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(54) **Title**: A PROCESS FOR THE PREPARATION OF TOLTERODINE TARTRATE

(57) **Abstract**: The present invention relates to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate, comprises a step of aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI).

WO 2010/092500 A2

Description

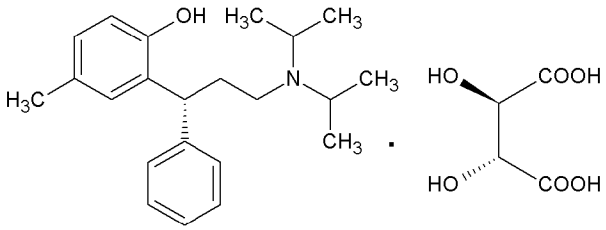
Title of Invention: A PROCESS FOR THE PREPARATION OF TOLTERODINE TARTRATE

Field of the Invention

[1]

[2] The present invention relates to a process for the preparation of (+)-(R)-Tolterodine-L-tartrate of formula (I)

[3]



formula (I)

[4]

[5]

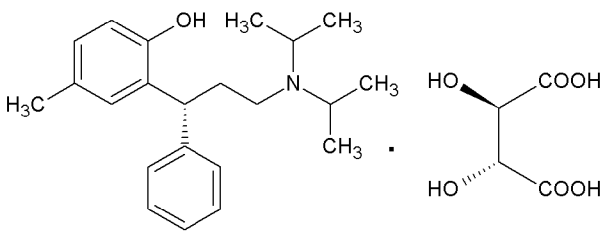
Background of the invention

[6]

[7] Tolterodine is a muscarinic receptor antagonist. The chemical name of Tolterodine tartrate is (+)- (R)-N, N-diisopropyl-3- (2-hydroxy-5-methylphenyl) - 3-phenylpropanamine-L-hydrogen tartrate and molecular formula is $C_{26}H_{37}NO_7$and molecular weight is 475.28 . (+)-(R)-Tolterodine tartrate is represented by formula (I):

[8]

[9]



formula (I)

[10]

[11] Tolterodine tartrate is marketed by Pharmacia & Upjohn under brand name Detrol® and is indicated for the treatment of Urinary incontinence.

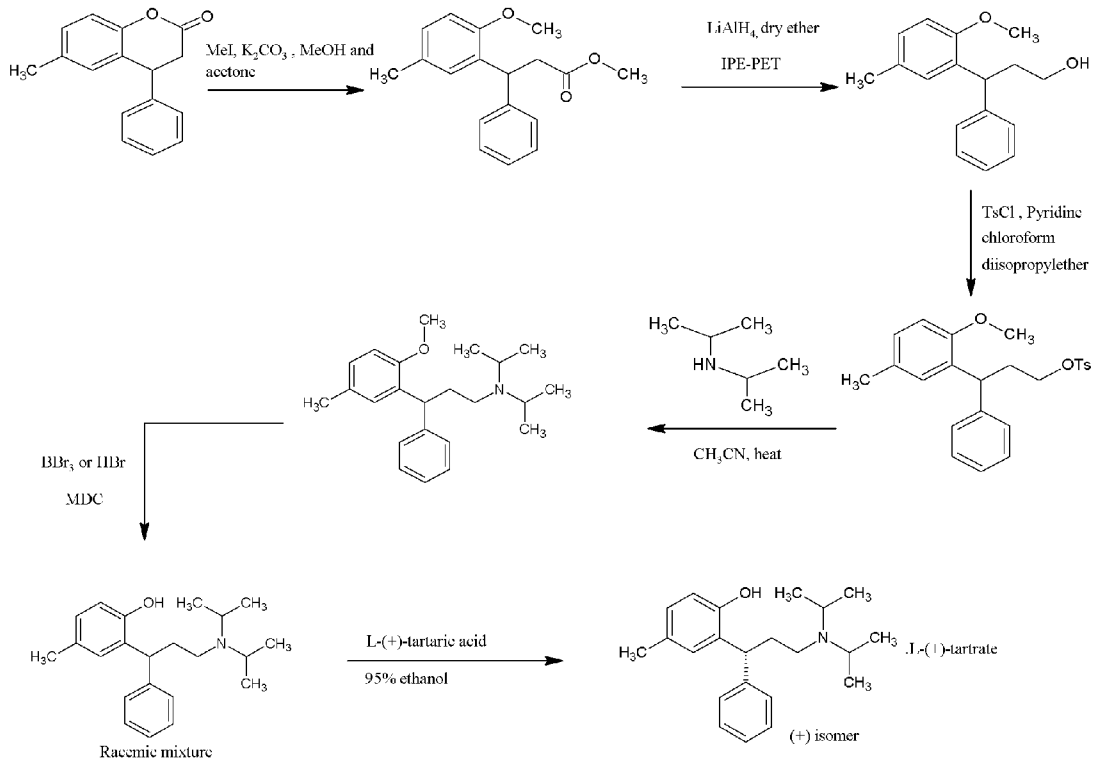
[12]

[13] US Patent no. 5,382,600 discloses a process for the preparation of Tolterodine tartrate as shown in Scheme-1. This patent involves the reaction of 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one with methyl iodide and potassium carbonate in refluxing acetone/methanol to give methyl-

3-(2-methoxy-5-methylphenyl)3-phenyl propionate. The ester thus obtained is reduced with lithium aluminum hydride in ether to the corresponding propanol, which is reacted with tosyl chloride and pyridine to yield the tosylate, which on condensation with diisopropylamine in hot acetonitrile is converted into the tertiary amine. The tertiary amine is treated with boron tribromide in dichloromethane to give the amine as a racemic mixture, which is resolved with L-(+) tartaric acid.

[14]

[15]



Scheme-1

[16]

[17] Long reaction time and low overall yields makes this process very expensive and less productive. Further, the use of expensive and hazardous reagents like methyl iodide, lithium aluminum hydride, and boron tribromide also renders this process unsuitable and hazardous on a commercial scale. Moreover, the preparation of the tertiary amine by the condensation of tosylate with diisopropylamine in the presence of acetonitrile leads to form dimmer impurities which provides final product with low yields.

[18]

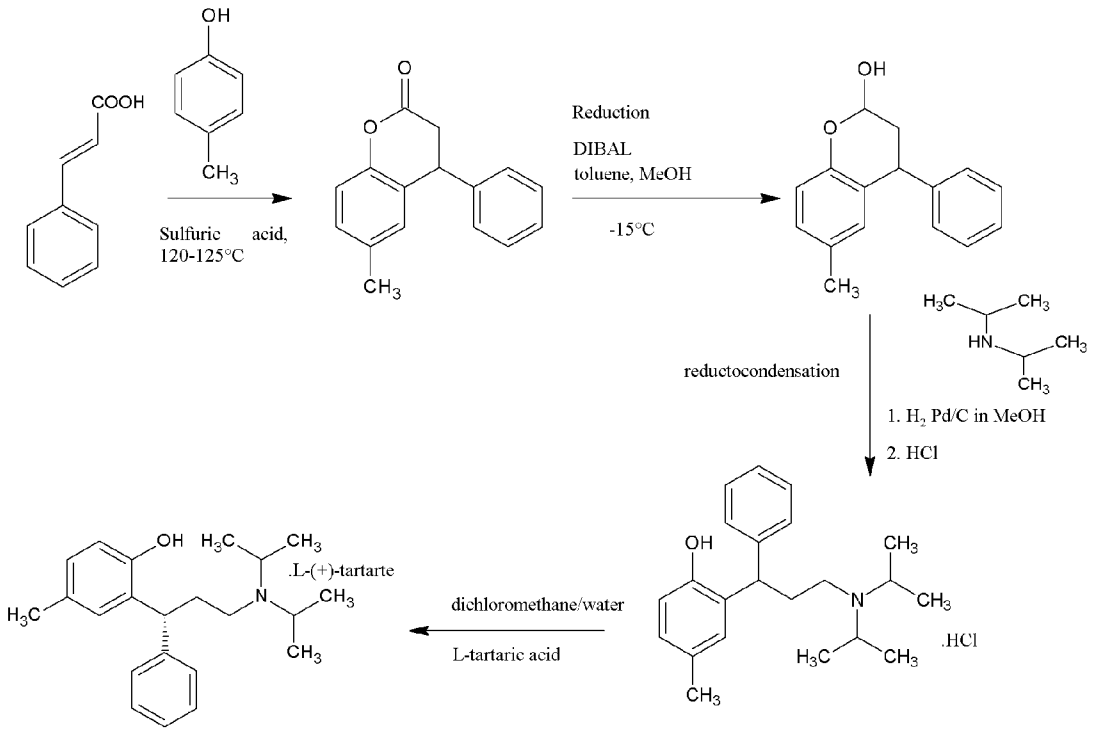
[19] U.S. Patent No. 5,922,914 provides an alternate method for the preparation of tolterodine as shown in scheme-2. The process involves the cyclization of trans-cinnamic acid with p-cresol in hot sulfuric acid to give 3,4-dihydro-6-methyl-4-phenyl-2H- benzopyran-2-one, which is reduced with diisobutyl aluminum hydride (DIBAL) in toluene to yield 6-methyl-4-phenyl-3,4- dihydro- 2H-1-benzopyran-2-ol.

This on reducto-condensation with diisopropylamine, by means of hydrogen over palladium on charcoal in methanol, affords racemic tolterodine, which is resolved with L-(+)-tartaric acid.

[20]

[21]

[22]



Scheme-2

[23]

[24]

[25] This process is also not commercially feasible since it makes use of an expensive and hazardous reagent DIBAL. Although the numbers of steps are reduced, the cost incurred to produce tolterodine is still high.

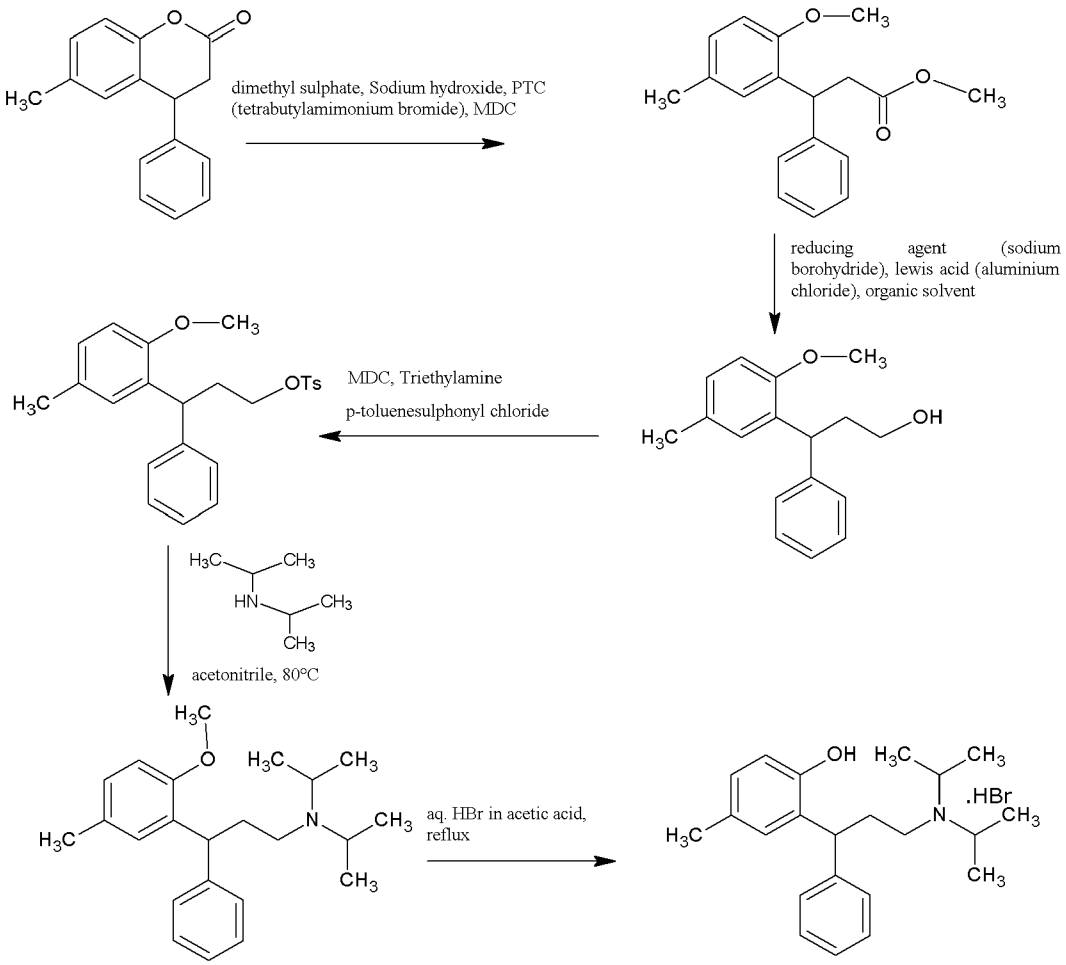
[26]

[27] U.S. Patent No. 6,822,119 provides another alternate method for the preparation of tolterodine as shown in Scheme-3. The process involves reacting 3,4-dihydro-6-methyl-4- phenyl-2H- benzopyran-2-one with dimethyl sulphate in the presence of sodium hydroxide, and a phase transfer catalyst to obtain methyl-3-(2-methoxy-5-methylphenyl) -3-phenyl propionate. Reducing the ester thus obtained with a reducing agent in the presence of a Lewis acid to obtain 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol. Protecting the hydroxy group of the alcohol to followed by aminating with diisopropylamine to give N, N-di-isopropyl-3- (2-methoxy-5-methylphenyl)-3-phenylpropylamine and removing the

hydroxy protecting group to obtain N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen bromide.

[28]

[29]



Scheme-3

[30]

[31]

[32] This process involves a large number of steps and isolation of intermediates at each step, leading to poor yields. Moreover, the preparation of the tertiary amine by the condensation of tosylate with diisopropylamine in the presence of acetonitrile leads to form dimmer impurities which provides final product with low yields.

[33]

[34] International Publication WO 2004/078700 describes preparation of pure tolterodine or a pharmaceutically acceptable salt thereof. It also discloses N, N-di-[3-[2-hydroxy-5-methylphenyl]-3-phenylpropyl] isopropyl amine, referred to as 'tolterodine dimer,' and a process for isolation of the same.

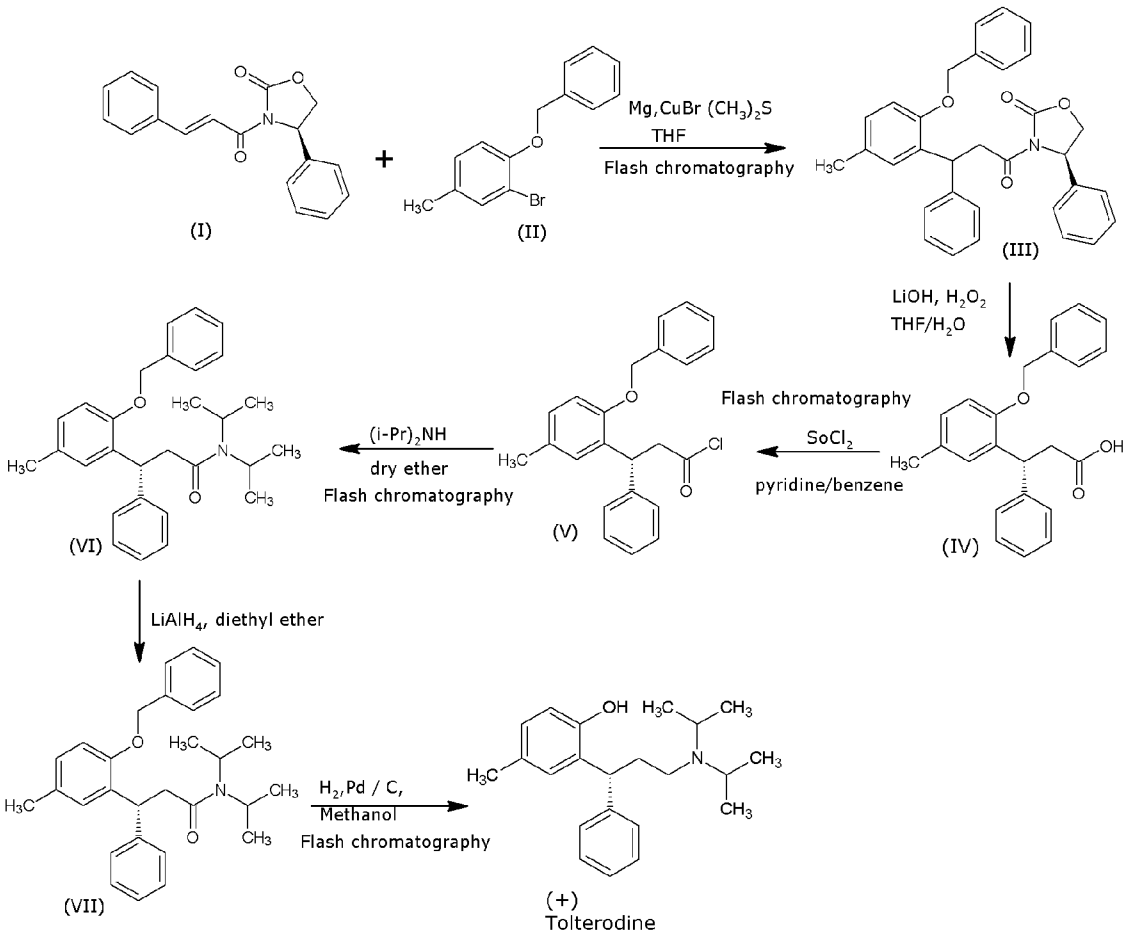
[35]

[36] Journal of Organic Chemistry, 1998, 63, 8067-8070 discloses asymmetric synthesis

of enantiomers of 3-(2-hydroxy-5- methylphenyl) -N, N- diisopropyl-3-phenylpropylamine as shown in scheme-4. It comprises copper-assisted asymmetric conjugate addition of aryl Grignard reagent to phenylpropenoyl derivative of oxazolidinone used as a chiral auxiliary. The regioselective addition of 2-benzyloxy-5-methylphenyl bromide (II) to 4(R)-phenyl-3-[3-phenyl-2 (E)-propenoyl]oxazolidin-2-one (I) by means of Mg/CuBr/dimethylsulfide in THF gives 3-[3(R)-(5-benzyloxy-2-methylphenyl) -3-phenylpropionyl]-4(R)-phenyloxazolidin-2-one (III), which is hydrolyzed with $LiOH/H_2O_2$ in THF/water to the corresponding free acid (IV). The reaction of (IV) with $SOCl_2$/pyridine in benzene yields the acid chloride (V), which is treated with diisopropylamine to afford the corresponding amide (VI). The reduction of (VI) with LiAlH4 in ethyl ether gives the tertiary amine (VII), which is finally, debenzylated by hydrogenation with H2 over Pd/C in methanol.

[37]

[38]



Scheme-4

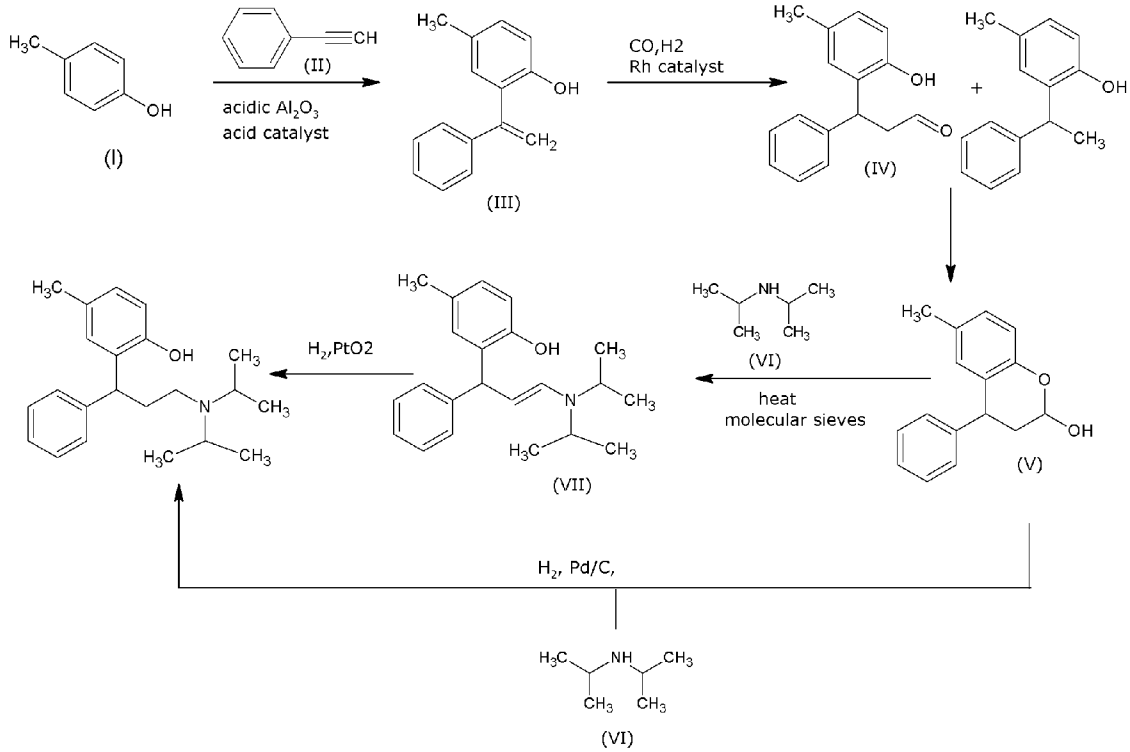
[39]

[40]

[41] Organic Process Research & Development (2002), 6(4), 379-383 discloses another

approach for the preparation of Tolterodine as shown in Scheme-5. It involves condensation of p-cresol (I) with phenylacetylene (II) by means of acidic activated alumina in refluxing dichlorobenzene gives 4-methyl-2-(1-phenylvinyl)phenol (III), which is hydroformylated with CO, H_2 and a Rh catalyst in hot toluene to yield 3-(2-hydroxy-5-methylphenyl)-3-phenylpropionaldehyde (IV), mostly in the hemiacetalic form (V). The reaction of (V) with diisopropylamine (VI) in hot toluene catalyzed by molecular sieves gives the enamine (VII), which is finally hydrogenated with H2 over PtO_2 in refluxing toluene to afford the target racemic tolterodine. Alternatively, the reductocondensation of hemiacetal (V) with diisopropylamine (VI) by means of H_2 over Pd/C in hot methanol provides directly the target racemic tolterodine.

[42]



Scheme-5

[43]

[44] Consequently, there is a long-felt need for a process for the preparation tolterodine which not only overcomes the problems in the art processes as mentioned above, but is also safe, cost effective, and industrially feasible.

[45]

[46] The present inventors had tried amination of hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI) which serendipitously leaded to reduce dimmer impurities and the resulting quality of the final product was improved.

[47]

[48] When the present inventors had carried out amination of hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diiso-propylamine in the presence of water to obtain N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI) and the final compound was surprisingly obtained with high yield and purity. The present inventors also found that amination process can be carried out without use of autoclave method which makes this process cost effective and industrially feasible.

[49]

[50]

Summary of the Invention

[51]

[52] The present invention relates to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate , comprises a step of aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diiso-propylamine in the presence of water to obtain N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI).

[53]

[54] The present invention relates to provide an improved process for the preparation of (+)-(R)-Tolterodine-L-tartrate, comprises steps of

[55] a) reacting 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one of formula (II) with dimethyl sulphate in the presence of aqueous alkali metal hydroxide followed by treatment with an inorganic acid to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid of formula (III);

[56] b) reducing 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid of formula (III) in the presence of a reducing agent, an acidic reagent and a solvent to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV);

[57] c) converting 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in an alcohol;

[58] d) aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N,N-diisopropyl-3- (2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI);

[59] e) converting N,N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VI) into organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula

(VII);

[60] f) treating organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VII) with aqueous HBr in the presence of acetic acid to obtain hydrobromide salt of N,N-diisopropyl-3- (2-hydroxy-5-methylphenyl) -3-phenylpropyl amine of formula (VIII);

[61] g) treating hydrobromide salt of N,N-diisopropyl-3- (2-hydroxy-5-methylphenyl) -3-phenylpropyl amine of formula (VIII) with base in the presence of a solvent, optionally isolating free base followed by resolution with L-(+)-tartaric acid in the presence of alcohol to obtain (+)-(R)-Tolterodine-L-tartrate.

[62]

[63]

Object of the Invention

[64]

[65] Therefore, it is an object of the invention is to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate of formula (I).

[66]

[67] Another object of the invention is to provide process for the preparation of process for the preparation of (+)-(R)-Tolterodine-L -tartrate of formula (I) having high purity.

[68]

[69] Yet another object of the present invention is to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate , comprises a step of aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N, N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VI).

[70]

[71] Further object of the present invention is to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate, comprises steps of

[72] a) reacting 3,4-dihydro-6- methyl-4- phenyl-2H-benzopyran-2-one of formula (II) with dimethyl sulphate in the presence of aqueous alkali metal hydroxide followed by treatment with an inorganic acid to obtain 3-(2-methoxy-5-methylphenyl) -3-phenyl propionic acid of formula (III);

[73] b) reducing 3-(2-methoxy-5-methylphenyl) -3-phenyl propionic acid of formula (III) in the presence of a reducing agent, an acidic reagent and a solvent to obtain 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (IV);

[74] c) converting 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in alcohol;

[75] d) aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N,N-diisopropyl-3- (2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VI);

[76] e) converting N,N-diisopropyl-3- (2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VI) into organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VII);

[77] f) treating organic acid salt of N,N-diisopropyl-3- (2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VII) with aqueous HBr in the presence of acetic acid to obtain hydrobromide salt of N,N-diisopropyl-3- (2-hydroxy-5-methylphenyl) -3-phenylpropyl amine of formula (VIII);

[78] g) treating hydrobromide salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine of formula (VIII) with base in the presence of a solvent, optionally isolating free base followed by resolution with L-(+)-tartaric acid in the presence of alcohol to obtain (+)-(R)-Tolterodine-L-tartrate.

[79]

[80] Yet further object of the present invention is to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate, comprises a step of converting 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in alcohol.

[81]

[82]

Detailed Description of the Invention

[83]

[84] Accordingly, the present invention relates to provide a process for the preparation of (+)-(R)-Tolterodine-L-tartrate , comprises a step of aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI).

[85]

[86] In a preferred embodiment of the present invention, the process for the preparation of (+)-(R)-Tolterodine-L-tartrate, comprises steps of

[87] a) reacting 3,4-dihydro-6-methyl-4- phenyl-2H-benzopyran-2-one of formula (II) with dimethyl sulphate in the presence of aqueous alkali metal hydroxide followed by

treatment with an inorganic acid to obtain 3-(2-methoxy-5-methylphenyl) -3-phenyl propionic acid of formula (III);

[88] b) reducing 3-(2-methoxy-5-methylphenyl) -3-phenyl propionic acid of formula (III) in the presence of a reducing agent, an acidic reagent and a solvent to obtain 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (IV);

[89] c) converting 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in alcohol;

[90] d) aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI);

[91] e) converting N,N-diisopropyl-3- (2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VI) into organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VII);

[92] f) treating organic acid salt of N,N-diisopropyl-3- (2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VII) with aqueous HBr in the presence of acetic acid to obtain hydrobromide salt of N,N-diisopropyl-3- (2-hydroxy-5-methylphenyl) -3-phenylpropyl amine of formula (VIII);

[93] g) treating hydrobromide salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine of formula (VIII) with base in the presence of a solvent, optionally isolating free base followed by resolution with L-(+)-tartaric acid in the presence of alcohol to obtain (+)-(R)-Tolterodine-L-tartrate.

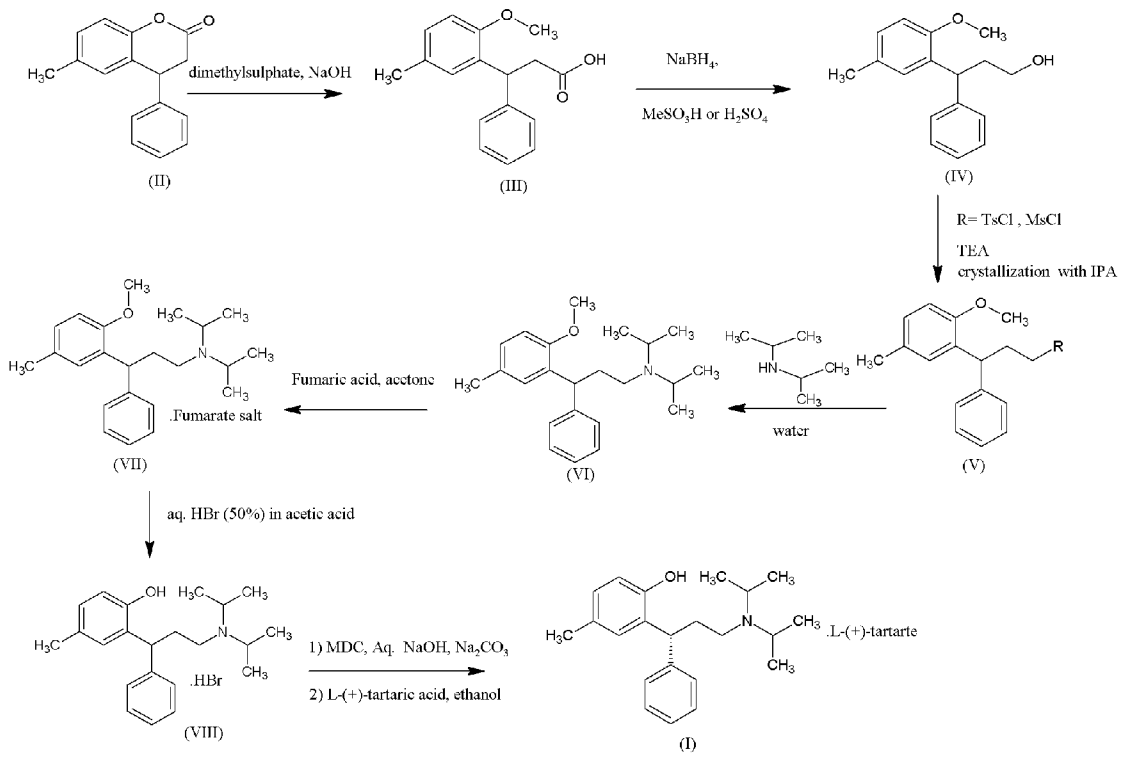
[94]

[95] Yet another preferred embodiment of the present invention, the process for the preparation of (+)-(R)-Tolterodine-L-tartrate , comprises a step of converting 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in alcohol.

[96]

[97] The process for the preparation of (+)-(R)-Tolterodine-L-tartrate for formula (I) depicts below in Scheme-6:

[98]



Scheme-6

[99]

[100] **Step-a:** The reaction of 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one with dimethylsulphate is carried out in the presence of an aqueous alkali metal hydroxide followed by treatment with an inorganic acid.

[101]

[102] The reaction is carried out at 70-90°C for 8-15 hrs. Alkali metal hydroxide is selected from group comprising of sodium hydroxide, potassium hydroxide or mixture thereof. Most preferable alkali metal hydroxide is sodium hydroxide. Inorganic acid is selected from group comprising of hydrochloride, hydrobromic acid, hydroiodic acid and sulfuric acid or mixture thereof. Most preferable inorganic acid is hydrochloride. After completion of reaction, the reaction mixture is cooled to RT. Conc. hydrochloric acid is added drop wise to the reaction mixture. The Reaction mixture is stirred for 1-2 hrs then filtered it & washed with DM water to obtain wet cake. The wet cake is dried to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid.

[103]

[104] **Step-b:** The reduction of 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid is carried out in the presence of a reducing agent, an acidic reagent and a solvent.

[105]

[106] The reaction is carried out at 60-75°C for 8-10 hrs. The reducing agent is selected from the group comprising of sodium borohydride. An acidic reagent is selected from the group comprising of methanesulfonic acid, sulfuric acid, trifluoroacetic acid or

mixture thereof. Most preferable acidic reagent is methanesulfonic acid. The solvent is selected from the group comprising of dioxane, tetrahydrofuran (THF), ethylene glycol dimethyl ether, methyl t-butyl ether, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dimethylacetamide or mixture thereof. Most preferable solvent is tetrahydrofuran (THF). After completion of reaction, the reaction mixture is cooled at 0-5°C. The reaction mixture is acidified with 1M aq. HCl up to pH 2-3, followed by extraction with ethyl acetate. The organic layers are washed with water and brine. The solvent is distilled out completely to dryness under reduced pressure to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol.

[107]

[108] **Step-c:** The conversion of hydroxy group of 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol into hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V) by using good leaving group in the presence of a base and a solvent optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in alcohol.

[109]

[110] The reaction is carried out at RT for 4-6 hrs. The good leaving group can be generated by using reagent selected from the group comprising of p-toluenesulfonyl chloride, methanesulfonyl chloride, p-nitrobenzenesulfonyl chloride. Most preferable leaving group is p-toluenesulfonyl chloride. The base is selected from the group comprising of inorganic or organic base. The inorganic base is selected from the group comprising of potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide or mixture thereof. The organic base is selected from the group comprising of triethylamine, trimethylamine, pyridine or mixture thereof. Most preferable base is triethylamine. The solvent is selected from the group comprising of dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, acetone, dichloromethane, toluene, xylene, methanol, ethanol, isopropanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dimethylacetamide or mixture thereof. Most preferable solvent is dichloromethane. The crystallization is carried out in the presence of alcohol. Alcohol is selected from the group comprising of methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol and the like or mixture thereof. Most preferable alcohol is isopropyl alcohol. After the completion of reaction, reaction mixture is acidified with 1M aq.HCl up to pH 2-3. Then it is extracted with dichloromethane. The organic layers are washed with DM water, brine & dried over sodium sulfate. The solvent is completely distilled out at reduced pressure. Crude hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) is dissolved in isopropyl alcohol and heat it up to 70-80°C for 1-3 hrs and then cool it

at RT. The solid is filtered & washed with isopropyl alcohol. The solid is dried at 50-55°C to obtain pure hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V).

[111]

[112] **Step-d:** The amination reaction of hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diiso-propylamine is carried out in the presence of water to obtain N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI).

[113]

[114] The reaction is carried out at 80-100°C for 130-150 hrs. After the completion of the reaction, product is extracted with dichloromethane. The organic layer is washed with DM water, 0.5 L brine & dried over sodium sulfate. The solvent was completely distilled out at reduced pressure (30-40mm Hg) to get crude and then basified it with 1M NaOH up to pH 11-12, then extracted it with dichloromethane. The organic layer is washed with DM water, brine & dried over sodium sulfate. The solvent was completely distilled out at reduced pressure to get crude N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI).

[115]

[116] **Step-e:** The conversion of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI) into organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VII).

[117]

[118] The reaction is carried out at 45-60°C for 1-2 hrs in the presence of a solvent. The solvent is selected from the group comprising of dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, acetone, dichloromethane, toluene, xylene, methanol, ethanol, isopropanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dimethylacetamide or mixture thereof. Most preferable solvent is acetone. The organic acid is selected from the group comprising of oxalic acid, acetic acid, formic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, phthalic acid, terephthalic acid, citric acid, tartaric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, trifluoroacetic acid, ascorbic acid and the like. Most preferable organic acid is fumaric acid.

[119]

[120] After the completion of the reaction, reaction mass is cool to ambient temperature then 0°C for 1-2 hrs. The solid is filtered & washed with acetone. The solid is dried at 50-55°C to obtain organic acid salt of N, N-di-

isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VII).

[121]

[122] **Step-f:** The treatment of organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VII) with aqueous HBr in the presence of acetic acid to obtain hydrobromide salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine of formula (VIII).

[123]

[124] The reaction is carried out at 100-125°C for 12-16 hrs in the presence of aqueous HBr (50%) and glacial acetic acid. After completion of reaction, the reaction mixture is cooled to RT to obtain a solid. The solid is filtered & washed with DM water till washing of cake was neutral. The solid is dried at 50-55°C to obtain hydrobromide salt of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine of formula (VIII).

[125]

[126] **Step-g:** The treatment of hydrobromide salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine of formula (VIII) with base in the presence of a solvent, optionally isolating free base followed by resolution with L-(+)-tartaric acid in the presence of alcohol to obtain (+)-(R)-Tolterodine-L-tartrate.

[127]

[128] The reaction is carried out at ambient temperature. The base is selected from the group comprising of inorganic base. The inorganic base is selected from the group comprising of potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide or mixture thereof. Most preferable base is sodium hydroxide. The solvent is selected from the group comprising of dioxane, tetrahydrofuran, methyl t-butyl ether, ethylacetate, dichloromethane, diethyl ether, acetonitrile or mixture thereof. Most preferable solvent is dichloromethane. The reaction mixture is cooled to RT. The solid is filtered and washed with DM water to obtain wet cake. The wet cake is dissolved in 2N NaOH & stirred and extracted it with dichloromethane. The organic layer is separated and washed with DM water, brine & dried over sodium sulfate. Optionally the solvent is completely distilled out at reduced pressure to obtain N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl) -3-phenylpropyl amine, followed by the resolution reaction is carried out at 75-85°C for 1-2 hrs. Alcohol is selected from the group comprising of methanol, ethanol, isopropyl alcohol, t-butanol or mixture thereof. Most preferable alcohol is ethanol. After completion of addition, the reaction mixture is cooled to RT and then at 0°C to obtain a solid. The solid is filtered & washed with ethanol. The solid is dried to obtain Crude (+)-(R)-Tolterodine-L-tartrate.

[129]

[130] Crude (+)-(R)-Tolterodine-L-tartrate is dissolved in ethanol and refluxed at 75-85°C for 2-3 hrs. The solution is concentrated to half the initial volume by distilling and gradually cooled to RT and then at 0°C for 1 hrs. The product is filtered and washed with ethanol. The product is dried under reduced pressure to obtain pure (+)-(R)-Tolterodine-L-tartrate.

[131]

[132] Following is the comparison of the result of the present invention vis-à-vis the process as disclosed in prior art.

[133]

[134] **Table-1**

[135] [Table 1]

[Table]

S. No	**Process**	**Yield (%)**	**Dimmer impurity**	**Purity (%)**
1	Amination stage by using acetonitrile (US5382600)	60%	6 to 12%	>98%
2	Amination stage by using water (Present invention)-without autoclave method	70%	< 2%	>99%

[136]

[137] The results clearly depicts that the use of water during amination stage significantly improves the purity and yield of the intermediate.

[138] The present invention provides process of preparation of (+)-(R)-Tolterodine-L-tartrate of formula (I), which is simple, environment friendly, economical and leads to an enhanced purity.

[139]

[140] Following are advantages of the present invention:

[141] i) The present invention provides process which is economical, operationally simple and industrially applicable.

[142] ii) The process provides desired purity of tolterodine tartrate having the content of dimer impurity acceptable by ICH guidelines.

[143] iii) The process avoids involve use of expensive and hazardous reagents.

[144] iv) The amination process can be carried out without use of autoclave method which makes this process cost effective and industrially feasible.

[145]

[146] The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

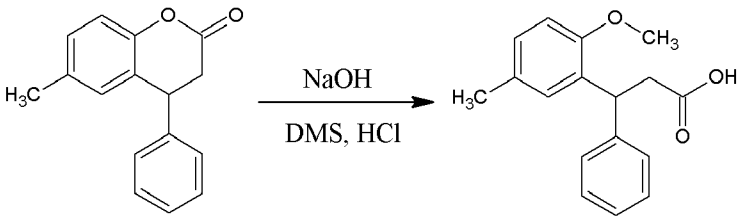
[147]

[148] **Example 1**

[149] **Preparation of 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid**

[150]

[151]



(II) (III)

[152]

[153] A reaction mixture of 0.75 kg 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one, 0.262 kg sodium hydroxide and 0.93 L DM water was stirred at 55-65°C for 2-3 hrs. The reaction was cooled to RT. 0.825 kg dimethylsulphate was added drop wise to reaction mixture within 1-2 hr. After the completion of addition, reaction mixture was stirred at same temperature for 1-2 hrs. Again solution of 0.186 kg sodium hydroxide in 0.93 L DM water was added at RT within 1 hr. The reaction mixture was stirred at 70-80°C for 3-5 hrs. After completion of reaction, reaction was cooled to RT. 0.3 L Conc. hydrochloric acid was added drop wise to the reaction mixture till washing is neutral. The reaction mixture was stirred for 1-2 hrs, then filtered & washed with 2.0 L DM water to obtain wet cake. The wet cake was dried at 55-60°C for 10-12 hrs to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid.

[154] (Yield: 0.71 kg, 83%).

[155] HPLC Purity: > 95 %.

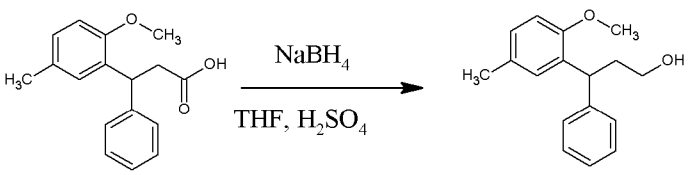
[156]

[157] **Example 2**

[158] **Preparation of 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol**

[159]

[160]



(III) (IV)

[161]

[162] A solution of 0.5 kg of 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid in 1.5 L tetrahydrofuran was added drop wise in the suspension of 0.105 Kg of sodium borohydride in 1 L ml tetrahydrofuran under stirring within 2-4 hrs. After completion of addition, reaction mixture was stirred at RT for 2 hrs. 0.181 Kg of Conc. Sulfuric acid was added drop wise within 2-3 hrs. After completion of addition, reaction mixture was stirred at RT for 1-2 hr. The reaction mixture was stirred at 65-70°C for 6-10 hrs. After completion of reaction, reaction mixture was cooled to 25-30°C. Saturated brine solution was added to reaction mass and the solution was stirred for 15 min. The organic layer was separated out and distilled it completely. The reaction mass was mixed with aqueous layer and then extracted with dichloromethane (1L x 2). The organic layers were combined and washed with 1 L water & 1 L brine. The solvent was distilled out to dryness at reduced pressure (30-40 mm Hg) to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol.

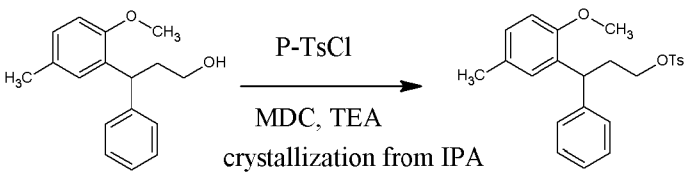
[163] (Yield 0402 Kg, 85%)

[164] HPLC Purity > 96%

[165]

[166] **Example 3**

[167] **Preparation of 3-(2-methoxy-5-methylphenyl)-3-phenyl propyl-p-toluene sulphonate**

[168] 

(IV) (V)

[169]

[170] 0.45 kg 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol in 2.25 L dichloromethane was stirred and cooled at 0^0C under stirring.0.27 kg triethylamine was added drop wise to the reaction mixture.0.388 kg p-toluene sulfonylchloride was added to the reaction mixture. The reaction mixture was stirred at 0-5°C for 1 hr and then at RT for 5-8 hrs. After the completion of reaction, the reaction mixture was acidified with 0.25 L 1M aq.HCl up to pH 2-3.Then reaction mixture was extracted with dichloromethane (0.5L x 2).The combined organic layers was washed with 1.0 L DM water,1.0 L brine & dried over 0.25 kg sodium sulfate. The solvent was completely distilled out at reduced pressure (30-40 mm Hg).Crude 0.78 kg 3-(2-methoxy-5-methylphenyl)-3-phenyl propyl-p-toluene sulphonate was dissolved in isopropyl alcohol (1.56 L) and heat it up to 80^0C for 2-3 hrs and then cool it at RT. The

solid was filtered & washed with isopropyl alcohol (0.450 L). The solid was dried at 50-55^{0}C to obtain pure 3-(2-methoxy-5-methylphenyl)-3-phenyl propyl-p-toluene sulphonate.

[171] Dry wt= 0.616 Kg

[172] Yield=85%

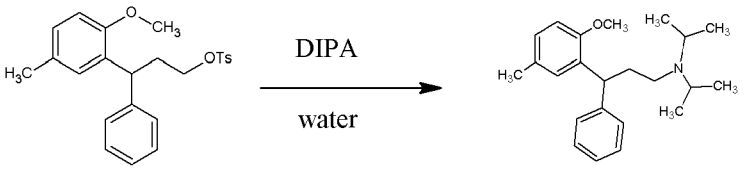
[173] Purity by HPLC= >98%

[174]

[175] **Example-4a (without autoclave)**

[176] **Preparation of N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine**

[177]

[178] 

(V) (VI)

[179]

[180] The solution of 0.100 kg 3-(2-methoxy-5-methylphenyl)-3-phenyl propyl-p-toluene sulphonate in 0.250 L water & 0.123 Kg diisopropyl amine was stirred at 80-100^{0}C for 130-150 hrs .After that product was extracted with dichloromethane (0.200 L x 2). The organic layers were washed with 1.0 L DM water, 0.5 L brine & dried over 0.1 kg sodium sulfate. The solvent was completely distilled out at reduced pressure (30-40mm Hg)to get crude and then basified it with 0.250 L 1M NaOH up to pH 11-12, then extracted it with dichloromethane (0.200 L x 2).The organic layers were washed with 1.0 L DM water,0.5 L brine & dried over 0.1 kg sodium sulfate. The solvent was completely distilled out at reduced pressure (30-40mm Hg) to get crude N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine.

[181] Dry wt = 0.080 Kg

[182] Yield=97%

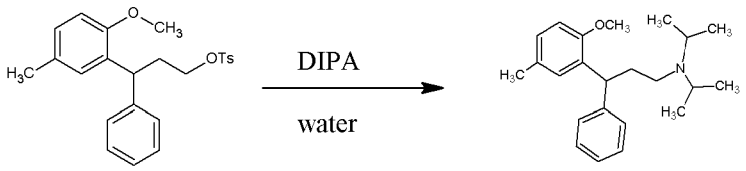
[183]

[184] **Example-4b (with autoclave)**

[185] **Preparation of N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine**

[186]

[187]



(V) (VI)

[188]

[189] The solution of 0.100 kg 3-(2-methoxy-5-methylphenyl)-3-phenyl propyl-p-toluene sulphonate in 0.250 L water & 0.123 Kg diisopropylamine was stirred in an autoclave at 80-120°C for 60-90 hrs. After that product was extracted with dichloromethane (0.200 L x 2). The organic layers were washed with 1.0 L DM water, 0.5 L brine & dried over 0.1 kg sodium sulfate. The solvent was completely distilled out at reduced pressure (30-40mm Hg) to get crude and then basified it with 0.250 L 1M NaOH up to pH 11-12, then extracted it with dichloromethane(0.200 L x 2).The organic layers were washed with 1.0 lit DM water,0.5 Lit brine & dried over 0.1 kg sodium sulfate. The solvent was completely distilled out at reduced pressure (30-40mm Hg) to get crude N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine.

[190] Dry wt = 0.070 Kg

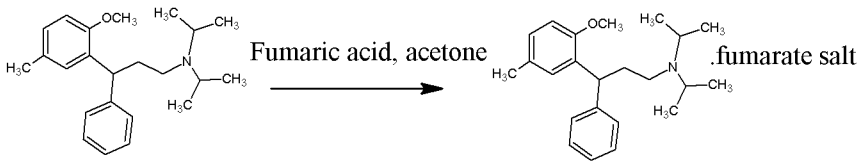
[191] Yield=85%

[192]

[193] **Example-5**

[194] **Preparation of fumarate salt of N, N-di-isopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine**

[195]

[196] 

(VI) (VII)

[197]

[198] Crude 0.080 kg N,N-diisopropyl-3- (2-methoxy-5-methylphenyl)-3- phenyl-propylamine was dissolved in Acetone (0.160 L) and add 0.041 kg fumaric acid portion wise with in 30 min then heat it up to 50-55°C for 1-2 hrs. After that cool it at RT then 0-5°C for 1-2 hrs. The solid was filtered & washed with acetone (0.080 L).The solid was dried at 50-55°C to obtain fumarate salt of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropylamine.

[199] Dry wt = 0.088 Kg

[200] Yield=80%

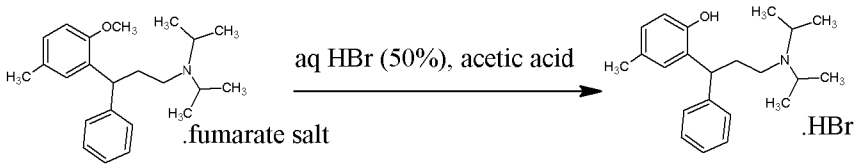
[201] Purity by HPLC= > 99%

[202]

[203] **Example-6**

[204] **Preparation of hydrobromide salt of N, N-di-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine**

[205]

[206] 

(VII) (VIII)

[207]

[208] A solution of 0.050kg fumarate salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine in 0.111 L aqueous hydrobromic acid & 0.66 L acetic acid was stirred at 100-125°C for 12-16 hrs till completion of reaction. The reaction mixture was cooled to RT to obtain a solid. The solid was filtered & washed with DM water till washing of cake was neutral. The solid was dried at 50-55°C to obtain hydrobromic salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine.

[209] Dry wt=0.030 Kg

[210] Yield=67%

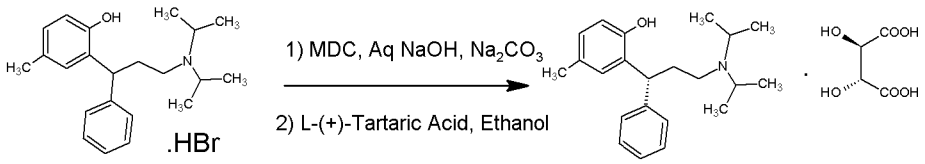
[211] Purity by HPLC= >98.5%

[212]

[213] **Example 7**

[214] **Preparation of (+)-(R)-Tolterodine-L-tartrate**

[215]

[216] 

(VIII) (I)

[217]

[218] Hydrobromic salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl amine was stirred with 2N NaOH (0.030 L), DM water (0.675 L) and dichloromethane (1.5 L). The organic layer was separated out and washed with DM water (1 L) and brine (1 L). The solvent was distilled out completely under reduced pressure to obtain oily free base (0.12 Kg). The oily free base (0.12 Kg) was stirred in ethanol (0.375 L) at 60- 65°C followed by addition of solution of 0.083 kg L-(+) Tartaric acid in 0.83 L ethanol. After completion of addition, the reaction mixture was stirred at 80-85 ° C for

1-2 hrs and cooled gradually to RT and then to 0°C to obtain a solid. The solid was filtered and washed with chilled ethanol (0.1 L x 2) to obtain wet cake. The wet cake was dried at 50-55°C for 10-12 hrs to get white solid of Crude (+)-(R)-Tolterodine-L-tartrate (Yield: 0.080 kg)

[219]

[220] 0.080 kg Crude (+)-(R)-Tolterodine-L-tartrate was dissolved in 3.2 L ethanol and refluxed at 80-85°C for 2-3 hrs to obtain a solution. The solution was concentrated to half the initial volume by distilling 1.6 lit of ethanol and gradually cooled to RT and then at 0°C for 1-2 hrs to obtain product. The product was filtered, washed with cooled ethanol (0.05 L x 2) & dried under reduced pressure (2-5 mm Hg) at 50-55°C for 12-14 hrs to obtain Tolterodine-L-(+)-tartrate -I

[221] (Yield: 0.07 kg, 39%)

[222] HPLC Purity > 99.5 %.

[223]

[224]

Claims

[Claim 1] **1.** A process for the preparation of (+)-(R)-Tolterodine-L-tartrate, comprises a step of aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI)

[Claim 2] **2.** A process for the preparation of (+)-(R)-Tolterodine-L-tartrate , comprises a step of converting 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (V) followed by crystallization in alcohol.

[Claim 3] **3.** A process according to claim 2, wherein protection of hydroxyl group is carried out in the presence of base selected from the group comprising of potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, triethylamine, trimethylamine, pyridine or mixture thereof, and solvent selected from the group comprising of dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, acetone, dichloromethane, toluene, xylene, methanol, ethanol, isopropanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dimethylacetamide or mixture thereof .

[Claim 4] **4.** A process according to claim 2, wherein the conversion of hydroxy group into leaving group is carried out by using p-toluene sulphonyl chloride, methanesulfonyl chloride or p-nitrobenzensulfonyl chloride.

[Claim 5] **5.** A process according to claim 2, wherein alcohol is selected from the group comprising of methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol or mixture thereof.

[Claim 6] **6.** A process for the preparation of (+)-(R)-Tolterodine-L-tartrate of formula (I), comprises steps of

a) reacting 3,4-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-one of formula (II) with dimethyl sulphate in the presence of aqueous sodium hydroxide followed by treatment with hydrochloride to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic acid of formula (III);

b) reducing 3-(2-methoxy-5-methylphenyl)-3-phenyl propionic

acid of formula (III) in the presence of a sodium borohydride, sulfuric acid and tetrahydrofuran to obtain 3-(2-methoxy-5-methylphenyl)-3-phenyl propanol of formula (IV);

c) converting 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (IV) into hydroxyl protected 3-(2-methoxy-5-xmethylphenyl) -3-phenyl propanol of formula (V), optionally isolating hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V) followed by crystallization in alcohol;

d) aminating hydroxyl protected 3-(2-methoxy-5-methylphenyl) -3-phenyl propanol of formula (V) with diisopropylamine in the presence of water to obtain N,N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VI);

e) converting N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VI) into organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropyl amine of formula (VII);

f) treating organic acid salt of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl) -3-phenylpropyl amine of formula (VII) with aqueous HBr in the presence of acetic acid to obtain hydrobromide salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl) -3-phenylpropyl amine of formula (VIII);

g) treating hydrobromide salt of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl) -3-phenylpropyl amine of formula (VIII) with aqueous sodium hydroxide and sodium carbonate in the presence of dichloromethane, optionally isolating free base followed by resolution with L-(+)-tartaric acid in the presence of ethanol to obtain (+)-(R)-Tolterodine-L-tartrate.

[Claim 7] **7.** A process according to claim 6, wherein the protection of hydroxy group in step (c) is carried out in the presence of base selected from the group comprising of potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, triethylamine, trimethylamine, pyridine or mixture thereof and solvent selected from the group comprising of dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, acetone,

dichloromethane, toluene, xylene, methanol, ethanol, isopropanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dimethylacetamide or mixture thereof.

[Claim 8] **8.** A process according to claim 6, wherein the conversion of hydroxy group in step (c) into leaving group is carried out by using p-toluene sulphonyl chloride, methanesulfonyl chloride or p-nitrobenzensulfonyl chloride.

[Claim 9] **9.** A process according to claim 6, wherein alcohol is selected from the group comprising of methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol or mixture thereof.

[Claim 10] **10.** A process according to claim 6, wherein conversion in step (e) is carried out at 45-60°C by using organic acid selected from the group comprising of oxalic acid, acetic acid, formic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, phthalic acid, terephthalic acid, citric acid, tartaric acid, methanesulfonic acid, ethane-sulfonic acid, p-toluenesulfonic acid, trifluoroacetic acid, and ascorbic acid in the presence of solvent selected from the group comprising of dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, acetone, dichloromethane, toluene, xylene, methanol, ethanol, isopropanol, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, dimethylacetamide or mixture thereof.