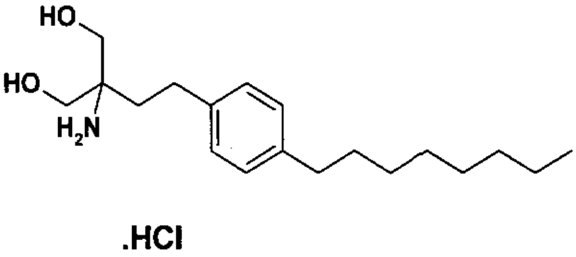
ABSTRACT

A process for preparation of diethyl 2-acetamido-2-(4-octyl phenyl)ethyl malonate (III), a key intermediate of fingolimod hydrochloride comprising reaction of 2-(4-octylphenyl)ethyl iodide (IV) with diethyl acetamido malonate in presence of a base and an iodinating agent and in an organic solvent. The compound of formula (III) thus obtained provided fingolimod hydrochloride (Ia) is having associated impurities below the regulatory limits.

We claim,

1. A process for preparation of fingolimod hydrochloride comprising,



Fingolimod hydrochloride (Ia)

reaction of 2-(4-octylphenyl)ethyl iodide with diethyl acetamidomalonate in presence of a base and an iodinating agent in a solvent to give diethyl 2-acetamido-2-(4-octylphenyl) ethyl malonate (III) followed by reduction with sodium borohydride and subsequent hydrolysis with a mineral acid to give fingolimod base, which was then isolated as its hydrochloride salt.

2. The process as claimed in claim 1, wherein the iodinating agent is selected from the group comprising of sodium iodide, potassium iodide, iodine and tetrabutyl ammonium iodide.

3. The process as claimed in claim 1, wherein the solvent is selected from dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, diethyl acetamide or a mixture thereof.

4. The process as claimed in claim 1, wherein the base is an inorganic base and is selected from the group comprising of sodium carbonate, lithium carbonate and cesium carbonate.

5. The process as claimed in claim 1, wherein fingolimod hydrochloride was obtained by treating fingolimod (I) with hydrochloric acid in an alcohol, filtration of the solid followed by recrystallizing from aqueous acetone gave fingolimod hydrochloride free from isomeric impurities.

6. The process as claimed in claim 1, wherein Fingolimod hydrochloride (Ia) has styrene impurity below 0.5% and isomeric impurity below 0.5%.

Dated this twenty-second day of November, 2013

(Signed) Bhat
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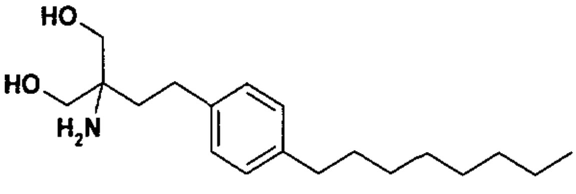
To,
The Controller of Patents
The Patent Office Branch, Mumbai

FIELD OF THE INVENTION

The present invention relates to a process for preparation of fingolimod hydrochloride conforming to regulatory specifications. Specifically, the invention relates to a process for preparation of fingolimod hydrochloride, which is free from associated impurities that are normally encountered during coupling of 2-(4-octylphenyl) ethyl iodide with diethyl acetamidomalonate.

BACKGROUND OF THE INVENTION

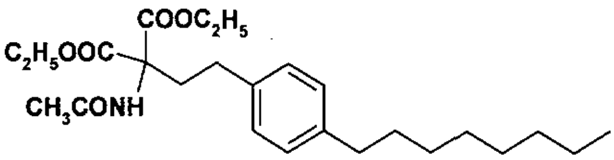
Fingolimod (I), chemically known as 2-amino-2-(2-(4-octylphenyl)ethyl)-propan-1,3-diol is administered as its hydrochloride salt (Ia) and is a sphingosine 1-phosphate receptor modulator indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Fingolimod hydrochloride capsule with proprietary name 'GILENYA' and strength of 0.50mg was approved by USFDA on September 21, 2010 for oral administration.



Fingolimod (I);

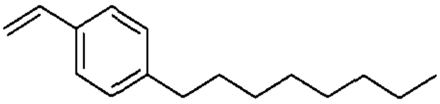
Fingolimod hydrochloride (I a)

Various researchers have attempted to synthesize fingolimod hydrochloride (Ia), however, these processes were fraught with impurity formation at various stages and more so during the condensation of 2-(4-octylphenyl)ethyl iodide with diethyl acetamidomalonate wherein the associated styrene impurity (II) to an extent of 10-15% was usually formed and required several purifications of the intermediate compound (III) for the removal of (II) from the said intermediate (III) as well as the final product.



2-acetamido-2-(4-octyl phenyl) ethyl malonate (III)

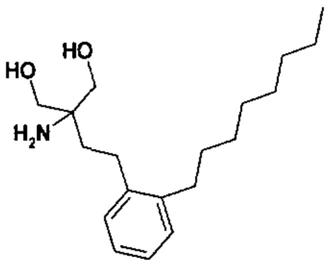
WO 2012146980 and Chemical & Pharmaceutical Bulletin, Vol. 56(4), pages 595-597, 2008 discloses that the prior art methods result in formation of impurities (II) during coupling of 2-(4-octylphenyl) ethyl iodide with diethyl acetamidomalonate in presence of sodium methoxide.



Styrene impurity (II)

It has been found that the use of base during this step results in high concentration of impurities like styrene (II) and other associated impurities, which eventually gives low yield. The same observation was also made by workers in Synthesis 2000, 4, 505-506.

WO2013111162 discloses a process for preparation of fingolimod containing thee regioisomeric impurity (Ib), wherein the disclosed method follows the multi-step process to eliminate the regioisomeric impurity from the fingolimod free base and its hydrochloride.



Isomeric impurity (Ib)

In order to circumvent the formation of the styrene impurity Philippe Durand et. al., employed an alternative route involving α-haloacetophenone derivative instead of 2-(4-octylphenyl)ethyl iodide. However, the method required an additional step involving reduction of the carbonyl group of acetophenone derivative in preparing desired intermediate like diethyl 2-acetamido-2-(4-octyl phenyl)ethyl malonate.

Chem. Pharm. Bull. 56(4)-2008, 595-597 discloses another method for minimizing the styrene impurity by subjecting the product containing the styrene impurity to Michael reaction followed by further reduction to yield diethyl 2-acetamido-2-(4-octylphenyl)ethyl malonate, the desired intermediate for preparation of fingolimod. However, this method requires additional step of Michael reaction followed by reduction, which significantly increases the cost of manufacture on a commercial scale.

Journal of Organic Chemistry 69(11), 3950-3952, (2004) provides a process wherein coupling reaction of 2-(4-octylphenyl) ethyl iodide with diethyl acetamido malonate in N,N-dimethylformamide (DMF) as solvent to eliminate formation of styrene impurity. However, duplication of these experiments reveals that styrene impurity to the extent of 5-10% is still formed.

From the foregoing, it would be evident that there are no prior art methods, which limits or considerably reduces the styrene impurity (II) in a single step and preferably in the same step when it is formed. Therefore, it was necessary to develop a process, which would significantly minimize or eliminate the styrene impurity during the conversion of dimethyl-2-acetamidomalonate to dimethyl-2-acetamido-2-(4-octyl phenyl) ethyl malonate (III) which is then converted to fingolimod. Thus, the present invention provides a solution to the above problem by providing an alternative and efficient process to prepare diethyl 2-acetamido-2-(4-octyl phenyl) ethyl malonate (III) intermediate in which the styrene impurity is minimized below regulatory limits and provides fingolimod hydrochloride (Ia) with isomeric and other associated impurities below regulatory limits and without any requirement of column chromatography or repeated crystallization for getting the desired purity.

OBJECTS OF THE INVENTION

An object of the present invention is to provide an improved process for preparation of fingolimod hydrochloride, which is free from associated impurities and does not utilize column chromatography or other purification methods.

Another object of the present invention is to provide a process for preparation of diethyl-2-acetamido-2-(4-octylphenyl) ethyl malonate (III) free from styrene impurity by utilizing an iodinating agent during reaction of 2-(4-octylphenyl) ethyl iodide with dimethyl 2-acetamidomalonate to obtain diethyl 2-acetamido-2-(4-octyl phenyl) ethyl malonate (III) of desired purity.

Another object of the present invention is to provide a process for preparation of fingolimod hydrochloride free from impurity (II) and its isomeric impurity without any additional steps, including purification.

SUMMARY OF THE INVENTION

An aspect of the present invention relates to an improved process for preparation of fingolimod hydrochloride comprising reaction of 2-(4-octylphenyl)ethyl iodide with diethyl acetamidomalonate in presence of an base and a iodinating agent in an solvent to give diethyl-2-acetamido-2-(4-octylphenyl)ethyl malonate (III), which on further reduction and subsequently hydrolysis with hydrochloric acid in organic solvent gave fingolimod hydrochloride of desired purity.

Another aspect of the present invention relates to a process for the preparation of diethyl-2-acetamido-2-(4-octylphenyl)ethyl malonate (III) comprising reaction of 2-

(4-octylphenyl) ethyl iodide with diethyl acetamidomalonate in an organic solvent and in presence of a inorganic base and an iodinating agent, reducing compound (III) with a metal hydride followed by hydrolysis and isolation of fingolimod hydrochloride conforming to regulatory specifications.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors while trying to develop a process to reduce substantially the styrene impurity (II) during the coupling reaction of 2-(4-octylphenyl)ethyl iodide (IV) with diethyl acetamidomalonate and base like metal carbonates in presence of organic solvent unexpectedly found during experimentation that the presence of an iodinating agent during the reaction substantially reduced the styrene impurity below regulatory limits.

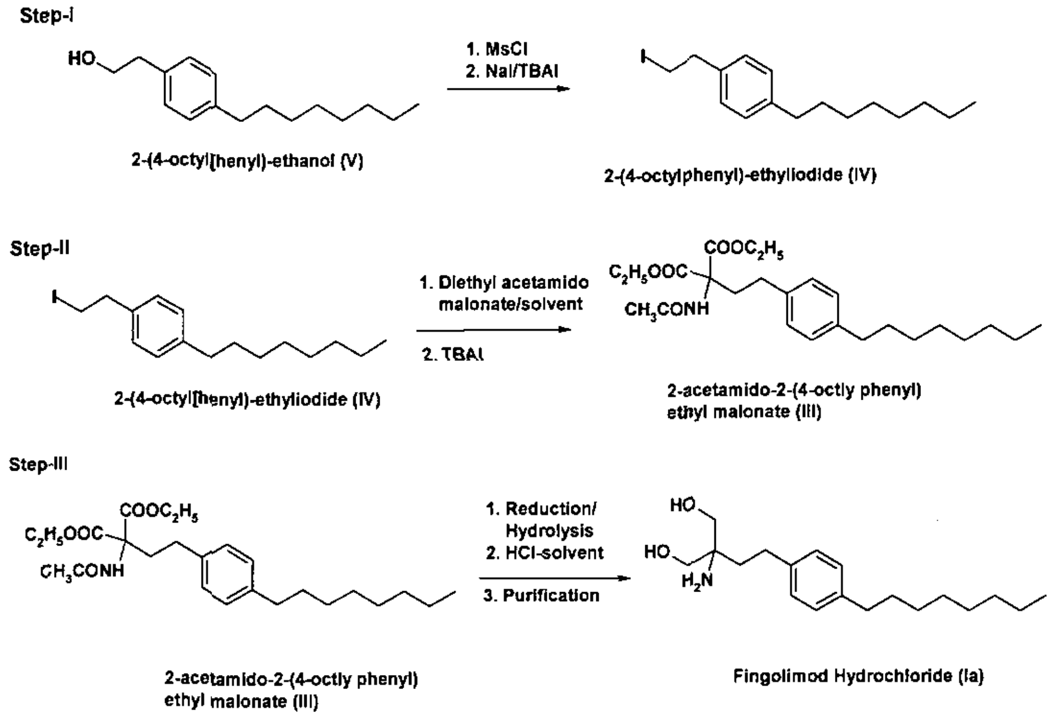
By following prior art methods, it was very difficult to restrict the formation of styrene impurity (II) during the preparation of intermediate (III) and extremely difficult to minimize during purification without compromising on yield. During the experimentation, the present inventors observed that the styrene impurity was bound to be formed during the reaction irrespective of the base used. Therefore, it was necessary to eliminate the formed impurity by purification, during work up or by suppressing its formation during the reaction. However, elimination of styrene impurity by purification was quite tedious and did not result in any improvement in the purity.

The method embodied in the present invention involves reaction of 2-(4-octylphenyl)-ethyl iodide (IV) with diethyl acetamidomalonate, in presence of a base and an iodinating agent and in an organic solvent.

It was found by the inventors that the formation of the styrene impurity of formula (II) was arrested in presence of the iodinating agent selected from the group of quaternary ammonium salts. These salts being water soluble are very easy to remove after the reaction either by washing with water or with dilute sodium thiosulphate solution. Thus, the inventors were successful in reducing the undesired styrene impurity below regulatory limits and were able to obtain the desired compound of formula (IV) without any additional step of purification.

Literature references reveal that the prior art methods suggest alternative and tedious route of synthesis for preparation of intermediate (III). However, the present invention provides a simple method to suppress the styrene impurity by employing an iodinating agent or any other halogenating agent.

The resulting fingolimod and its hydrochloride thus formed from intermediate (III) was found to be conforming to regulatory specification. Thus, an additional step of purification, which could considerably lower the yield, was avoided.



Scheme: Method for preparation of Fingolimod Hydrochloride

The detailed reaction process for preparation of fingolimod hydrochloride is described in the following steps:

1. reaction of 2-(4-octylphenyl)ethyl iodide (IV) with diethyl acetamidomalonate in presence of an iodinating agent and a base in an organic solvent to give diethyl 2-acetamido-2-(4-octylphenyl)ethyl malonate (III) of desired purity,
2. reduction of intermediate (III) to the corresponding alcohol formed insitu followed by hydrolysis to fingolimod free base which is then finally converted to its hydrochloride salt, by treating with hydrochloric acid in an organic solvent.

2-(4-Octylphenyl)ethyl iodide (IV) was obtained by treating 2-(4-octylphenyl)ethanol (V) with methane sulfonyl chloride and subsequent iodination with sodium iodide and a catalyst like quaternary ammonium iodide in a ketone organic solvent. The solvent was selected from the group comprising of acetone, methyl ethyl ketone, MIBK etc.

2-(4-Octylphenyl)-ethyl iodide (IV) was treated with diethyl acetamidomalonate in presence of a base and an iodinating agent in a solvent to give diethyl-2-acetamido-2-(4-octyl phenyl)ethyl malonate (III). The iodinating agent was selected from the group comprising of sodium iodide, potassium iodide, iodine, tetra butyl ammonium iodide (TBAI), preferably tetra butyl ammonium iodide (TBAI).

The organic solvent was selected from the group comprising of dimethylformamide, dimethyl sulfoxide, tetrahydrofuran and dimethylacetamide or their mixtures thereof.

The base was selected from the group of alkali metal carbonates like sodium carbonate, lithium carbonate, cesium carbonate etc.

The reaction mixture was heated between 80 and 90°C till completion of reaction. The mixture was quenched with water and filtered. The solid separating out was recrystallized from a non-polar solvent like hexane to give compound of formula (III) of desired purity and with the undesired styrene impurity below regulatory limits.

Prior art methods resulted in formation of styrene impurity to the extent of 15 to 20%, hence, these methods resulted in a loss of upto 42% in yield after purification. In stark contrast, the inventors by utilizing an iodinating agent were able to restrict the formation of styrene impurity below 2% and which could be easily removed during work up and isolation of intermediate (III).

The reduction of intermediate (III) to the corresponding alcohol is carried with sodium borohydride in presence of metal halide like calcium chloride and in an organic solvent selected from dimethylformamide, dimethyl sulfoxide and tetrahydrofuran. Subsequent hydrolysis of the corresponding alcohol N-(2-(4-octylphenyl)ethyl-1,3-dihydroxypropan-2-yl)acetamide with an acid and alcohol as solvent provided fingolimod free base, which was converted to its hydrochloride salt by treating with hydrochloric acid in an alcohol. The alcohol was selected from the group comprising of methanol, ethanol and isopropyl alcohol.

Fingolimod hydrochloride thus obtained, if required, was further purified by recrystallization to remove the isomeric impurity. The purification was carried out in an aqueous mixture of a ketone solvent. The ketone solvent was selected from the group comprising of acetone, methyl ethyl ketone and MIBK. The preferred aqueous ketone was a mixture of acetone and water in a proportion ranging from 99:1 to 75:25.

A further advantage of the invention is that the present invention did not utilize multiple crystallization or column chromatography for purification intermediate (III) or fingolimod free base (I) or its hydrochloride salt (Ia) as reported in prior art methods, which renders the process cost-effective.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The 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.

EXAMPLE:

Example 1: Preparation of 2-(4-octylphenyl)ethyl iodide (IV)

A mixture of 2-(4-Octylphenyl)ethanol (100gms; 0.427moles), dichloromethane (500ml) and triethylamine (108gms, 1.067moles) were cooled between 0°C and 5°C. Methanesulfonyl chloride (73.11gms, 0.64 moles) was added gradually under nitrogen atmosphere and stirred for 2-5 hours between 0°C and 30°C, till completion of the reaction based on TLC monitoring. The reaction mixture was quenched with water (500ml) and organic layer after separation was concentrated under reduced pressure to yield the corresponding mesyl derivative, which was dissolved in methyl isobutyl ketone (1064ml) containing tetrabutyl ammonium iodide (7.85gms) & sodium iodide (139.7gms). The reaction mixture was stirred for 3 hours and after completion of reaction, the reaction mixture was quenched with water (665 ml) and the organic layer concentrated under reduced pressure to give 2-(4-octylphenyl)ethyl iodide (IV).

Yield: 150 gms (96.53%)

Example 2: Preparation of diethyl 2-acetamido-2-(4-octylphenyl) ethyl malonate (III)

Diethyl acetamidomalonate (59.86 gms), cesium carbonate (89.67gm, 0.27moles) and tetrabutyl ammonium iodide (21.42gms; 0.05moles) in DMSO (400ml) were stirred at 25 to 30°C. 2-(4-Octylphenyl)ethyl iodide (IV) (100gms, 0.29moles) was gradually added to the reaction mixture under nitrogen atmosphere and stirred at 80 to 85°C till completion of reaction. Water (250 ml) was added to the mixture and filtered to provide a residue containing 2-acetamido-2-(4-octylphenyl) ethyl malonate (III) which was crystallized from hexane.

Yield: 110.8gms (88%); Purity: 99.95%

Example 3: Preparation of Fingolimod hydrochloride.

2-Acetamido-2-(4-octylphenyl) ethyl malonate (III) (100gms, 0.23moles) was dissolved in tetrahydrofuran and cooled to 5-10°C. Sodium borohydride (43.8 gms) followed by trifluoroacetic acid were added below 10°C and stirred for 3-4 hours at 25 to 30°C. After completion of reaction, based on TLC, the reaction mixture was quenched with water and extracted with ethyl acetate (700 ml). The organic layer was concentrated under reduced pressure and the residue treated with hydrochloric acid dissolved in isopropyl alcohol and stirred for 2-3 hours at 80 to 100°C. The reaction mixture was cooled to 5-10°C, quenched with sodium carbonate solution (20%) and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to yield a residue containing fingolimod free base.

Isopropyl alcohol containing hydrochloride acid was added to the residue and stirred for 1 hour. The mixture was stirred at 5-10°C, filtered, washed with isopropyl alcohol and dried.

Yield: 59.4 gms (75%); Purity: 99.91%

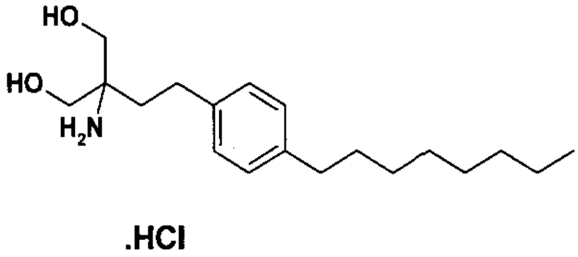
Example 4: Purification of Fingolimod hydrochloride

Fingolimod hydrochloride (50 gms, 0.1 mole) was dissolved in acetone (1600 ml) and stirred for 1-2 hours at 55-55°C. Water (25ml) was added at 50-55°C and stirred for 1 hour. The mixture was cooled to 25-30°C, and the solid separating out was filtered and dried.

Yield 46 gm, (92 %); Purity: 99.98%; Isomeric impurity: 0.01%.

We claim,

1. A process for preparation of fingolimod hydrochloride comprising,



Fingolimod hydrochloride (Ia)

reaction of 2-(4-octylphenyl)ethyl iodide with diethyl acetamidomalonate in presence of a base and an iodinating agent in a solvent to give diethyl 2-acetamido-2-(4-octylphenyl) ethyl malonate (III) followed by reduction with sodium borohydride and subsequent hydrolysis with a mineral acid to give fingolimod base, which was then isolated as its hydrochloride salt.

2. The process as claimed in claim 1, wherein the iodinating agent is selected from the group comprising of sodium iodide, potassium iodide, iodine and tetrabutyl ammonium iodide.

3. The process as claimed in claim 1, wherein the solvent is selected from dimethylformamide, dimethyl sulphoxide, tetrahydrofuran, diethyl acetamide or a mixture thereof.

4. The process as claimed in claim 1, wherein the base is an inorganic base and is selected from the group comprising of sodium carbonate, lithium carbonate and cesium carbonate.

5. The process as claimed in claim 1, wherein fingolimod hydrochloride was obtained by treating fingolimod (I) with hydrochloric acid in an alcohol, filtration of the solid followed by recrystallizing from aqueous acetone gave fingolimod hydrochloride free from isomeric impurities.

6. The process as claimed in claim 1, wherein Fingolimod hydrochloride (Ia) has styrene impurity below 0.5% and isomeric impurity below 0.5%.

Dated this twenty-second day of November, 2013

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