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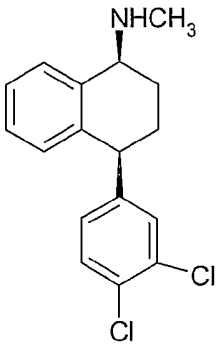
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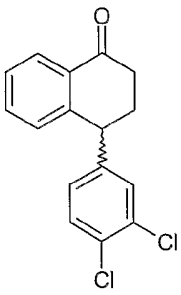
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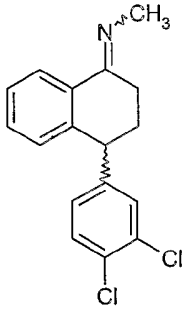
(54) Title: PROCESS FOR THE PREPARATION OF (1S, 4S)-4-(3,4-DICHLOROPHENYL)-1,2,3,4-TETRAHYDRO-N-METHYL-1-NAPHTHYLAMINE



(1)



(2)



(3)

(57) Abstract: A process for the preparation of (1S, 4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, compound of formula (1), said process comprising (a) reacting (3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenone, compound of formula (2), with methylamine in an acyclic or cyclic polyether to yield N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine, compound of formula (3) (b) converting compound of formula (3) to a mixture of compound of formula (1) and its stereoisomers; and (c) isolating compound of formula (1).

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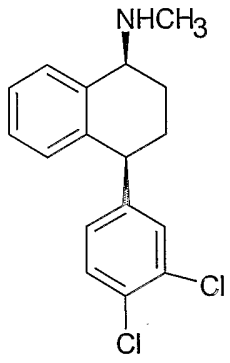
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PROCESS FOR THE PREPARATION OF (1S,4S)-4-(3,4-DICHLOROPHENYL)-1,2,3,4-TETRAHYDRO-N-METHYL-1 –NAPHTHYLAMINE

FIELD OF THE INVENTION

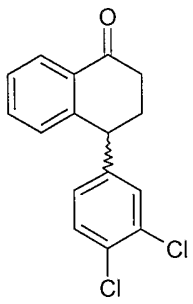
The present invention relates to a process for the preparation of (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, compound of formula 1. (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, commonly known as sertraline (INN name), is useful in the treatment of depression, obsessive-compulsive disorder and panic disorder.



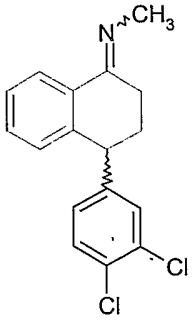
formula 1

BACKGROUND OF THE INVENTION

(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine and a process for making it is disclosed in **United States Patent No. 4,536,518** (hereinafter described as **'518**, Indian Reference not available) assigned to Pfizer, Inc. This patent discloses the preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine, compound of formula 3, by reaction of 4-(3,4-dichlororphenyl)-3,4-dihydro-1(2H)-naphthalenone, compound of formula 2, with methylamine in tetrahydrofuran in the presence of a lewis acid viz. $TiCl_4$.



formula 2



formula 3

This invention uses $TiCl_4$ as a catalyst and a dehydrating agent. It is very reactive with water and forms dense white fumes with slightest exposure to atmosphere making its handling and usage very inconvenient. The process of the present invention prepares compound of formula 1 starting with preparation of compound of formula 3 without a dehydrating agent in an acyclic or cyclic polyether solvent.

United States Patent No. 4855500, assigned to Pfizer, Inc. discloses preparation of compound of formula 3 by contacting the compound of formula 2 with methylamine in a reaction inert aprotic organic solvent in the presence of molecular sieves acting as dehydrating agent. This invention uses molecular sieves which need to be regenerated involving an additional step. The process of the present invention prepares compound of formula 1 starting with preparation of compound of formula 3 without the requirement of a dehydrating agent making it economical.

United States Patent No. 6232500, assigned to Pfizer, Inc., claims a process for preparing N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine, compound of formula 3, comprising reaction of the compound of formula 2 with monomethylamine in an alcohol solvent having a boiling point that is greater than about 55^0 C in 92% yield. The process of the present invention prepares compound of formula 1 starting with preparation of compound of formula 3 in a non-alcoholic solvent in almost

quantitative yields.

PCT publication 9957095, assigned to Egis Gyogyszergyar RT., provides a process for the preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenylidene]methanamine, compound of formula 3, by reacting the compound of formula 2 with methylamine in the absence of a dehydrating agent in a lower alkanol to yield 90-95% of compound of formula 1. The process of the present invention prepares compound of formula 1 starting with preparation of compound of formula 3 in a non-alcoholic solvent in almost quantitative yields.

PCT publication 0136378, assigend to Ciba Speciality Chemicals Holding Inc., provides a process for the preparation of compound of formula 3 by reacting compound of formula 2 with methylamine in the presence of

(a) a C_1-C_{24} amine or C_1-C_{12} nitrile as solvent OR

(b) a sulfonic acid catalyst and a non-alcoholic solvent.

Compound of formula 3 prepared by this published invention could contain traces of sulfur compounds (due to sulfonic acid), which would be detrimental for subsequent hydrogenation since these can poison the hydrogenation catalyst. The process of the present invention prepares compound of formula 1 starting with preparation of substantially pure compound of formula 3 in a non-alcoholic solvent in the absence of a catalyst.

We have found a process for the preparation of compound of formula 1 in high yields by reaction of compound of formula 2 with methylamine in an acyclic or cyclic polyether followed by conversion to a mixture of compound of formula 1 and its stereoisomers and subsequent isolation of compound of formula 1. Whereas prior art **United States Patent No. 4,536,518** used tetrahydrofuran an ether solvent, together with $TiCl_4$ as catalyst we

have surprisingly found that polyether solvents when used provide high yield without the need of a catalyst. The process of the present invention avoids the use of dehydrating agent like molecular sieves, $TiCl_4$ etc. or a catalyst like sulfonic acid rendering it environmentally friendly and commercially viable. Also, the process of the present invention gives better conversion resulting in substantially pure compound of formula 3 substantially free of compound of formula 2.

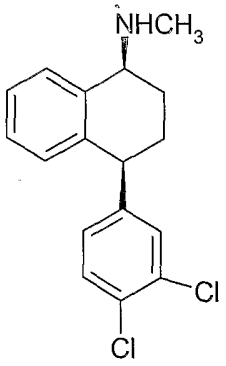
The process of the present invention prepares compound of formula 3 in almost quantitative yields in an acyclic or cyclic polyether solvent which is hitherto not reported.

OBJECT OF THE INVENTION

The object of the present invention is to prepare, (1S, 4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, compound of formula 1, starting with the preparation of compound of formula 3 in an environmentally friendly, non-hazardous reaction inert solvent without the use of dehydrating agent or catalyst.

SUMMARY OF THE INVENTION

The process of the present invention prepares compound of formula 1

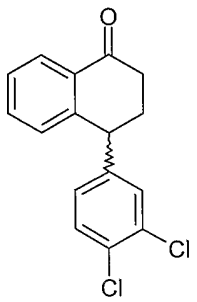


formula 1

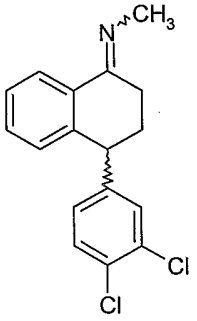
by

(a) reacting (3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenone, compound of formula

2, with methylamine in an acyclic or cyclic polyether to yield N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine, compound of formula 3;



formula 2



formula 3

(b) converting compound of formula 3 to a mixture of compound of formula 1 and its stereoisomers; and

(c) isolating compound of formula 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes a method for the preparation of compound of formula 1 by reacting compound of formula 3 with methylamine to yield compound of formula 3 in an acyclic or cyclic polyether solvent and then converting compound of formula 3 to a mixture of (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, compound of formula 1, and its steroisomers followed by isolation of (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, compound of formula 1. The stereoisomers of (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine are

- (1R,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine
- (1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine
- (1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine

(a) Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, compound of formula 3

According to one embodiment of the process of the present invention step (a) i.e. reaction of compound of formula 3 with methylamine is carried out in an acyclic or cyclic polyether in the absence of an additional catalyst or a dehydrating agent.

The acyclic or cyclic polyether used in the present invention may be selected from the group comprising 1,2-dimethoxyethane, 1,4-dimethoxybutane, poly(alkylene glycol)s such as poly(ethylene glycol)s (PEGs), diglyme, 1,4-dioxane, crown ethers, mono alkylated or dialkylated poly(alkylene glycol)s wherein the alkyl group is selected from C_1 to C_6 linear or branched alkyl, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether, triethylene glycol diethyl ether, tetraethylene glycol dimethyl ether (tetraglyme) & the like and mixtures thereof. The poly(alkylene glycol)s and monoalkylated or dialkylated poly(alkylene glycol)s being a mixtures are defined by an average molecular weight and do not have a specific boiling point, for e.g. PEG 200, poly(ethylene glycol) dimethyl ether 250 and the like.

The preferred polyether being an acyclic polyether, which includes polyether such as mixtures of poly(alkylene glycol)s like poly(ethylene glycol) 200 (PEG 200) having an average molecular weight of about 200, or poly(ethylene glycol) dimethyl ether with an average molecular weight of about 250.

The process of the present invention step (a) is optionally carried out in the presence of catalytic amount of acid addition salt of an organic amine or an acid selected from mineral or an organic acid which can generate the acid addition salt insitu. The organic amine may be selected from C_1 to C_4 alkyl mono, di or tri substituted amines such as triethylamine, diethylamine, monoethylamine, trimethylamine, dimethylamine, monomethylamine and the like. The organic acid may be selected from acetic acid, citric acid, succinic acid, maleic acid, fumaric acid, oxalic acid, benzoic acid, pamoic acid,

xinafoic acid, ascorbic acid and the like; alkylsulfonic acids such as methanesulfonic acid, ethanesulfonic acid and the like; halomethanesulfonic acids such as trifluoromethane sulfonic acid, fluoromethanesulfonic acid, chloromethanesulfonic acid, dichloromethanesulfonic acid, trichloromethane sulfonic acid and the like; substituted and unsubstituted aqueous arylsulfonic acids such as benzenesulfonic acid, para-toluenesulfonic acid, 4-chlorobenzenesulfonic acid and the like. Mineral acid may be selected from halogen acids, sulfuric, phosphoric and the like may be used. The preferred being mineral acid, preferably halogen acid such as hydrochloric acid.

According to another embodiment of the process of the present invention, step (a) is carried out at temperature ranging from about –20 to 100^0C, preferred being about 0 to 80^0C.

According to yet another embodiment of the process of the present invention step (a) reaction is carried out under pressure ranging from atmospheric to about 10 bars, preferably about 0.5 to 5 bars.

The reaction of compound of formula 2 with methylamine to yield compound of formula 3 is carried out for about 5 to 25 hours, preferably for about 15 to 25 hours.

The reaction of compound of formula 2 with methylamine may be carried out in an open or closed reaction system, preferred being closed reaction system such as an autoclave.

At the end of the reaction the reaction mass may be worked up using standard techniques known to those skilled in the art such as solvent extraction, precipitation or solvent recovery. For instance, additional polyether or an antisolvent may be added to precipitate the product and the precipitated product filtered out, or the polyether distilled out along with excess of methylamine, and a solvent added to the residue to precipitate or crystallize the product.

The compound of formula 3 may be optionally dried using standard techniques known to those skilled in the art such as in an air oven at elevated temperatures, fluid bed drying, tray drying, rotatory drying techniques with or without application of vacuum and / or under inert conditions.

The compound of formula 3 may be optionally further purified by methods known to those skilled in the art.

(b) Conversion of compound of formula 3 to a mixture of compound of formula 1 and its stereoisomers

Compound of formula 3 may be converted to a mixture of compound of formula 1 and its stereoisomers using any process known to a person skilled in the art, preferably as disclosed in our **Indian Patent IN 187170.** The same is incorporated herein by reference.

(c) Isolation of compound of formula 1

Compound of formula 1 may be isolated from the mixture of compound of formula 1 and its stereoisomers by any process known to a person skilled in the art, preferably as disclosed in our **Indian Patent IN 187170.** The same is incorporated herein by reference.

The invention is further illustrated but not restricted by the description in the following examples.

Examples

Example 1

Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, Compound of formula 3

A mixture of poly(ethylene glycol)-200 (125 ml), 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (25g, 0.086 mol.) and methylamine (47.62g, 1.53 mol) is stirred at 48-50°C for 20 hrs in an autoclave. Thereafter, water (100 ml) is added under stirring, the product filtered, and washed with water (100ml). The product is suck dried, and further dried in air oven at 55-60°C. Weight of dry N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine is 26.0g (99.6%). M.P.145° C.

Example 2

Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, Compound of formula 3

A mixture of poly(ethylene glycol)-200 (125 ml), 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (25g, 0.086 mol.) and methylamine (26.4g, 0.85 mol) is stirred at 50-55°C for 20 hrs in an autoclave. Thereafter, water (100 ml) is added under stirring, the product filtered, washed with water (100ml). The product is suck dried, and further dried in air oven at 55-60°C. Weight of dry N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine is 25.9g (99.2%). M.P., 143-146° C.

Example 3

Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, Compound of formula 3

A mixture of poly(ethylene glycol)-200 (125 ml), 4-(3,4-dichlorophenyl)-3,4-dihydro-

1(2H)-naphthalenone (25g, 0.086 mol.) and methylamine (12.5g, 0.41 mol) is stirred at 50-55°C for 20 hrs in an autoclave. Thereafter, water (100 ml) is added under stirring, the product filtered, washed with water (100ml). The product is suck dried, and further dried in air oven at 55-60°C. Weight of dry N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine is almost quantitative.

Example 4

Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, Compound of formula 3

Reaction is carried out in a similar manner as in example 1 using 1,2-dimethoxyethane (175ml) as solvent, instead of poly(ethylene glycol)-200. However in this case the solvent (alongwith excess methylamine) was distilled out under reduced pressure at 50-60° C until a thick slurry resulted. Water (100ml) was added and the product recovered as in example 1.

Example 5

Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, Compound of formula 3

Reaction is carried out using 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (5g, 0.017 mol.) in a similar manner as in example 2 using 1,2-dimethoxyethane (30ml) as solvent in a closed reaction flask, at ambient temperature for 20 hrs. Reaction is worked-up in manner similar to example 2 to get N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine.

Example 6

Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine, Compound of formula 3

Reaction is carried out using 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (1g, 0.0034 mol.) in a similar manner as in example 3 using 1,4-dimethoxybutane (30ml)

as solvent, at ambient temperature for 20 hrs. At the end of the reaction the solvent (alongwith excess methylamine) is distilled out at below 60° C. To the resulting syrup

was added 2-propanol (5 ml) and the precipitated N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine is filtered and dried.

Example 7

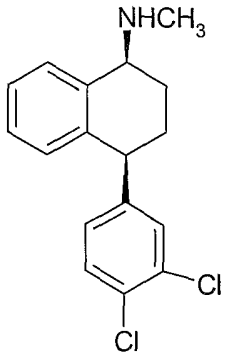
Preparation of N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene] methanamine ,Compound of formula 3

A mixture of 4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (150g, 0.515mol), methylamine (300g, 9.67mol), methylamine hydrochloride (7.50g, 0.11mol) in 1,2-dimethoxyethane (750ml) is stirred at 55-60°C for 18hrs in an autoclave. Thereafter, the solvent (along with excess methylamine) was distilled out under reduced pressure at 50-60° C and the residual mass is stirred with 2-propanol (750ml) at 25-35° C. The product is filtered, washed with 2-propanol (300ml) and dried in an air oven at 55-60° C, IR spectrum shows absence of carbonyl peak at 1675cm^{-1}. (purity >99.5%)

N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine, compound of formula 3, prepared by Examples 1 to 7 was converted to a mixture of compound of formula 1 and its stereoisomers followed by isolation of compound of formula 1 using the process as described in our **Indian Patent 187170**.

We claim :

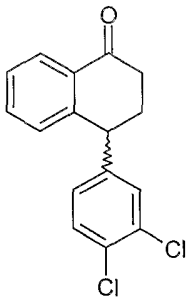
1. A process for the preparation of (1S, 4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine, compound of formula 1,



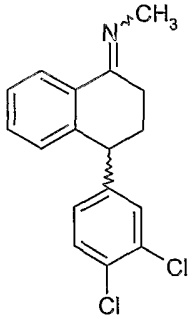
formula 1

said process comprising

(a) reacting (3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenone, compound of formula 2, with methylamine in an acyclic or cyclic polyether to yield N-[4-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-napthalenylidene]methanamine, compound of formula 3;



formula 2



formula 3

(b) converting compound of formula 3 to a mixture of compound of formula 1 and its stereoisomers; and

(c) isolating compound of formula 1.

2. A process as claimed in claim 1 wherein in step (a) the acyclic or cyclic polyether is selected from 1,2-dimethoxyethane, 1,4-dimethoxybutane, poly(alkylene glycol)s, monoalkylated poly(alkylene glycol)s, dialkylated poly(alkyleneglycol)s diglyme, 1,4-dioxane, crown ethers and mixtures thereof.
3. A process as claimed in claim 2 wherein the poly(alkylene glycol) is poly(ethylene glycol) 200.
4. A process as claimed in claim 2 wherein the alkylated polypoly(alkylene glycol) is poly(ethylene glycol) dimethyl ether 250.
5. A process as claimed in claim 1 wherein step (a) is carried out at temperature ranging from about 0 to 80^0C.
6. A process as claimed in claim 1 wherein step (a) is carried out under pressure ranging from about 0.5 to 5 bar.
7. A process as claimed in claim 1 wherein step (a) is carried out for about 15 to 25 hrs.
8. A process as claimed in claim 1 wherein step (a) is optionally carried out in the presence of catalytic amount of acid addition salt of an organic amine or an acid selected from mineral or an organic acid which can generate the acid addition salt insitu.
9. A process as claimed in claims 1 to 9 substantially as herein described and illustrated by examples 1 to 7.