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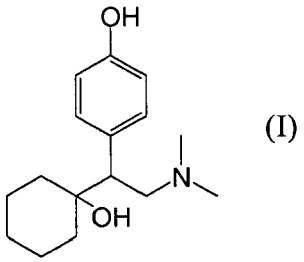
(54) Title: METHOD OF PREPARING DESVENLAFAXINE AND ITS SALTS



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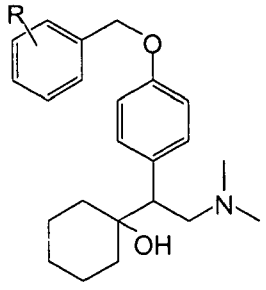

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(57) Abstract: A method for the preparation of 4-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl) phenol of formula (I), known under generic name desvenlafaxine, and its pharmaceutically acceptable salts, which comprises (a) mixing of the starting material *O*-benzyldesvenlafaxine or its derivative of formula (II), wherein R is H, 4-methyl, 4-methoxy, 3,4-dimethoxy, 2-nitro, 4-nitro, 4-chloro, 4- bromo, 2,6-dichloro or 2,6-difluoro, in an organic solvent or a mixture of solvents, and subsequent dissolving of the starting material by decreasing the pH to a value of 3 to 8 by addition of an inorganic or organic acid, or dissolving of *O*-benzyldesvenlafaxine or its derivative of formula (II) in an organic solvent or a mixture of solvents, wherein the compound of formula (II) is in the form of a salt with an inorganic or organic acid and the pH of the solution has a value of 3 to 8, (b) converting *O*-benzyldesvenlafaxine or its derivative of formula (II) to desvenlafaxine I by catalytic hydrogenation on a Raney catalyst, (c) removing the catalyst from the desvenlafaxine solution by filtration and subsequent increasing the pH to a value of 8 to 11 by addition of an inorganic or organic base, (d) isolating the desvenlafaxine base I by filtration, (e) converting the desvenlafaxine base I to a pharmaceutically acceptable salt. Formulae (I), (II)

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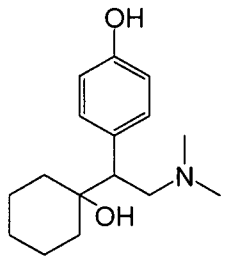
METHOD OF PREPARING DESVENLAFAXINE AND ITS SALTS

Technical Field

The invention relates to a method for the preparation of 4-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl)phenol of formula I



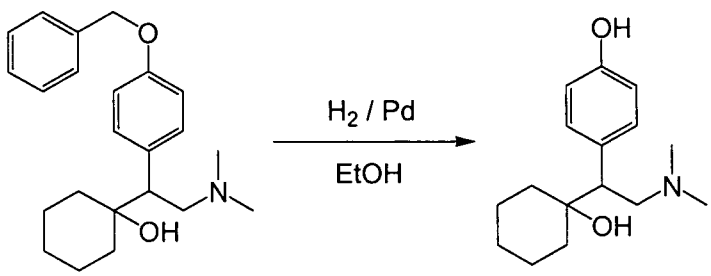
(I)

known under a generic name desvenlafaxine, and its pharmaceutically acceptable salts.

Background Art

Desvenlafaxine was authorized for treatment of depressions and vasomotoric symptoms associated with menopause (*Drugs of the Future* **2006**, 31(4), 304-309).

Patent US 4,535,186 describes, in Example 19, preparation of desvenlafaxine by debenzylation of starting "*O*-benzyldesvenlafaxine"; *Scheme 1*.



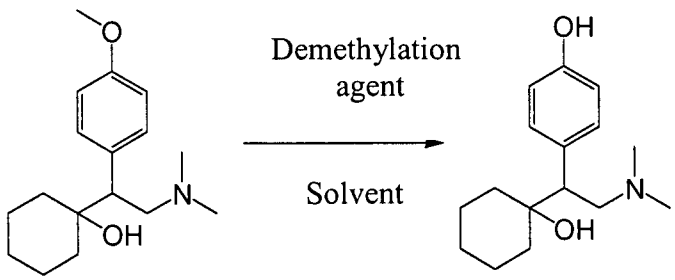
O-Benzyldesvenlafaxine (I)

Scheme 1

The reaction therein is performed in high dilution, i.e. 1 g in 100 ml of solvent; the product is obtained by evaporating the solution after removing the catalyst, i.e. palladium on charcoal (Pd/C), by filtration. The solid evaporation residue, i.e. the desvenlafaxine base, is converted by action of fumaric acid in an acetone-ethanol mixture to the salt characterized by a melting point of from 140 to 142 °C. When reproducing the procedure according to patent US 4,535,186 the desvenlafaxine base was obtained which shows the characteristic peaks of powder X-ray diffraction: 12.1, 13.2, 15.9 and 20.4, 22.4 and 26.6 ±0.2 theta. This polymorph was later identified as Form A in WO 2007/120925.

A similar procedure (*Scheme 1*) describes, in Example 4 of WO 2008/093142, preparation of the desvenlafaxine base, in which 1.3 g of the desvenlafaxine base is prepared from 2 g of *O*-benzyldesvenlafaxine dissolved in 50 ml of ethanol by catalytic hydrogenation using Pd/C. Following debenzylation, the catalyst is removed by filtration from the reaction mixture and the solvent is evaporated from the filtrate. The evaporation residue is triturated in hexane and the solid product is isolated by filtration.

Other patented methods (e.g. US 7,026,508, US 6,673,838, WO 03/048104, WO 2007/071404, WO 2007/120923) relate to preparation of desvenlafaxine by demethylation of venlafaxine, *Scheme 2*. As demethylation agents e.g. thiolates are used.



Venlafaxine (I)

Scheme 2

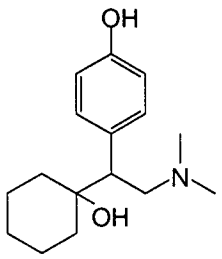
The above-mentioned methods of preparing desvenlafaxine by catalytic hydrogenation of *O*-benzyldesvenlafaxine suffer form the drawbacks of the necessity of high dilution during

debenzylation (only 1 to 4% solution) which is given by low solubility of the starting material and, in particular, of the product in solvents generally used for catalytic hydrogenation, the high price of catalyst, i.e. Pd/C, and its sensitivity to catalytic poisons. The described processing is also inappropriate for the industrial scale since evaporating of organic solvents into the evaporation residue is hardly feasible and energy-demanding in large scale.

The present invention provides a convenient solution to the preparation of high-purity desvenlafaxine and its pharmaceutically acceptable salts.

Disclosure of Invention

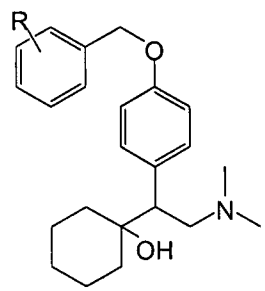
The invention relates to a method for the preparation of 4-(2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl) phenol of formula I



(I)

known under generic name desvenlafaxine, and its pharmaceutically acceptable salts, which comprises

(1) mixing of *O*-benzyldesvenlafaxine or its derivative of formula II,



(II)

wherein R is H, 4-methyl, 4-methoxy, 3,4-dimethoxy, 2-nitro, 4-nitro, 4-chloro, 4-bromo, 2,6-dichloro or 2,6-difluoro,

in an organic solvent or a mixture of solvents, followed by dissolving the starting material by lowering the pH to a value of 3 to 8 by addition of an inorganic or organic acid, or dissolving *O*-benzyldesvenlafaxine or its derivative of formula II in an organic solvent or a mixture of solvents, wherein the compound of formula II is in a form of a salt with an inorganic or organic acid and pH of the resulting solution has a value of 3 to 8,

(2) converting *O*-benzyldesvenlafaxine or its derivative of formula II to desvenlafaxine I by catalytic hydrogenation on a Raney catalyst,

(3) removing the catalyst from the desvenlafaxine solution of a pH value 3 to 8 by filtration, followed by increasing the pH to a value higher than 8 and lower than 11 by addition of an inorganic or organic base,

(4) isolating the desvenlafaxine base by filtration,

(5) converting the desvenlafaxine base to a pharmaceutically acceptable salt.

Detailed Description of the Invention

Debenzylation of *O*-benzyldesvenlafaxine or its derivative of formula II can be carried out using common precious metals on a suitable carrier, e.g. palladium on carbon (Pd/C). The use of catalysts containing palladium have the drawback in their sensitivity to catalytic poisons, which may occur in trace amounts in the substrate and inactivate ("poison") the catalyst. In reproduction of the debenzylation of *O*-benzyldesvenlafaxine according to the described procedures (e.g. according to WO 2008/093142), conversion to desvenlafaxine was only 45 % at most (for example, the mixture resulting after debenzylation contained approximately 28% of desvenlafaxine and approximately 71% of unreacted starting material). A probable reason of such low conversion might be the content of analytically non-identifiable amount of a catalytic poison. Even after repeated addition of another amount of the catalyst the conversion of *O*-benzyldesvenlafaxine to desvenlafaxine only succeeded in no more than 80%. It is thus

obvious that if *O*-benzyldesvenlafaxine contains as little as an immeasurable amount of a catalytic poison, use of a palladium catalyst for debenzylation is impossible from the practical point of view (long reaction time, high consumption of the expensive catalyst).

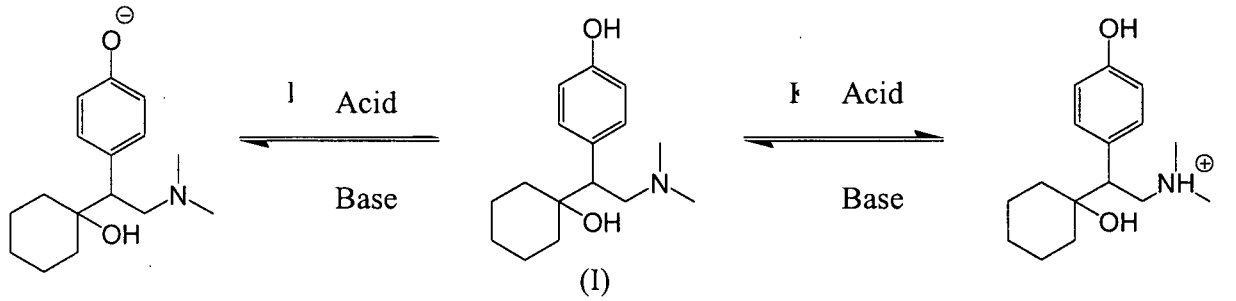
Palladium on carbon is, in terms of its activity, sensitive to presence of numerous catalytic poisons, including organic and inorganic sulfur compounds (e.g. thiols, sulfides), dichloroethane, quinoline, salts of mercury, lead and zinc and others, in as low concentrations as from tens of ppb (parts per billion, 10^{-9}). The trace quantities of these poisons in the substrate probably originate in the process of its production. *O*-benzyldesvenlafaxine can be produced cheaply not only by reduction of the respective benzyldesvenlafaxine amide, but also by demethylation of venlafaxine and intermediates of its preparation using sulfur compounds (e.g. sodium sulfide, sodium dodecane thiolate), followed by benzylation of the phenolic hydroxyl.

We have surprisingly found out that metals other than Pd can be used for debenzylation of *O*-benzyldesvenlafaxine as well. Use of Raney nickel (Ra-Ni) and Raney cobalt (Ra-Co), optionally containing promoters (Pd, Fe, Cr, Al, Mo) have shown to be particularly preferred. Ra-Ni and Ra-Co in amounts of 0.1 to 4 fold of the weight of substrate, preferably 0.2 to 0.4 fold, most preferably 0.25 fold of the substrate weight, can be used for debenzylation. Ra-Ni, or Ra-Co, tolerates any potential presence of catalytic poisons in the substrate and poisoning of the catalyst does not occur. When using Ra-Ni, or Ra-Co, it is possible to debenzylate also a substrate containing catalytic poisons, i.e. a substrate which cannot be debenzylated if Pd is used as the catalyst. Hydrogen can be introduced into the reaction mixture from an external source and the pressure of hydrogen during catalytic hydrogenation can be 0.1 MPa to 10 MPa, preferably 0.1 MPa to 1 MPa. The reaction can be conducted in a temperature range of from 20 °C to the boiling temperature of the reaction mixture, preferably in the range of from 30 °C to 70 °C.

In this design the conversion is almost quantitative and no by-products are formed. Considering the low price of Ra-Ni and Ra-Co, use of these catalysts is roughly significantly more cost-effective than use of Pd/C; costs for the catalyst are about 5 times lower. Pd toxicity is considerably lower than that of Ni and Co, which reflects in the maximum allowed limits in the active ingredient (API) applicable for pharmaceutical purposes. The maximum allowed limits of heavy metals in API's are as follows:

- Pd – 5 ppm orally, 0.5 ppm parenterally
- Ni, Co – 10 ppm orally, 1 ppm parenterally

The molecule of desvenlafaxine I contains both acidic and alkaline functional groups and thus can form salts at pH values higher or lower than the so-called isoelectric point, i.e. pH of the solution at which the molecule does not carry any charge and is usually the least soluble in protic solvents (e.g. alcohols or mixtures of organic solvents and water). In the case of desvenlafaxine I the corresponding pH value is about 9.5 (*Scheme 3*).



Scheme 3

While adding an acid or base to a suspensions of desvenlafaxine I in a protic solvent, pH of the solution changes, thus causing gradual protonation of the amine function when pH of the solution decreases, or gradual deprotonation of the aromatic hydroxyl when pH of the solution increases, which results in gradual increase of the solubility, associated with an increasing portion of ionized desvenlafaxine in the mixture. On the contrary, when adjusting pH of a solution of protonated or deprotonated desvenlafaxine to 8 to 11, preferably to 9 to 10, its solubility decreases to a minimum.

This characteristic of desvenlafaxine I can be advantageously used in preparation thereof from *O*-benzyldesvenlafaxine or its derivative of formula II. *O*-benzyldesvenlafaxine is, like its derivatives of formula II, better soluble in protic solvents than desvenlafaxine I and its solubility increases with decreasing pH due to presence of an amine function in the molecule.

With respect to lower stability of desvenlafaxine I in strongly acidic solutions, it is appropriate to adjust pH of the solution during debenzylation at 3 to 8, at the best at 5 to 6. Any inorganic or organic acid can be used for the adjustment of pH. Appropriately, an acid having the pK_a value between 1 and 5 will be used, e.g. formic acid, acetic acid or phosphoric acid. By lowering pH of the reaction mixture the solubility of *O*-benzyldesvenlafaxine or its derivatives of formula II and, in particular, of desvenlafaxine I can be increased to more than 20 mg in 100 ml of solvent, depending on the solvent, acid, temperature of reaction mixture and the pH value used. In this manner the volume of the organic solvent used can be easily reduced and thus costs of raw materials and ecological challenge can be reduced.

The reaction mixture after debenzylation contains desvenlafaxine I and suspended catalyst, which is filtered out. After pH of the filtrate is adjusted using an appropriate base (e.g. an aqueous solution of ammonia) to 8 – 11, preferably to 9 – 10, the precipitated desvenlafaxine base is filtered, washed with water, or a suitable organic solvent, and dried. Processing of the reaction mixture is very simple and does not require use of any other organic solvents or laborious and expensive evaporation of them.

The above-mentioned procedure requires use of only minimum amounts of organic solvents and is simple in terms of the carrying out; moreover in the final processing the chemical purity of crude desvenlafaxine is increased. This purifying effect can thus be used for the preparation of a highly pure desvenlafaxine base, wherein the desvenlafaxine base is dissolved in a slightly acidic solution and pH is adjusted to 8-11, preferably 9-10, with a suitable base. Non-ionized, and hence low soluble, desvenlafaxine I is thus obtained in high yield and purity. Suitable solvents include water, or a mixture of water with a water-miscible organic solvent selected from the group consisting of methanol, ethanol, 2-propanol, n-butanol, tetrahydrofuran, dioxane, dimethylsulfoxide, dimethylformamide, or mixtures thereof.

The purified desvenlafaxine base is then converted to a pharmaceutically acceptable salt, preferably succinate hydrate or hemioxalate.

The invention is illustrated in more detail in the working examples that follow. The examples, which illustrate the improvement of the process according to the invention, are of purely illustrative character exclusively, and do not limit the scope of invention in any respect.

Examples

Example 1: Preparation of desvenlafaxine base I – reproduction of debenzylation on Pd/C according to prior procedure (WO2008/093142, Example 4)

O-Benzyldesvenlafaxine of formula II (R = H), base (2 g) is dissolved in ethanol (50 ml). Pd/C 20% (0.2 g) is added to the resulting solution and the mixture is heated to 50 °C under intensive stirring. The mixture is bubbled with gaseous hydrogen under the atmospheric pressure (0.1 MPa) for 2 hours. Yield 1.45 g (98 %), HPLC purity 28%, content of *O*-benzyldesvenlafaxine ~ 71%.

Example 2: Preparation of desvenlafaxine base I

O-Benzyldesvenlafaxine of formula II (R = H), base (39 g) is stirred in methanol (100 ml). Concentrated hydrochloric acid is added to the suspension until pH 5 is obtained. Raney nickel washed with methanol (9.75 g) is added to the resulting solution and the mixture is heated to 50 °C under intensive stirring. The mixture is hydrogenated with gaseous hydrogen at the atmospheric pressure (0.1 MPa) for 2 hours. The mixture is then filtered through diatomaceous earth. The pH value of filtrate is adjusted to 9.5 by dropwise addition of a 25% aqueous solution of ammonia. The suspension is then stirred at a laboratory temperature for 1 hour and then filtered. The filtration cake is washed with water and dried. Yield 28.5 g (98 %), HPLC purity 99.7%.

Example 3: Preparation of desvenlafaxine base I

O-Benzyldesvenlafaxine of formula II (R = H), base (39 g) is stirred in methanol (100 ml). Concentrated acetic acid is added to the suspension until pH 5 is obtained. Raney nickel washed with methanol (9.75 g) is added to the resulting solution and the mixture is heated to 50 °C under intensive stirring. The mixture is hydrogenated with gaseous hydrogen at the pressure of 1 MPa for 2.5 hours. The mixture is then filtered through diatomaceous earth. The pH value of the filtrate is adjusted to 9.5 by dropwise addition of a 25% aqueous solution of ammonia. The suspension is then stirred at a laboratory temperature for 1 hour and then filtered. The filtration cake is washed with water and dried. Yield 27 g (93%), HPLC purity 99.6%.

Example 4: Preparation of desvenlafaxine base I

O-Benzyldesvenlafaxine of formula II (R = H), hydrochloride (46.9 g) is dissolved in methanol (100 ml). Raney nickel washed with methanol (11.75 g) is added to the solution and the mixture is heated to 50 °C under intensive stirring. The mixture is hydrogenated with gaseous hydrogen at the pressure of 5 MPa for 2 hours. The mixture is then filtered through diatomaceous earth. The pH value of the filtrate is adjusted to 9.5 by dropwise addition of a 25% aqueous solution of ammonia. The suspension is then stirred at a laboratory temperature for 1 hour and then filtered. The filtration cake is washed with water and dried. Yield 28.5 g (98%), HPLC purity 99.8%.

Example 5: Preparation of desvenlafaxine base I

O-Benzyldesvenlafaxine of formula II (R = H), hydrochloride (46.9 g) is dissolved in methanol (100 ml). Raney nickel washed with methanol (11.75 g) is added to the solution and the mixture is heated to 50 °C under intensive stirring. The mixture is hydrogenated with gaseous hydrogen at atmospheric pressure (0.1 MPa) for 3 hours. The mixture is then filtered through diatomaceous earth. The pH value of the filtrate is adjusted to 9.5 by dropwise addition of a 25% aqueous solution of ammonia. The suspension is then stirred at a laboratory temperature for 1 hour and then filtered. The filtration cake is washed with water and dried. Yield 27.5 g (95%), HPLC purity 99.6%.

Example 6: Preparation of desvenlafaxine base I

O-Benzyldesvenlafaxine of formula II (R = H), hydrochloride (46.9 g) is dissolved in methanol (100 ml). Raney cobalt washed with methanol (47 g) is added to the solution and the mixture is heated to 50 °C under intensive stirring. The mixture is hydrogenated with gaseous hydrogen at atmospheric pressure (0.1 MPa) for 6 hours. The mixture is then filtered through diatomaceous earth. The pH value of the filtrate is adjusted to 9.5 by dropwise addition of a 25% aqueous solution of ammonia. The suspension is then stirred at a laboratory temperature for 1 hour and then filtered. The filtration cake is washed with water and dried. Yield 28 g (96%), HPLC purity 99.6%.

Example 7: Preparation of desvenlafaxine base I

By the procedure described in Example 2, in which *O*-(4-methoxybenzyl)-venlafaxine of formula II (R = MeO) was used as the starting substance, and a mixture of methanol and

tetrahydrofuran was used as the solvent, 85% of desvenlafaxine of formula I having HPLC purity 99.4% was obtained.

Example 8: Purification of desvenlafaxine base I

Desvenlafaxine base (52 g, HPLC purity 99.2%) is stirred in methanol (200 ml) and 2M hydrochloric acid is added dropwise until the pH value of the solution is 4. The solution is mixed with charcoal and filtered through diatomaceous earth. The pH value of the filtrate is adjusted to 9.6 by dropwise addition of a 2M solution of sodium hydroxide. The suspension is then stirred at 0 °C for 1 hour and then filtered. The filtration cake is washed with water and with cold 2-propanol. Yield 49 g (94%), HPLC purity 99.9%.

Example 9: Preparation of desvenlafaxine hydrogensuccinate hydrate

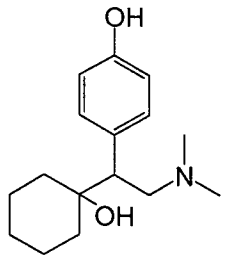
Desvenlafaxine base (25 g) is stirred in a mixture of acetone (210 ml) and water (70 ml) for 30 minutes. Succinic acid (12.5 g) is added to the suspension. The mixture is then stirred at 60 °C for 1 hour. The almost limpid solution is filtered through diatomaceous earth. The mixture is cooled to 30 °C and stirred at this temperature for 1 hour, then cooled to 5 °C and stirred for 1 hour. The crystals are aspirated and washed with acetone. Yield 33 g (91%).

Example10: Preparation of anhydrous desvenlafaxine hemioxalate

Desvenlafaxine base (11.0 g) and oxalic acid dihydrate (2.52 g) are dissolved in methanol (60 ml) at 50 °C. The mixture is cooled slowly to 0 °C and stirred for 1 hour. The crystals are aspirated and washed with methanol. Yield 10.1 g (78%).

CLAIMS

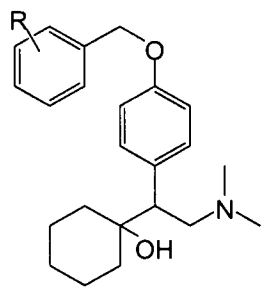
1. A method for the preparation of 4-(2-(dimethylamino)-1-(1-hydroxy-cyclohexyl)ethyl)phenol of formula I



(I)

i.e., desvenlafaxine, and its pharmaceutically acceptable salts, which comprises

(a) stirring of starting material *O*-benzyldesvenlafaxine or its derivative of formula II,



(II)

wherein R is H, 4-methyl, 4-methoxy, 3,4-dimethoxy, 2-nitro, 4-nitro, 4-chloro, 4-bromo, 2,6-dichloro or 2,6-difluoro, in an organic solvent or a mixture of solvents, and subsequent dissolving of the starting material by lowering the pH to a value of 3 to 8 by addition of an inorganic or organic acid, or dissolving of *O*-benzyldesvenlafaxine or its derivative of formula II in an organic solvent or a mixture of solvents, wherein the compound of formula II is in the form of a salt with an inorganic or organic acid and pH of the resulting solution is 3 - 8,

(b) converting *O*-benzyldesvenlafaxine or its derivative of formula II to desvenlafaxine I by catalytic hydrogenation on a Raney catalyst,

(c) removing the catalyst from the solution of desvenlafaxine by filtration, followed by increasing the pH to 8 – 11 by addition of an inorganic or organic base,

(d) isolating the desvenlafaxine base I by filtration,

(e) converting the desvenlafaxine base I to a pharmaceutically acceptable salt.

2. The method according to claim 1, characterized in that the solvent is a water-miscible organic solvent or a mixture of more water-miscible organic solvents.

3. The method according to claims 1-2, characterized in that the organic solvent is selected from the group consisting of methanol, ethanol, 2-propanol, n-butanol, tetrahydrofuran, dioxane, dimethyl sulfoxide, dimethylformamide and their mixtures.

4. The method according to claim 1, characterized in that the catalyst is Raney nickel.

5. The method according to claim 1, characterized in that the catalyst is Raney cobalt.

6. The method according to claims 1, 4, 5, characterized in that the catalyst contains at least one promoter from the group consisting of Pd, Fe, Cr, Al and Mo metals.

7. The method according to claim 6, characterized in that the catalyst is used in a 0.1 to 4-fold amount with respect to the weight of the substrate.

8. The method according to claim 7, characterized in that the catalyst is used in a 0.25-fold amount with respect to the weight of the substrate.

9. The method according to claim 1, characterized in that the starting material of formula II is dissolved by adjusting the pH to a value of 5 to 6 by addition of an inorganic or organic acid.

10. The method according to any one of the preceding claims, characterized in that the starting material of formula II is used in the form of hydrochloride.

11. The method according to any one of the preceding claims, characterized in that an external source of hydrogen is used for the catalytic hydrogenation.

12. The method according to claim 11, characterized in that the catalytic hydrogenation is performed at a pressure of hydrogen ranging from 0.1 MPa to 10 MPa.

13. The method according to any one of the preceding claims, characterized in that the reaction is performed at a temperature ranging from 20 °C to the boiling temperature of the reaction mixture, preferably in the range of from 30 °C to 70 °C.

14. The method according to any one of the preceding claims, characterized in that after removing the catalyst by filtration pH is adjusted to a value of from 8 to 11 using an inorganic or organic base.

15. The method according to claim 14, characterized in that after removing the catalyst by filtration pH is adjusted to a value of from 9 to 10 using an inorganic or organic base.

16. The method according to claims 16-17, characterized in that an aqueous solution of ammonia is used for pH adjustment.