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(54) **Title:** METHOD FOR PREPARING MEDETOMIDINE AND ITS SALTS

(57) **Abstract:** The invention provides an improved, highly efficient method for preparing Medetomidine, and its salts, in particular its pharmaceutically acceptable salts. The method utilizes the high reactivity of halogenated imidazoles towards transmetalation with Grignard reagents and the subsequent reaction with 2,3- dimethylbenzaldehyde.

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Method for preparing medetomidine and its salts

Description

Field of the invention

[0001] The present invention concerns an improved, highly efficient method for preparing (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride (international non-proprietary name "medetomidine") and salts, in particular pharmaceutically acceptable salts, thereof.

Background art

[0002] (±)-5-[1-(2,3-Dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride having the formula (I) following below is a synthetic α-2-adrenoreceptor agonist with sedative and analgesic properties

[0003] **US 4544664** discloses the leading multi-step process for preparing (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride. The process starts with 2,3-dimethylmagnesium bromide, which is prepared from magnesium and 2,3-dimethylbromobenzene, while in a separate step this Grignard reagent is added to 4-imidazolecarboxylic acid methyl ester. The intermediate is hydrogenated in the presence of a palladium on carbon catalyst in hydrochloric acid.

[0004] **GB 2069481** discloses the preparation of 5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride via the intermediate 4-[(2',3'-dimethylphenyl)-ethyl]-*N*-acetylimidazole or 4-[(2',3'-dimethylphenyl)-ethyl]-*N*-benzylimidazole. In the processes described therein acetyl and benzyl groups are used as protecting groups of the intermediate products for increasing product yield.

[0005] In a further process described in this patent *N*-(trimethylsilyl)imidazole is used as a starting material, which is reacted with titanium tetrachloride in dry chloroform. In this case as protecting group a trimethylsilyl group is used. The use of a benzyl group as a protecting group is also mentioned therein.

[0006] The main disadvantage of the methods described in the above prior art documents is that medetomidine is obtained in low yields.

[0006A] The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented

that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

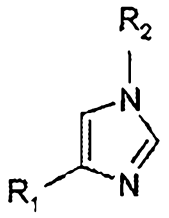
Disclosure of the invention

Technical problem

[0007] It would be desirable to prepare (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole and its salts, especially its pharmaceutically acceptable salts, in higher yields than before.

Technical solution

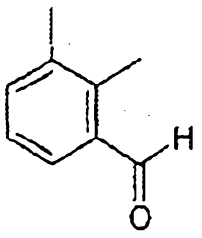
[0008] According to the present invention, there is provided a process for preparing the above compounds using as a starting material 4-iodo-1-trityl-1H-imidazole or a derivative thereof (I)



[I]

wherein R_1 is halogen, preferably iodine or bromine, and R_2 is a suitable protecting group, preferably a trityl group, a benzyl group or a trimethylsilyl group, which is reacted with 2,3-dimethylbezaldehyde (II)

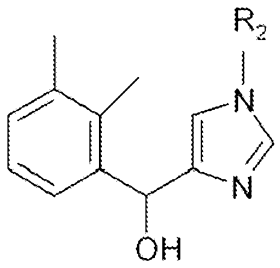
[0009]



[II]

[0010] In order to prepare (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl) methanol (III):

[0011]

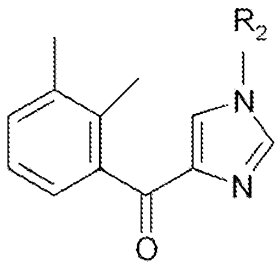


[III]

wherein R_2 is defined as before (step a).

[0012] Thereafter (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl) methanol (III) is oxidised with an oxidizing agent, preferably manganese (IV) oxide, to yield (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl) methanone (IV):

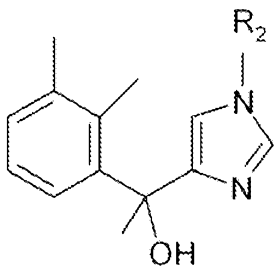
[0013]



[IV]

[0014] wherein R_2 is defined as before (step b).

[0015] In a further step a compound of formula (V) is formed by a Grignard reaction in which a compound of the above formula (IV) is reacted with a compound of formula: R_3MgHal wherein R_3 is alkyl and Hal is halogen:

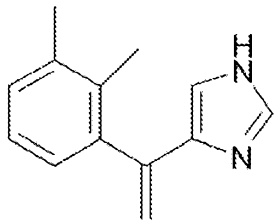


[V]

wherein R_2 is defined as before (step c).

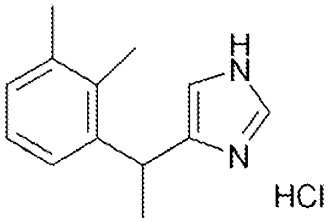
[0016] The removal of the protecting group can be performed in different ways, and depends on the particular protecting group. Thereafter the compound of formula (V) is treated with an appropriate acidic solution, preferably with a hydrochloric acid solution and 5-[1-(2,3-dimethylphenyl) vinyl]-1*H*-imidazole (VI) is obtained (step d):

[0017]



[VI]

[0018] Finally, the compound of formula (VI) is hydrogenated in the presence of a suitable catalyst, preferably palladium on carbon or Raney nickel, in an appropriate acidic solution, preferably in hydrochloric acid media (step e), and after crystallization 5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride hydrate (VII) is obtained as the desired product (VIII) (step f):



[VIII]

[0019] The pharmaceutically acceptable salts of these compounds are also within the scope of the invention.

[0020] The compounds of formula (VIII) may be reacted with both organic and inorganic acids. They can thus form many usable acid addition salts, as, for instance, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

Advantageous effects

[0021] The method of preparation of (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride and other salts, especially pharmaceutically acceptable salts thereof is advantageous in that the above new conditions of the preparation increase the yield of the product.

[0022] By using 4-iodo-1-trityl-1H-imidazole or its derivatives as a starting material and by increasing the process steps to 6 steps instead of 4 steps as described in US 4544664 surprisingly a substantially higher yield of (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride and its salts, especially its pharmaceutically acceptable salts, can be obtained.

[0023] Another advantageous effect that can be mentioned is that by using a trityl group as a protecting group this group can be removed more easily than a benzyl group as used in US 4544664. Trityl alcohol, which is obtained in the synthesis process, can be regenerated to trityl chloride, thereby comparatively high costs of the trityl group can be reduced.

[0024] The complete process of the present invention is illustrated in the enclosed Fig. 1.

Best mode for carrying out the invention

[0025] The present invention will be better understood by reference to the following Examples, which are provided as exemplary of the invention, and not as a limitation.

[0026] **Example 1 (step a)**

[0027] **Preparation of (2,3-Dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl)methanol**

[0028] A solution of isopropylmagnesium bromide in tetrahydrofuran (48 mL, 0.046 mol) was added to a stirred solution of 4-iodo-1-trityl-1*H*-imidazole (19.0 g, 0.046 mol) in dichloromethane (180 mL) at 10 to 15°C. The reaction mixture was allowed to warm to the ambient temperature and was stirred at ambient temperature for 1 hour. The reaction mixture was then cooled to 10-15°C, at which point a solution of 2,3-dimethylbenzaldehyde (6.2 mL, 0.046 mol) in dichloromethane (10 mL) was added, while not exceeding 20 to 25°C. After additional stirring for 1 hour at ambient temperature a 10% aqueous ammonium chloride solution (200 mL) was added to the reaction mixture. The organic layer was separated and washed with an aqueous sodium chloride solution (150 mL), thereafter the organic layer was concentrated to a volume of 40 mL.

[0029] A precipitate of (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl)methanol was obtained upon cooling the distillation residue to 4°C and it was separated by filtration, then washed with dichloromethane (50 mL).

[0030] The intermediate (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl)methanol was dried at ambient temperature. The yield was 17.4 g (84 %) of a white or off-white powder, having a melting temperature of 203.0 to 207.0°C.

[0031] **Example 2 (step b)**

[0032] **Preparation of (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl) methanone**

[0033] 2,3-Dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl)methanol (248 g, 0.558 mol) was added to stirred dichloromethane (5000 mL) in a 10-liter glass reactor, fitted with a reflux condenser and a thermometer. Thereafter manganese (IV) oxide (305 g, 3.51 mol) was added to the reaction mixture. The reaction mixture was heated at reflux for 2 hours at 40°C. The precipitate of manganese oxides was separated by filtration; the damp cake on the filter was washed with dichloromethane (700 mL).

[0034] The clear filtrate was poured into a 10-liter glass reactor, fitted with a stirrer, a distillation condenser and a thermometer. The reaction mixture was stirred while dichloromethane was distilled off at 40°C. Thereafter 96% ethanol (1000 mL) was added to the reaction mixture and the residual dichloromethane was removed by distillation at 50 to 55°C.

[0035] The reaction mixture was stirred and cooled to -1 to -3°C. The precipitate was separated by filtration and washed with cold (0-5°C) 96% ethanol (200 mL). The yield was 216 g (90.3 %) of white crystalline (2,3-dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl)methanone, having a melting temperature of 172.5°C to 174.0°C.

[0036] **Example 3 (step c)**

[0037] **Preparation of 1-(2,3-dimethylphenyl)-1-(3-trityl-3*H*-imidazol-4-yl)ethanol**

[0038] (2,3-Dimethylphenyl)-(3-trityl-3*H*-imidazol-4-yl)methanone (216 g, 0.488 mol) was added to stirred tetrahydrofuran (3000 mL) in a 6-liter glass reactor fitted with a mechanical stirrer, a thermometer, a dropping funnel and a tube for argon introduction into the reaction mixture.

[0039] A methylmagnesium chloride solution in tetrahydrofuran (190 mL, 0.584 mol) was added dropwise to the reaction mixture at 0°C under an argon atmosphere. The reaction mixture was maintained at 0°C. After addition of a methylmagnesium chloride solution the reaction mixture was warmed to 25°C over 3,5 hours, at which point 10 % aqueous ammonium chloride solution (90 mL) was added to the reaction mixture. The organic layer was separated and washed with saturated sodium chloride solution (700 mL). The organic layer was concentrated *in vacuo* to 20% of the original volume; the residue was cooled and allowed to crystallize at 0 to 5°C for 1 hour.

[0040] The precipitate was separated by filtration and washed with cold (0 to 5°C) tetrahydrofuran (360 mL).

[0041] The obtained intermediate 1-(2,3-dimethylphenyl)-1-(3-trityl-3*H*-imidazol-4-yl)ethanol was dried at a reduced pressure at 40–50°C.

The yield was 214.2g (97.5 %) of white crystalline 1-(2,3-dimethylphenyl)-1-(3-trityl-3*H*-imidazol-4-yl)ethanol, having a melting temperature of 226.5°C to 228.5°C.

[0042] **Example 4 (step d)**

[0043] **Preparation of 5-[1-(2,3-dimethylphenyl)vinyl]-1*H*-imidazole**

[0044] 1-(2,3-dimethylphenyl)-1-(3-trityl-3*H*-imidazol-4-yl)ethanol (212 g, 0.462 mol) was added to hydrochloric acid (2120 mL) in a 6-liter glass reactor, fitted with a reflux condenser and a thermometer. The reaction mixture was heated to reflux (99–101°C) and maintained at 99–101°C for 2 hours, at which point it was cooled to 17–23°C. The precipitate of triphenylcarbinol was separated by filtration; the damp cake on the filter was washed with water (700 mL).

[0045] Water (2,5 L) was added to the filtrate, and the mixture was poured into a 10-liter glass reactor. The stirred reaction mixture was cooled to 0°C, at which point 10% of an aqueous sodium hydroxide solution (2120 mL) was added to the reaction mixture. The reaction mixture was heated to 20–25°C and stirred for 60–90 minutes.

[0046] The suspension was filtered; the product cake on filter was washed with water (700 mL).

[0047] The obtained intermediate 5-[1-(2,3-dimethylphenyl)vinyl]-1*H*-imidazole was dried at ambient conditions for 10-12 hours and at 50 to 60°C under reduced pressure for 8–10 hours. The yield was 82.2 g (89.2 %) of white crystalline 5-[1-(2,3-dimethylphenyl)vinyl]-1*H*-imidazole, having a melting temperature of 145.7°C to 146.6°C.

[0048] **Example 5 (step e)**

[0049] **Preparation of 5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride hydrate**

[0050] 5-[1-(2,3-dimethylphenyl)vinyl]-1*H*-imidazole (80.0 g, 0.406 mol) and methanol (800 mL) were mixed in a 2-liter beaker. The reaction mixture was poured into a stirred laboratory autoclave. Palladium catalyst (1.9 g of 5% Pd/C) was weighed and immediately suspended in water (25 mL). The suspension was poured into the autoclave. The autoclave was closed and flushed 2 times with hydrogen to

0.21×10^6Pa. The hydrogen was supplied to autoclave to 0.21×10^6Pa. The reaction mixture was stirred and warmed to 44-46°C over 20-25 minutes. At the end of the hydrogenation, the hydrogen absorption ceased, and the pressure in the autoclave remained constant. The typical hydrogenation time was 1.5 hours. After hydrogenation the autoclave was flushed with nitrogen, the reaction mixture was filtered to remove the catalyst. The autoclave and the catalyst were washed with methanol (200 mL).

[0051] The solvent was removed by distillation at a reduced pressure. Hydrochloric acid (4 M, 350 mL) was added to the distillation residue at 38 to 42°C. At first the reaction mixture was stirred without cooling for 30 minutes; then the reaction mixture was cooled to -5 to -10 °C for 2 to 2.5 hours.

[0052] The precipitates were separated by filtration. The obtained intermediate 5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride hydrate was dried at ambient temperature for 15 to 17 hours. The yield was 94.8g (89-98%) of an off-white powder.

[0053] **Example 6 (step f)**

[0054] **Preparation of (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride**

[0055] 5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride hydrate (89 g), acetone (855 mL) and water (34 mL) were mixed in a 2-liter flask, fitted with a thermometer and a reflux condenser. The reaction mixture was heated to 56-58°C for 15 minutes, at which point it was filtered. The filtrate was at first cooled to 20-30°C over 1 to 1.5 hours, and then it was cooled to 0 to -10) °C for 2.5 to 3.5 hours.

[0056] The precipitates were separated by filtration and the product cake on the filter was washed with cooled (0-5°C) acetone (80-100 mL). The (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride was dried at a reduced pressure for 2-3 hours. The yield was 78.4 g (98.5 %) of colorless crystalline powder, melting at 168°C to 172°C.

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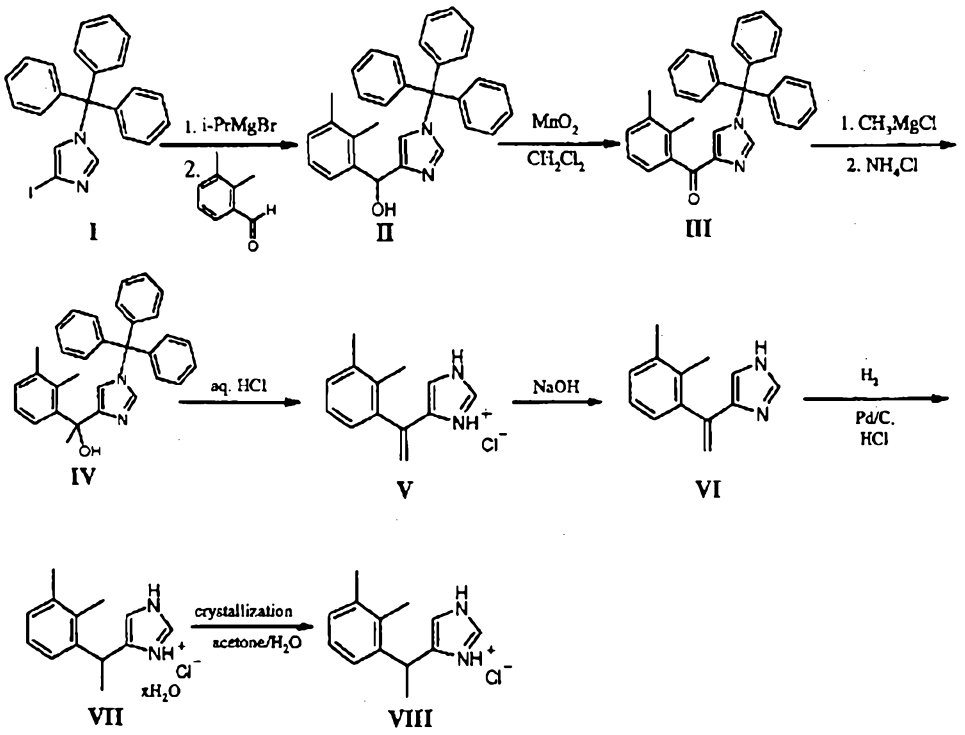

[0057] Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

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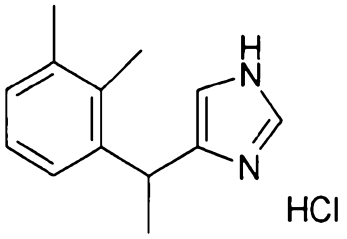
The claims defining the invention are as follows:

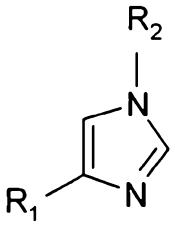
1. A process for preparation (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride of formula (VIII)



[VIII]

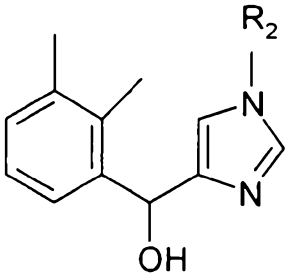
which comprises the steps of:

a) reacting of the 4-imidazole derivative of formula (I)



[I]

wherein R_1 is halogen, and R_2 is an easily removable leaving group, with 2,3-dimethylbenzaldehyde to obtain compound of formula (III)



[III]

wherein R_2 is defined above;

b) oxidation of the compound of formula (III) to obtain compound of formula (IV)

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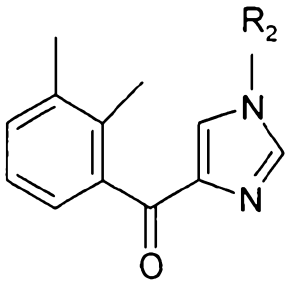
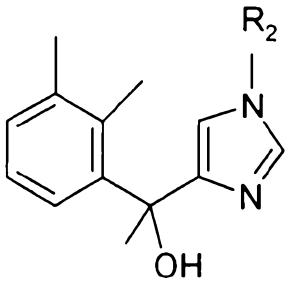


[IV]

wherein R_2 is defined above;

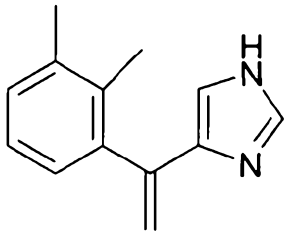
c) reaction of the compound of formula (IV) with Gringard reagent R_3MgHal, wherein R_3 is alkyl and Hal is halogen, to obtain compound of formula (V)



[V]

wherein R_2 is defined above;

d) removing the group R_2 from the compound of formula (V) to obtain the compound of formula (VI)



[VI]

e) hydrogenation of the compound of formula (VI) to obtain compound of formula (VII).

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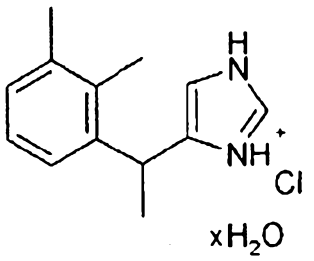

[VII]

f) crystallization of the compound of formula (VII) to obtain the compound of formula (VIII).

2. The process according to claim 1, wherein in the reaction in step a) R_1 is I.

3. The process according to claim 1, wherein in the reaction in step a) R_2 is an easily removable leaving group selected from consisting of group benzyl, trimethylsilyl or trityl protecting group.

4. The process according to claim 2 and claim 3, wherein R_1 is I and R_2 is trityl group, and the compound of formula (I) is 4-iodo-1-trityl-1H-imidazole.

5. The process according to any one of claims 1 to 4, wherein the reaction in step a) is carried out in the presence of a Grignard reagent selected from the group consisting of alkylmagnesium halide derivatives.

6. The process according to claim 5, wherein a derivative of alkylmagnesium halide is isopropylmagnesium bromide.

7. The process according to any one of claims 1 to 6, wherein the reaction in step a) is carried out in the presence of a solvent selected from the group consisting of halogenated solvents.

8. The process according to claim 7, wherein the halogenated solvent is dichloromethane.

9. The process according to any one of claims 1 to 8, wherein the oxidation reaction in step b) is carried out in the presence of manganese (IV) oxide.

10. The process according to any one of claims 1 to 9, wherein step b) is carried out at a temperature from 20°C to 80°C.

11. The process according to any one of claims 1 to 10, wherein in the reaction in the step c) the Grignard reagent is methylmagnesium chloride.

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12. The process according to any one of claims 1 to 11, wherein the reaction step c) is carried out in the presence of a solvent, tetrahydrofuran.
13. The process according to any one of claims 1 to 12, wherein step d) is carried out at a temperature from 30°C to 150°C.
14. The process according to any one of claims 1 to 13, wherein step d) comprises a reaction medium selected from the group consisting of strong acids.
15. The process according to claim 14, wherein the strong acid is hydrochloric acid.
16. The process according to any one of claims 1 to 15, wherein hydrogenation in step e) is carried out with a palladium on carbon.
17. The process according to any one of claims 1 to 16, wherein step e) is conducted in the presence of a solvent, aqueous hydrochloric acid.
18. The process according to any one of claims 1 to 17, wherein reaction in step f) is carried out at a temperature of from 30°C to 120°C.
19. The process according to any one of claims 1 to 18, wherein in step f) the crystallization is carried out with a solvent selected from the group consisting of ketones.
20. The process according to claim 19, wherein the solvent is acetone.
21. A process for preparation (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride, which process is substantially as herein described with reference to the Examples.
22. (±)-5-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride when prepared by the process of any one of claims 1 to 21.