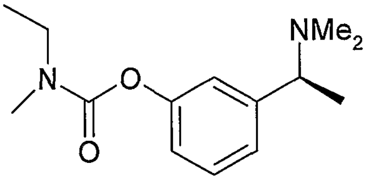


(I)

(S)-3-[(1-dimethyl amino)ethyl]- phenyl-N-ethyl-N-methyl-carbamate (I) is the active ingredient of the pharmaceutical composition referred in US 5,602,176. This compound is also used to induce selective inhibition of acetylcholinesterase activity in the brain.

BACKGROUND OF THE INVENTION

The method for preparation of the compound (I) i.e. (S)- 3- [(1-dimethyl amino)ethyl]-phenyl-N-ethyl-N-methyl-carbamate (I) is known in literature.



(I)

For preparation of Compound (I), as referred in WO 2004/037771, the intermediate 3-(1-dimethylaminoethyl)phenol is needed. The said intermediate is prepared by using $Ti(OiPr)_4$ i.e. titanium tetraisopropoxide, sodium borohydride and dimethyl amine in first step. In the second step, HBr is used. The process, due to the use of $Ti(OiPr)_4$, becomes expensive. $Ti(OiPr)_4$ is difficult to handle because it is flammable liquid and also it is irritant. Furthermore, for the work-up of the reaction, ammonia is used and moreover the titanium residue left at the end of the reaction creates effluent treatment problems and remains as environmental pollutant. Sodium borohydride is one of the expensive reducing agent used and handling of the same is hazardous and requires very skilled personnel for addition as well as work-up of the reaction. HBr causes severe burns during handling. HBr is also toxic. Also, J. Labeled Comp. and Radiopharm. 1997, 39(8), 651-668 uses HBr for the same step of demethylation. Use of HBr for demethylation of methoxy function has disadvantage in the quality of final product. For industrial scale, the quantities of such reagents used are very much high and hence there is a need to avoid the use of such unsafe reagents.

EP 359647 discloses the method of preparation of morphinane analogue, wherein for demethylation of ortho-methoxy compound, sulfonic acid like methane sulfonic acid is used. However, on industrial scale such an expensive, corrosive and toxic reagent needs to be avoided.

The process of preparation as disclosed in US 4,948,807 and US 5,602,176 for compound (I) is via isocyanates or carbamoyl halides, wherein the compound (I) has the substituents on phenyl carbamate as lower alkyl.. The isocyanates, especially the one with lower alkyl group as substituents are hazardous due to their toxic properties. Use of the solvent such as dry acetonitrile or benzene are necessary for the preparation of compound (I) via isocyanates or carbamoyl halides. The industrial process using such costly, carcinogenic solvents needs to be avoided as such solvents could cause spontaneous explosions. Use of base such as sodium hydride can be avoided for the large scale reactions because it demands several safety measures, in term of storage, handling as well as processing of the reaction. Also, sodium hydride used is in the tune of 200%, which during work-up of the reaction apart from the safety hazards, causes uncontrollable exothermicity leading to the generation of various impurities.

WO 03/101917 discloses the process, wherein one of the key intermediates is N-ethyl-N-methyl-4-nitrophenyl carbamate obtained from 4-nitrophenyl chloroformate. This process does not teach the preparation of 3-(1-dimethylamino ethyl) phenol. Rather the method of preparation is by using [1-(3-methoxyphenyl) ethyl] diethylamine. The demethylation reaction is carried out by using 50% sulfuric acid and DL-methionine. The use of DL-methionine on industrial scale need to be avoided as it is skin, eye and respiratory irritant. Also, the use of DL-methionine increases the cost of production.

The reaction time is also at least 28 hrs, which increases the time to complete the whole reaction sequence till rivastigmine. Thus, obtaining 3-(1-dimethylamino ethyl) phenol is through more number of steps. Thus, there is a need to reduce the number of steps for obtaining 3-(1-dimethylamino ethyl) phenol.

Jiang et. al. (Huadong Shifan Daxue Xuebao, Ziran Kexueban (2001), (1), 61-65. / CAN 136:183572 AN 2001:429602) disclosed that the Rivastigmine can be obtained from ketone by (i) converting it into oxime (ii) reducing to amine followed by (iii) dimethylation of amine and finally (iv) converting the same into carbamate to get the racemic N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate (II). Thus, there are practically four functional group interconversions, only to obtain the racemic carbamate (II). The higher number of functional group interconversions lead to mainly loss of yield as well as higher cost of reagents & solvents, higher reactor occupancy, more utilities, more manpower etc. Thus, the need of efficient preparation of intermediate and in turn final rivastigmine is very essential for industrial scale.

WO 2005/061446 A1 discloses a method for preparation of Rivastigmine starting from the hydroxy phenyl ketone. The starting compound is treated with triethyl amine and ethyl methyl carbamoyl chloride to give the phenyl carbamate ketone, which when treated with dimethyl amine in the presence of sodium cyanoborohydride gives amino alkyl phenyl carbamate, which is then resolved with di-O-p-toluyl tartaric acid in aqueous methanol to give rivastigmine. This method has the drawback of employing a toxic compound like sodium cyanoborohydride, which is quite hazardous, when employed on an industrial scale. Rivastigmine thus prepared has to be crystallized several times for getting the desired purity. The repeated steps of purification reduces the overall yield considerably.

Thus, there is a need to develop the method of preparation, wherein the number of steps are reduced. Similarly, the use of $Ti(OiPr)_4$ is required to be avoided to make the method of preparation to be economically more viable, industrial friendly and environment friendly. Avoiding use of sodium borohydride would make the process simpler, more safe at the same time very cost efficient. Also, use of HBr need to be avoided and the method of preparation should be devoid of use of isocynate and carbamoyl chloride.

OBJECT OF THE INVENTION

The object of the present invention is to avoid the use of $Ti(OiPr)_4$, sodium borohydride and HBr.

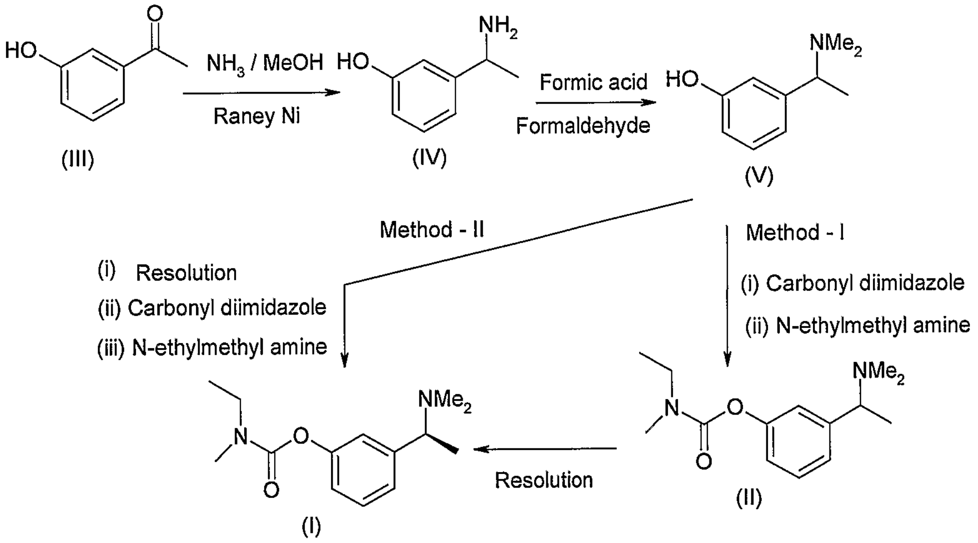
Another object of the invention is to provide the process, which is economical for large scale preparation.

Yet another objective is to provide the process without using isocynate and carbamoyl chloride.

Still another object of the invention is to provide rivastigmine by using carbonyl diimidazole.

DETAILED DESCRIPTION OF THE INVENTION

A method of preparation acccording to the instant invention is according to SCHEME-1. The compound (III) is reacted with ammonia in presence of catalyst to give the product of reductive amination 3-(1-amino ethyl) phenol i.e. compound (IV). The catalyst used is Raney-Nickel. The solvent used for the reaction is alcohol such as methanol, ethanol, isopropanol, n-propanol etc. The preferable alcoholic solvent is methanol.



SCHEME - 1: Different methods as per the present invention for the preparation of (S)-Rivastigmine

As referred in the SCHEME-1, according to the instant invention, the racemic amine (IV) i.e. 3-(1- amino ethyl) phenol is converted in to dimethylamine product (V) i.e. 3-(1-dimethylaminoethyl)phenol. Dimethylation of amine is carried out by using formic acid and formaldehyde. Thus, racemic compound (V) i.e. 3-(1-dimethylaminoethyl)phenol is obtained. Using compound (V), two methods are adopted: METHOD – 1: conversion of phenolic compound (V) into carbamate; followed by resolution of the carbamate. METHOD - 2 resolution of 3-(1-dimethylaminoethyl)phenol followed by carbamate formation.

METHOD – 1:

a) Preparation of 3-hydroxyl-1-phenyl ethyl amine (III).

The first step in Method-I comprises reductive amination of compound (III) with Raney nickel in the presence of ammonia.

In the present embodiment, the method for preparation of compound (IV) comprises addition of 3-hydroxy acetophenone of formula (III) to an organic solvent selected from the group comprising of hydroxylic solvents, like alcohol, water or mixture thereof.

The alcohol employed is selected from the group comprising of methanol, ethanol, isopropanol, n-propanol, n-butanol etc

The preferred alcohol is methanol.

The reductive amination is carried out in alcohol either alone or in combination with water. Ammonium hydroxide followed by Raney nickel is added. The mixture is heated under pressure in an autoclave in the presence of hydrogen gas till completion of the reaction. Raney nickel was removed by filtration and the filtrate concentrated. The residue is optionally purified through the formation of their acid addition salts.

b) Preparation of 3-(1-dimethylaminoethyl)phenol (V).

The step relates to a method for methylation of the amino group by reaction with formaldehyde in the presence of formic acid.

3-(1-dimethylaminoethyl)phenol of formula (IV) was methylated in the presence of excess formic acid and formaldehyde at reflux temperature.

The compound of formula (V) was isolated by neutralization with an aqueous solution of an inorganic base followed by extraction with an organic solvent followed by concentration of the organic layer.

c) Preparation of 3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methyl carbamate (II).

This step relates to the preparation of a carbamate by reaction of ethylmethylcarbamoyl chloride with compound of formula (V) in an organic solvent and in the presence of a base.

3-[1-(dimethylamino)ethyl]phenol of formula (V) was added to an organic solvent, selected from the group comprising of aliphatic hydrocarbons, esters, chlorinated hydrocarbons, nitriles etc, preferably a nitrile like acetonitrile.

Ethylmethyl carbamoyl chloride was added to the reaction mixture.

And the reaction mixture heated till completion of reaction. The compound of formula (II) was isolated by cooling the reaction mixture to ambient temperature and extracted with an organic solvent. The organic layer was concentrated to give compound of formula (II).

The above obtained carbamate of formula (II) was resolved to get (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate (I).

METHOD – 2:

3-(1-Dimethylamino ethyl) phenol is resolved using various resolving agents such as selected from the group comprising of optically active tartaric acid, di-O-tolyl tartaric acid, dibenzyl tartaric acid, mandelic acid, camphor sulfonic acid etc

In the further reaction, the optically pure compound (V-A) is used for preparation of the desired carbamate i.e. (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate (I).

The carbamate formation is carried out by various methods, wherein the agent to insert the carbonyl moiety between amine and phenolic component are different; such as carbonyldiimidazole, triphosgene, methyl carbonate etc. The carbonyl insertion reagent can be first reacted with phenolic OH group followed by reaction with amine component. Optionally, the carbonyl insertion reagent is first reacted with amine and followed by reaction with phenolic OH group.

Alternatively, 4-nitrophenyl chloroformate is reacted with 3-(1-dimethylamino ethyl) phenol and followed by reaction of the said product with N-ethylmethylamine.

Among the carbonyl inserting agents it was carbonyldiimidazole, which was found to be the reagent of choice, because reaction was faster and isolation of the product of formula (II) was easier.

Method-II is similar to Method-I, till the preparation of compound (V).

i) **Resolution of 3-(1-dimethylaminoethyl)phenol of formula (V) to give (S)- 3-(1-dimethylaminoethyl)phenol of formula (V-a).**

The first step in Method-II relates to resolution of compound (V) by utilizing camphor sulphonic acid to give 3-(1-dimethylaminoethyl)phenol of formula (V) to give (S)- 3-(1-dimethylaminoethyl)phenol of formula (V-a).

ii) **Preparation of Rivastigmine.**

a) **Preparation of Rivastigmine by utilizing carbonyl diimidazole and ethyl methyl amine.**

The preparation of Rivastigmine comprises reaction of (S)-3-{1-(dimethylaminoethyl)phenol or its racemic mixture with ethyl methyl amine in the presence of carbonyl diimidazole (CDI). This reaction involves preparation of the carbamate derivative of compound (V-a), i.e. rivastigmine of formula (I) by insertion of the carbonyl group between the phenolic oxygen and the nitrogen atom of ethyl methyl amine.

It is pertinent to mention that carbonyl diimidazole has been employed for the first time for the preparation of rivastigmine, avoiding hazardous reagents like ethyl methyl carbamoyl chloride, isocyanates, phosgene etc.

The reaction comprises addition of (S)-3-{1-(dimethylaminoethyl)phenol (V-a) or its racemate of formula (V) to an organic solvent.

The organic solvent is selected from the group comprising of aliphatic hydrocarbons, esters, chlorinated solvents etc.

The preferred solvent is a chlorinated solvent.

The chlorinated solvent is selected from the group comprising of dichloromethane, ethylene dichloride, and chloroform.

The preferred chlorinated solvent is dichloromethane.

The amount of the chlorinated solvent employed is between 2 volumes and 20 volumes per gram of compound (V-a) or (V).

The preferred volume of the solvent employed is between 4 volumes and 10 volumes per gram of compound (V-a) or (V).

Carbonyl diimidazole is added to the reaction mixture.

The amount of carbonyl diimidazole added is between 1.5 mole and 3.0 moles per mole of compound (V-a) or (V).

The preferred amount of carbonyl diimidazole added is between 1.75 mole and 2.0 moles per mole of compound (V-a) or (V).

The reaction mixture is refluxed for duration between 10 and 15 hours and the reaction monitored by HPLC.

The reaction mixture is cooled between 0°C and 10°C, and ethyl methyl amine added.

The amount of ethyl methyl amine added is between 1.0 moles and 3.0 moles per mole of compound (V-a) or (V).

The preferred amount of ethylmethyl amine added is between 1.75 moles and 2.25 moles per mole of compound (V-a) or (V).

The reaction mixture is stirred at ambient temperature for 4-6 hours.

After completion of the reaction, the mixture is quenched with water. The organic layer is separated and washed with a dilute aqueous solution of an inorganic base.

The inorganic base is selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide etc.

The preferred inorganic base is sodium hydroxide.

The organic layer is washed with a dilute solution of a mineral acid like hydrochloric acid, sulphuric acid etc.

The preferred mineral acid is hydrochloric acid.

The organic layer is then treated with dilute solution of ammonium hydroxide and extracted with an organic solvent.

The organic solvent is selected from the group comprising of aliphatic hydrocarbons, chlorinated hydrocarbons, esters etc.

The preferred organic solvent is an aliphatic hydrocarbon selected from the group comprising of hexane, cyclohexane, heptane etc.

The organic layer after extraction is concentrated to give compound of formula (I) having an optical purity of 99% or compound of formula (II), i.e. .racemic rivastigmine, which is then resolved by standard methods to give Rivastigmine of formula (I).

Thus by avoiding resolution of racemic rivastigmine of formula (II) in the last step and by employing a very much less hazardous, safe, readily available regent like carbonyl diimidazole, and ethylmethyl amine the process becomes cost-effective, environmental friendly and more suitable for industrial purpose.

Preparation of Rivastigmine from (S)-3-{1-(dimethylaminoethyl)phenol (V-a) by employing ethylmethyl carbamoyl chloride.

The method comprises reaction of (S)-3-{1-(dimethylaminoethyl)phenol (V-a) with ethylmethyl carbamoyl chloride in the presence of a mild inorganic base or organic base.

It is pertinent to mention that prior art methods, which disclose the above reaction, disclose utilization of a strong base like sodium hydride, which is hazardous on industrial scale. Further, it is also important to note that when the desired isomer of the intermediate (S)-3-{1-(dimethylaminoethyl)phenol (V-a) is employed for preparing Rivastigmine, only half the amount of ethylmethyl carbamoyl chloride is required, thereby making the process cost-effective for industrial scale.

3-[1-(Dimethylamino)ethyl]phenol of formula (V) was added to an organic solvent, selected from the group comprising of aliphatic hydrocarbons, esters, chlorinated hydrocarbons, nitriles etc.

The preferred solvent is a nitrile.

The nitriles are selected from the group comprising of acetonitrile, propionitrile, butyronitrile etc.

The preferred solvent is acetonitrile.

The volume of acetonitrile employed is between 5 and 20 times volume of acetonitrile per gram of compound (V-a).

The preferred volume of acetonitrile is between 10 and 15 times volume of acetonitrile per gram of compound (V-a).

A base selected from the group comprising of an inorganic base or an organic base is added to the mixture.

The preferred base is an inorganic base.

The inorganic base is selected from the group comprising of a carbonate, bicarbonate, alkoxide of a alkali metal or the carbonate, bicarbonate of an alkaline earth metal.

The preferred inorganic base is the carbonate of an alkali metal.

The inorganic base is selected from the group comprising of lithium carbonate, sodium carbonate or potassium carbonate.

The preferred inorganic base is potassium carbonate.

The amount of potassium carbonate employed is between 1 .0 moles and 4.0 moles per mole of compound of formula (V-a).

The preferred amount of potassium carbonate is between 2.75 moles and 3.25 moles per mole of compound of formula (V-a).

Ethylmethyl carbamoyl chloride was added to the reaction mixture.

The amount of ethyl methyl carabamoyl chloride added is between 1.0 and 1.5 mole per mole of compound of formula (V-a).

The reaction was carried out at a temperature between 60°C and 90°C. The preferred temperature was 70°C-80°C.

After completion of the reaction, the mixture was cooled to ambient temperature and concentrated. The residue was diluted with water and extracted with an organic solvent to give the product of formula (I).

Thus the advantage lies in utilizing only half the amount of ethyl methyl carbamoyl chloride, thereby making the process cost-effective and suitable for industrial scale.

The process of present invention is described herein below with reference to examples, which are illustrative only and should not be construed to limit the scope of the present invention in any manner.

EXAMPLES

Preparation of 3-hydroxyl-1-phenyl ethylamine (IV)

Reductive amination was carried on 3-hydroxy acetophenone (25gm) with ammonical methanol (250ml) in the presence of Raney nickel (5 gm) at 80°C and 10kg /cm2 of hydrogen pressure in an autoclave. After 12-14 hours the product was isolated by removing Raney nickel and concentrating the filtrate. The product was further purified by making its hydrochloride salt, extracting with ethyl acetate (100 ml) and neutralizing with caustic solution till pH 11-12 was attained which gave a yield of 70%.

Yield: 21.25 gms.

% Yield: 85%.

HPLC Purity: 98-99%.

Preparation of 3-(1-dimethylaminoethyl) phenol (V)

N-Alkylation was carried on 3-hydroxy–1-phenylethylamine (10gm) with 2 eq. of formaldehyde and 4 eq. of formic acid. The reaction was carried at 90°C for 10-12 hours. The reaction mixture was neutralized with caustic solution and extracted with ethyl acetate (3 X 50 l). Further concentration gave the desired product with 70% yield.

Yield: 80-90 gms

%Yield: 70%

HPLC Purity: 97%.

Preparation of 3-[1-(dimethylamino) ethyl] phenyl-N-ethyl-N-methylcarbamate (II)

Condensation reaction of 3-(1-dimethylaminoethyl) phenol (10 gm) and ethylmethylcarbamoyl chloride (10gm) was carried in the presence of potassium carbonate (25 gm) and acetonitrile (150 ml) at 70-80° C. After completion of reaction, the reaction mixture was quenched in water (250 ml) at 30-35° C and extracted in ethyl acetate (100ml). Evaporation of ethyl acetate gave the desired compound in 70% yield.

Yield: 80-85 gms.

%Yield: 66.0%

HPLC Purity: 99%.

Preparation of (-)-S-3-[1-(dimethylamino) ethyl] phenyl-N-ethyl-N-methylcarbamate (I)

The resolution of racemic compound (10gm) with (+)-O, O'-ditoluyltartaric acid (16gm) in methanol (20ml) and water (10ml) gave 6 gm of desired isomer under cold condition. The pure isomer was obtained after crystallization (thrice) in mixture of water and methanol (1:2). The tartrate salt (6 gm) was treated with caustic solution, extracted with dichloromethane and concentrated in vacuum to yield 2 gm of pale yellow oil.

Yield: 20-25gms.

%Yield: 20%(w/w).

HPLC Purity: 99%.

Preparation of (S)-3-(1-dimethylaminoethyl) phenol (V-a).

3-(1-Dimethylaminoethyl) phenol (25g, 0.15mole) was added to Ethyl acetate (125ml) followed by D-(+)-10-camphor sulphonic acid (35 g, 0.15 mole). The reaction mass was heated to reflux temperature. Methanol (17ml) was added. The reaction mass was refluxed for 30 minutes and filtered at 10°C to give compound of formula (V-a). Optionally, the salt was further recrystallized from a mixture of ethyl acetate and methanol.

Yield: 6.25-7.5 gms

%Yield: 25-30%

HPLC Purity: 98%

Preparation of Rivastigmine from (S)-3-(1-dimethylaminoethyl) phenol (V-a) by utilizing ethylmethyl carbamoyl chloride.

(S)-3-(1-dimethylaminoethyl) phenol (V-a; 25gm; 0.15mole) was reacted with Ethyl methyl carbamoyl chloride (20gm, 0.165 mole) in presence of anhydrous.potassium carbonate (31.5 gm, 0.228 moles) and acetonitrile (250ml) and heated. After completion of reaction the reaction mixture was filtered and the filtrate concentrated to give product. The product was optionally purified by acid base treatment.

Yield: 27 gm

Yield: 74%

Purity: 99% (by HPLC)

Preparation of 3-[1-(dimethylamino) ethyl] phenyl-N-ethyl-N-methylcarbamate via CDI and ethylmethyl amine

3-(1-dimethylaminoethyl) phenol (10 gm, 0.06 moles) was added to dichloromethane (50ml) followed by addition of carbonyl diimidazole (20g, 0.123mole). The reaction mass was refluxed for 12 hours and the reaction mass was then cooled to 5-10°C. Ethylmethyl amine (7.08gms; 2.0 moles) was added to the mixture and stirred for 4-6 hours till completion of reaction. Water (100 ml) was added to quench the reaction. The dichloromethane layer was separated and treated with 10% NaOH solution (50ml) at 10-15°C. The organic layer was then treated with dilute hydrochloric acid, neutralized with ammonia solution and extracted with Hexane. The hexane layer was concentrated to give compound (I).

Preparation of Rivastigmine hydrogen tartrate.

(-)-S-3-[1-(dimethylamino)ethyl]phenyl-N-ethyl-N-methylcarbamate (I) (100gms;1.0 mole) and L-tartaric acid (60gms; 1.0mole) were added to acetone (1000ml) and the mixture heated at 60°C for 1.0 hour to get a clear mixture, which was then cooled for complete precipitation of the tartrate salt of compound (I). The tartrate salt of compound was filtered and dried.

Yield:135 gms.

%Yield: 85%.

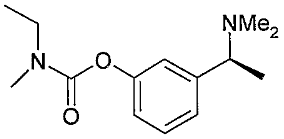
HPLC Purity: 99%.

The advantage of the instant process is:

1. The method utilizes a readily available, industrially safe raw material like N,N-carbonyl diimidazole for obtaining the carabamoyl function. It has to be noted that N,N-carbonyl diimidazole has not been used before for preparing rivastigmine.
2. The reagent used for preparation of carbamate such as N-ethyl-N-methyl carbamoyl chloride are highly expensive. The reagents such as N,N-carbonyl diimidazole used for preparation of carbamate will be used only in half the quantities, especially because the undesired isomer (being absent) does not take the part in the reaction. Thus, the method of preparation is industrially cost effective.

CLAIMS:

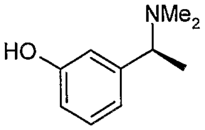
1. A process for the preparation of rivastigmine of formula (I)



(I)

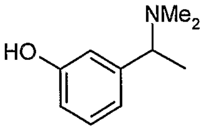
comprising

a) reacting (S)-3-(1-dimethylaminoethyl) phenol of formula (V-a) with carbonyl diimidazole and



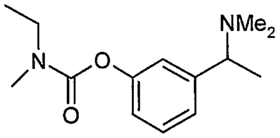
(V-a)

b) performing a step selected from reacting the product of step–a with ethyl methyl amine in an organic solvent to obtain compound (I); or reacting racemic 3-(1-dimethylaminoethyl) phenol of formula (V) with carbonyl diimidazole and



(V)

reacting the product of step b with ethyl methyl amine in an organic solvent to give compound of formula (II), and



(II)

resolving the compound (II) to yield compound (I).

2. A process according to claim 1a, wherein the amount of carbonyl diimidazole employed is between 1.5 moles and 3.0 moles per mole of compound of formula (V) or compound of formula (V-a).

3. A process according to claim 1c, wherein the amount of carbonyl diimidazole employed is between 1.5 moles and 3.0 moles per mole of compound of formula (V) or compound of formula (V-a).

4. A process according to claim 2 and 3 , wherein the amount of carbonyl diimidazole employed is preferably between 1.75 moles and 2.25 moles per mole of compound of formula (V) or compound of formula (V-a).

5. A process according to claim 1b, wherein the amount of ethylmethyl amine employed is between 1.0 mole and 3.0 moles per mole of compound of formula (V) or compound of formula (V-a).

6. A process according to claim 1d, wherein the amount of ethylmethyl amine employed is between 1.0 mole and 3.0 moles per mole of compound of formula (V) or compound of formula (V-a).

7. A process according to claim 5 or 6 , wherein the amount of ethylmethyl amine employed is between 1.75 moles and 2.25 moles per mole of compound of formula (V) or compound of formula (V-a).

8. A process according to claim 1a and 1c, wherein the solvent employed is selected from the group comprising of aliphatic hydrocarbon, esters, chlorinated solvents.

9. A process according to claim 8, wherein the preferred solvent is a chlorinated hydrocarbon.

10. A process according to claim 9, wherein the chlorinated solvent is selected from the group comprising of dichloromethane, chloroform, and ethylene dichloride.

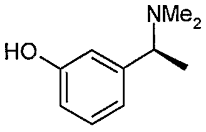
11. A process according to claim 10, wherein the chlorinated hydrocarbon is preferably dichloromethane.

12. A process according to claim 1b, wherein the compound of formula (I) is isolated from the reaction mixture, by quenching the mixture with water, followed by extraction with an organic solvent and concentration of the organic layer.

13. A process according to claim 1d, wherein the compound of formula (I) is isolated from the reaction mixture, by quenching the mixture with water, followed by extraction with an organic solvent and concentration of the organic layer.

14. A process according to claim 1d, wherein the compound of formula (I) is isolated from the reaction mixture, by quenching the mixture with water, followed by concentration of the organic layer to give compound of formula (II), which is resolved by employing an optically active acid like D-camphor sulphonic acid.

15. A process for preparation of rivastigmine of formula (I) comprising reaction of (S)-3-(1-dimethylaminoethyl) phenol of formula (V-a) with ethylmethyl carbamoyl chloride in an inert organic solvent and in the presence of an inorganic base at a elevated temperature and isolating compound of formula (I).



(V-a)

16. A process according to claim 14, wherein the organic solvent is selected from the group comprising of aliphatic hydrocarbons, esters, chlorinated hydrocarbons, nitriles.

17. A process according to claim 15, wherein the preferred organic solvent is a nitrile.

18. A process according to claim 16, wherein the nitrile is selected from the group comprising of acetonitrile, propionitrile, butyronitrile.

19. A process according to claim 17, wherein the preferred nitrile is acetonitrile.

20. A process according to claim 18, wherein the volume of acetonitrile employed is between 10 and 15 volumes per gram of compound (V-a).

21. A process according to claim 14, wherein the inorganic base is selected from the group comprising of carbonates, bicarbonate, alkoxides of alkali or alkaline earth metals.

22. A process according to claim 20, wherein the preferred inorganic base is the carbonate of an alkali metal.

23. A process according to claim 21, wherein the inorganic base is selected from the group comprising of lithium carbonate, sodium carbonate and potassium carbonate.

24. A process according to claim 22, wherein the preferred inorganic base is potassium carbonate.

25. A process according to claim 23, wherein the amount of potassium carbonate utilized is between 1.0 and 4.0 moles per mole of compound (V-a).

26. A process according to claim 14, wherein the amount of ethylmethyl carbamoyl chloride employed for the reaction is between 1.0 and 1.5 moles per mole of compound (V-a).

27. A process according to claim 14, wherein the compound of formula (I) is isolated from the reaction mixture, by quenching the mixture with water, followed by extraction with an organic solvent and concentration of the organic layer

28. A process for preparing Rivastigmine of formula (I) substantially as described in foregoing examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/003237

A. CLASSIFICATION OF SUBJECT MATTER
C07C269/04 C07C269/00 C07C271/44

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)
C07C

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

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

EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/037771 A (ZENTIVA, A.S; STEPANKOVA, HANA; HAJICEK, JOSEF; SIMEK, STANISLAV) 6 May 2004 (2004-05-06) page 12 - page 13; claim 1	15-28
A	abstract	1

X	US 4 948 807 A (ROSIN ET AL) 14 August 1990 (1990-08-14) column 6, line 27 - column 7, line 14; table 1; compound RA7 HCL column 10, lines 3-5	15-28

	-/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 23 February 2006	Date of mailing of the international search report 07/03/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer van Laren, M

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOEZIO, ALESSANDRO A. ET AL: "Asymmetric, Catalytic Synthesis of .alpha.-Chiral Amines Using a Novel Bis(phosphine) Monoxide Chiral Ligand" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 125(47), 14260-14261 CODEN: JACSAT; ISSN: 0002-7863, 2003, XP002367724 page 14261, right-hand column -----	15-28
P,X	US 2005/096387 A1 (VERHEIJEN, JEROEN C. ET AL) 5 May 2005 (2005-05-05) examples 1,2,4,5,10-13 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/003237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004037771 A	06-05-2004	AU 2003277795 A1	13-05-2004
		CZ 20023555 A3	14-01-2004
		EP 1556338 A1	27-07-2005
US 4948807 A	14-08-1990	AU 595504 B2	05-04-1990
		AU 5428486 A	11-09-1986
		CA 1284501 C	28-05-1991
		CY 1748 A	03-06-1994
		DE 3675408 D1	13-12-1990
		DE 19875046 I1	04-09-2003
		DK 99186 A	06-09-1986
		EP 0193926 A2	10-09-1986
		ES 8801193 A1	01-03-1988
		FI 860914 A	06-09-1986
		GR 860586 A1	07-07-1986
		HK 130293 A	03-12-1993
		HU 41718 A2	28-05-1987
		IE 58838 B1	17-11-1993
		IL 74497 A	09-02-1990
		JP 1629293 C	20-12-1991
		JP 2055416 B	27-11-1990
		JP 61225158 A	06-10-1986
		KR 9410764 B1	11-11-1994
		LU 90312 A9	06-01-1999
		NL 980031 I1	04-01-1999
		NZ 215348 A	26-04-1990
		PH 23325 A	14-07-1989
		PL 146301 B1	31-01-1989
		PT 82127 A	01-04-1986
		ZA 8601653 A	28-10-1987
US 2005096387 A1	05-05-2005	NONE	