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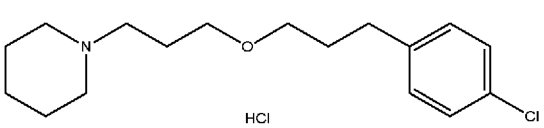
(54) Title: PROCESS FOR THE SYNTHESIS OF PITOLISANT HCl



Pitolisant HCl

(I)

(57) Abstract: Disclosed is a process for the synthesis of pitolisant HCl of formula (I), from piperidine and 1-bromo-3-chloropropane. The process according to the invention is economically efficient and easily industrially scalable.

WO 2021/023634 A1

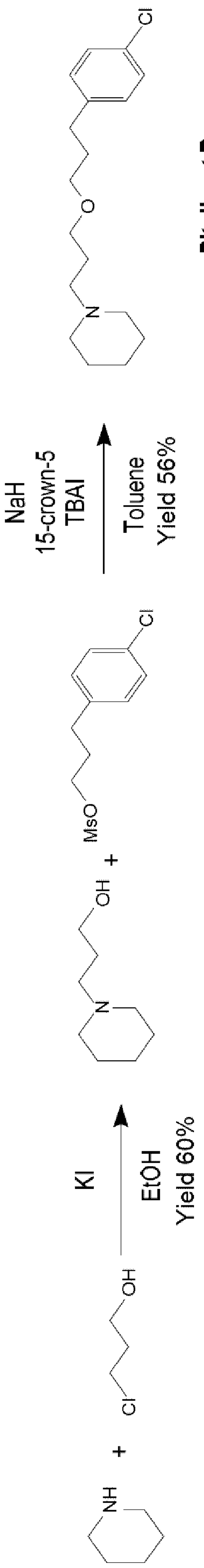
PROCESS FOR THE SYNTHESIS OF PITOLISANT HCl

The present invention relates to a process for the preparation of pitolisant hydrochloride.

BACKGROUND TO THE INVENTION

The known processes for the preparation of pitolisant HCl (**I**) are mainly characterised by multi-step reactions involving a number of drawbacks, such as poor cost-effectiveness and low yield (Eur. J. Pharm. Sci. 13 (2001) 249-259; WO200684833A1; WO200706708A1; CN103435575; CN104447620).

Eur. J. Pharm. Sci. 13 (2001) 249-259 describes a method for obtaining pitolisant base (**6**) from piperidine (**2**) and 3-chloropropanol (**3**), in the presence of potassium iodide, to give the intermediate 3-(piperidin-1-yl)propan-1-ol (**4**), which is used in the reaction with the commercially available compound 3-(4-chlorophenyl)propyl methanesulphonate (**5**) to obtain pitolisant base (**6**) (Scheme 1).



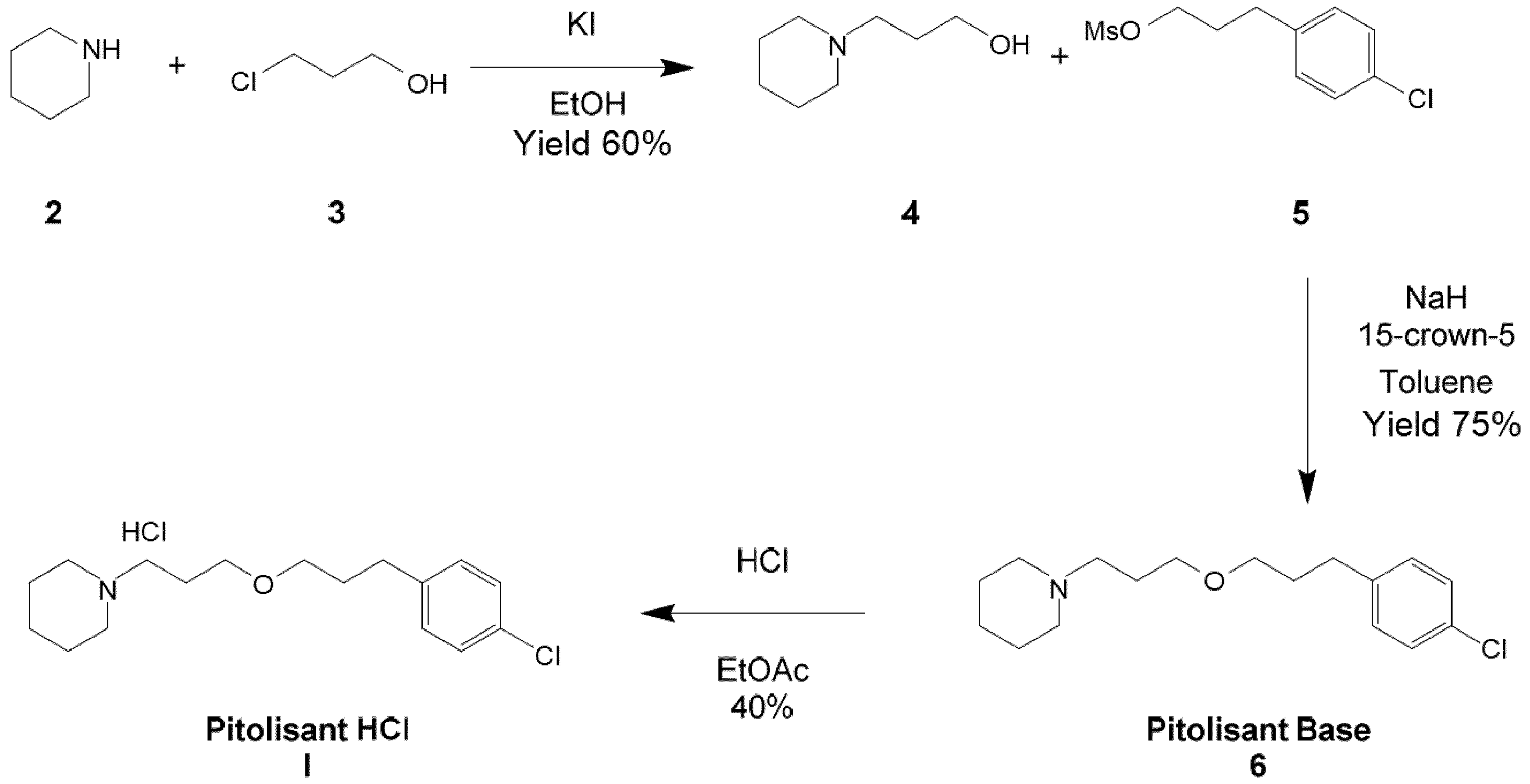
2 3 4 5

Pitolisant Base
6

Scheme 1

The yields of said process are low on the whole: 60% for the first step and 56% for the second. One disadvantageous aspect relates to the use of crown ether (15-crown-5) to promote the deprotonation of compound (**4**) by sodium hydride during the second step; said reagent is rather expensive, and it can be difficult to remove during the work-up steps. Moreover, the reagent 3-(4-chlorophenyl)propyl methanesulphonate (**5**), always used in the second step, has a very high cost. These two aspects make the process particularly disadvantageous.

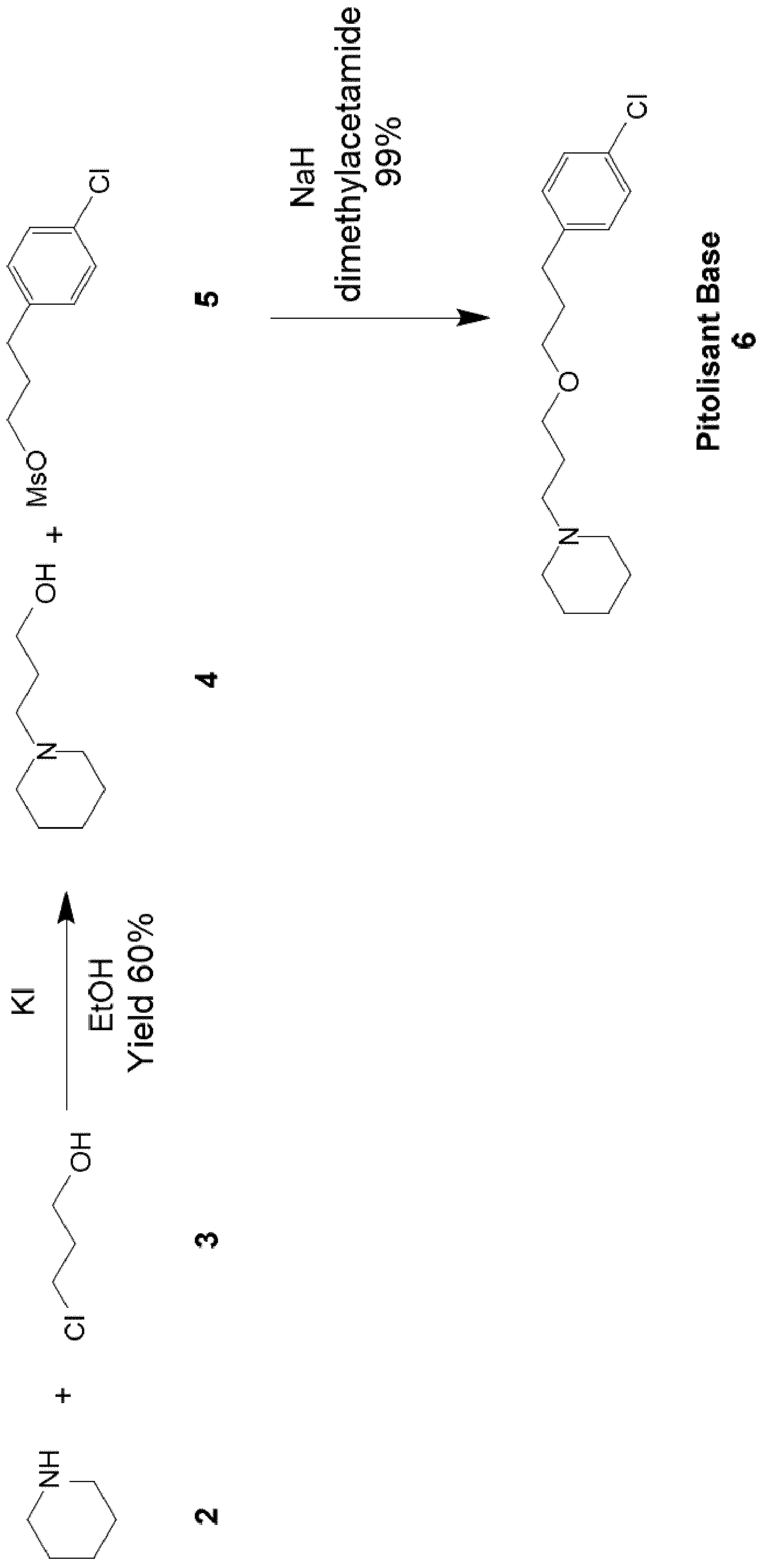
WO200684833A1 discloses a synthesis of pitolisant HCl (**I**) similar to that reported in Eur. J. Pharm. Sci. 13 (2001) 249–259. The process involves three steps, starting with piperidine (**2**) and 3-chloropropanol (**3**), to give the intermediate 3-(piperidin-1-yl)propan-1-ol (**4**), which is reacted with 3-(4-chlorophenyl)propyl methanesulphonate (**5**) to give pitolisant base (**6**), which is finally salified with gaseous hydrochloric acid to give pitolisant HCl (**I**), as reported in Scheme 2.


NH
Cl
OH
KI
EtOH
Yield 60%
N
OH
MsO
Cl
2
3
4
5
NaH
15-crown-5
Toluene
Yield 75%
HCl
N
O
Cl
HCl
EtOAc
40%
N
O
Cl
Pitolisant HCl
I
Pitolisant Base
6

Scheme 2

The economic drawbacks deriving from the use of crown ether (15-crown-5) and 3-(4-chlorophenyl)propyl methanesulphonate (**5**), as described above, are also present in this process, which is even more disadvantageous because of the low yield of the last step, not exceeding a total of 40%.

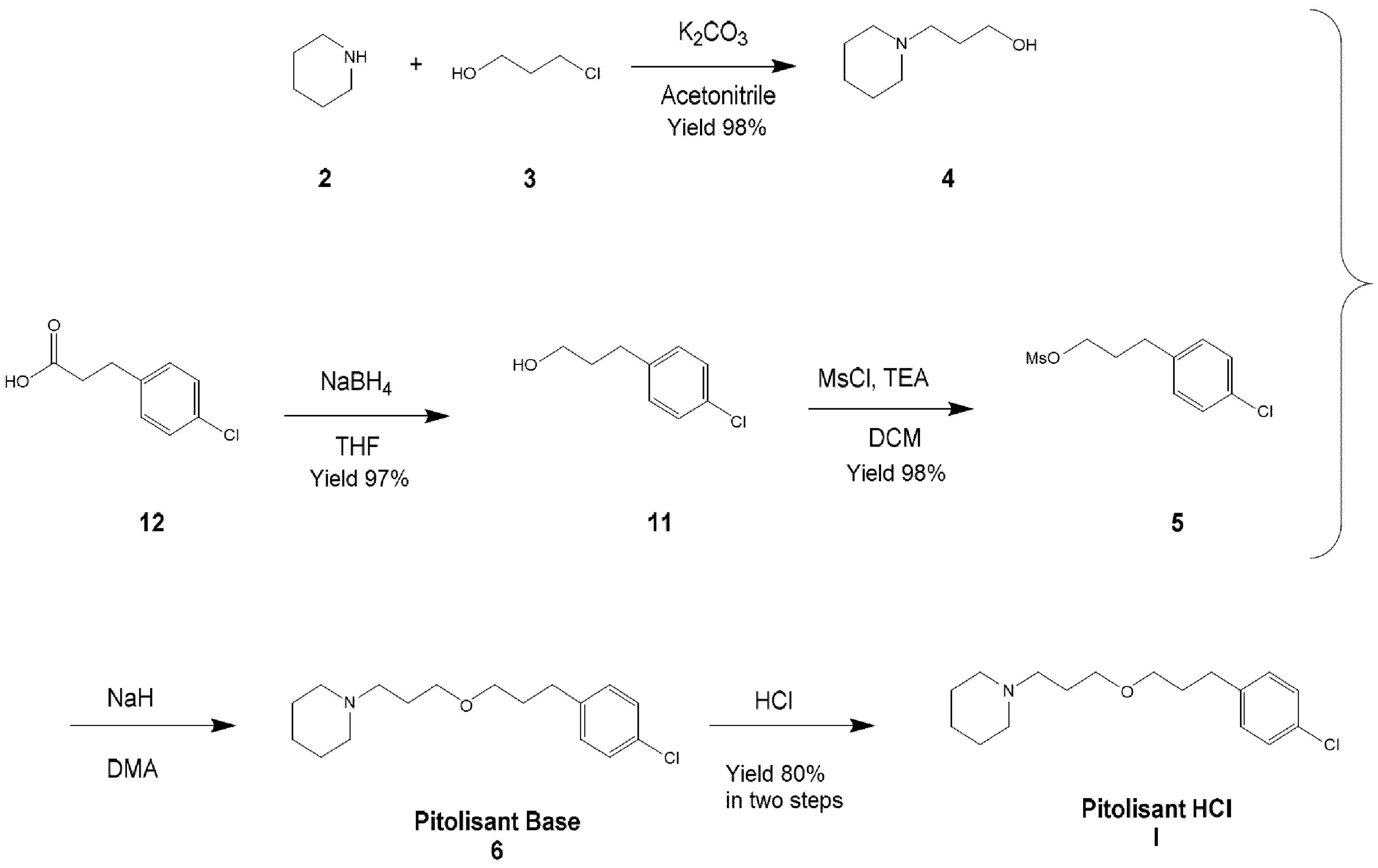
WO200706708 discloses the production of pitolisant base (**6**) in a very similar way to that reported in the two references cited above; the process involves a nucleophilic substitution reaction between 3-(piperidin-1-yl)propan-1-ol (**4**) and 3-(4-chlorophenyl)propyl methanesulphonate (**5**), to give pitolisant base (**6**) (Scheme 3).


2
3
KI
EtOH
Yield 60%
4
5
NaH
dimethylacetamide
99%
Pitolisant Base
6

Scheme 3

The significant drawbacks of this process relate to the use of the very expensive reagent 3-(4-chlorophenyl)propyl methanesulphonate (**5**) and the use of dimethylacetamide, the toxicity of which makes its use inadvisable during the final synthesis steps in the production of an active ingredient.

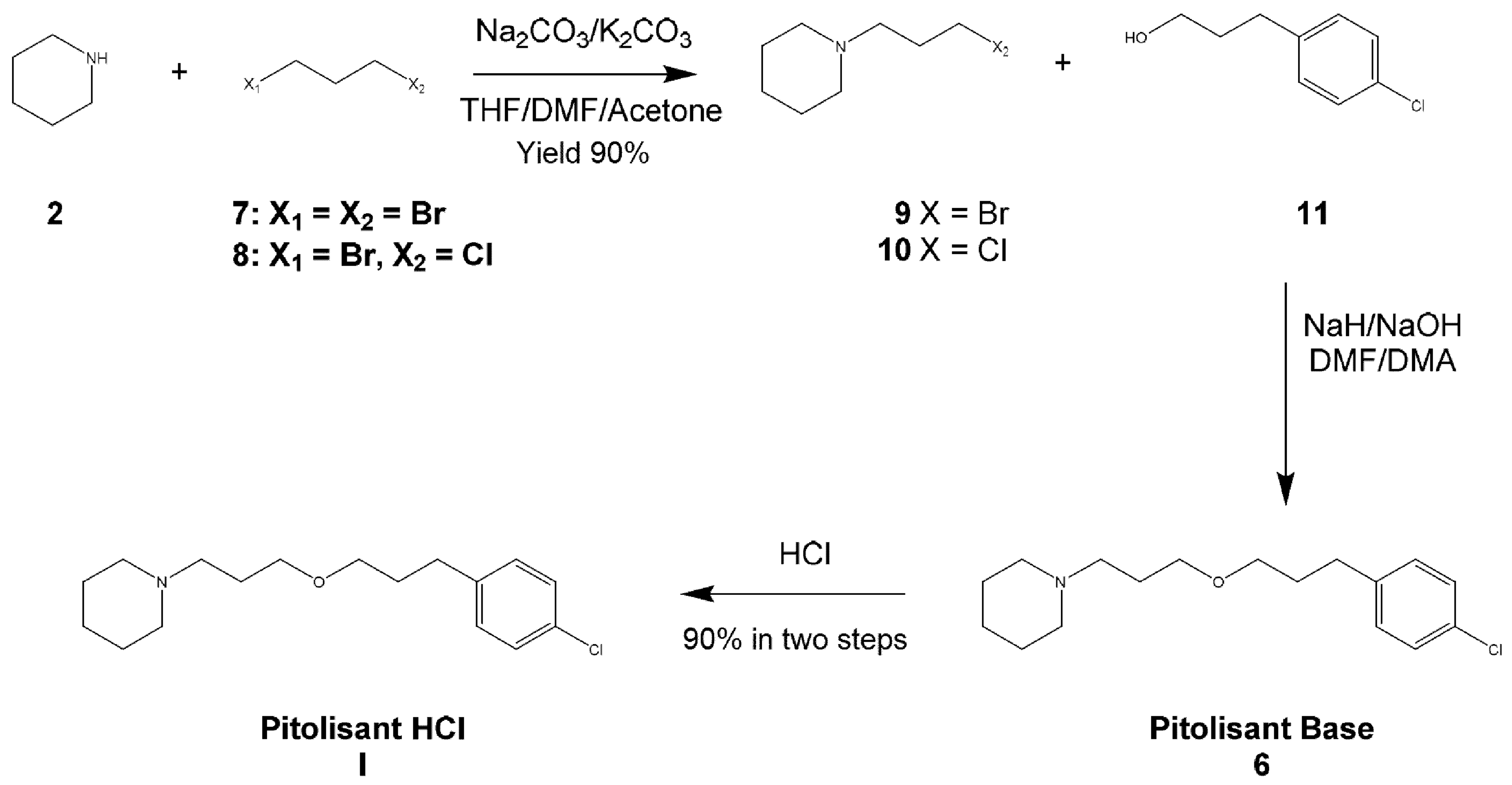
CN103435575 discloses the synthesis of pitolisant HCl (I) and production of the intermediate 3-(4-chlorophenyl)propyl methanesulphonate (**5**), starting from 3-(4-chlorophenyl)propanoic acid, as indicated in Scheme 4.


NH
+
HO
Cl
K2CO3
Acetonitrile
Yield 98%
N
OH
2
3
4
O
HO
Cl
NaBH4
THF
Yield 97%
HO
Cl
MsCl, TEA
DCM
Yield 98%
MsO
Cl
12
11
5
NaH
DMA
N
O
Cl
HCl
Yield 80%
in two steps
N
O
Cl
Pitolisant Base
6
Pitolisant HCl
I

Scheme 4

The main drawback of said process relates to the large number of steps, a total of five, which make the process unproductive and poorly cost-effective. Moreover, dimethylacetamide is also used in this case.

A further approach used in the synthesis of pitolisant HCl (**I**) disclosed in CN104447620 involves the synthesis of a bromo- (**9**) or chloro-substituted intermediate (**10**), which is subsequently used to generate pitolisant base (**6**) by nucleophilic substitution reaction with 3-(4-chlorophenyl)propan-1-ol (**11**), followed by salification to give pitolisant HCl (**I**) (Scheme 5).


NH
+
X1
X2
Na2CO3/K2CO3
THF/DMF/Acetone
Yield 90%
N
X2
+
HO
Cl
2
7: X1 = X2 = Br
8: X1 = Br, X2 = Cl
9 X = Br
10 X = Cl
11
NaH/NaOH
DMF/DMA
HCl
90% in two steps
N
O
Cl
Pitolisant HCl
I
Pitolisant Base
6

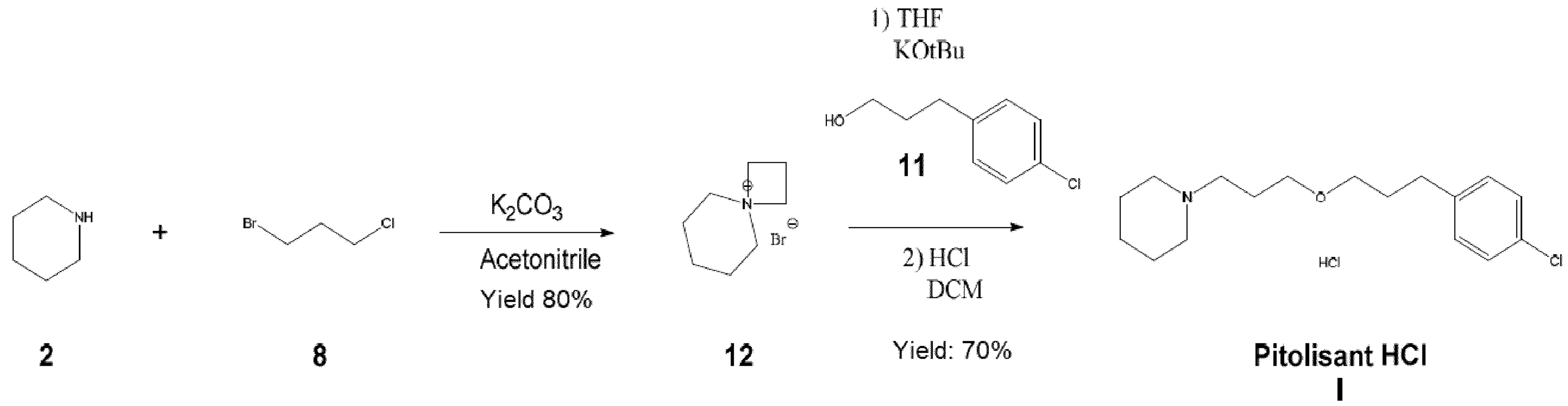
Scheme 5

One of the drawbacks of said process relates to the first step, because the reaction of piperidine (**2**) with a bis-halogen derivative can lead to the formation of dimeric by-products of the reaction which are difficult to remove during the work-up steps. A further drawback relates to the use of toxic solvents, such as dimethylformamide or dimethylacetamide, during the second step.

DESCRIPTION OF THE INVENTION

The object of the present invention is a novel process for the synthesis of pitolisant HCl (**I**) from piperidine (**2**) and 1-bromo-3-chloropropane (**8**). Both reagents are commercially available, and were reacted in such a way as to obtain the bromide salt of the spiro intermediate 4-azaspiro[3.5]nonan-4-ium (**12**; Scheme 6). Intermediate **(12)** is novel, and constitutes a further object of the invention.

Spiro derivative (**12**) undergoes selective opening by 3-(4-chlorophenyl)propan-1-ol (**11**), which is commercially available or easily obtainable by known procedures (CN103435575), in the presence of an inorganic base. The opening of spiro ring (**12**) is followed by a simple acid work-up that produces, in a single step with a high yield, pitolisant HCl (**I**), which can subsequently be purified by crystallisation or trituration.


NH
2
+
Br
Cl
8
K2CO3
Acetonitrile
Yield 80%
N
Br
12
1) THF
KOtBu
HO
Cl
11
2) HCl
DCM
Yield: 70%
N
O
HCl
Cl
Pitolisant HCl
I

Scheme 6

The process is cost-effective because piperidine and 1-bromo-3-chloropropane are readily available and very cheap. Moreover, the process according to the invention, unlike the procedures reported in WO200684833 and WO200706708, does not require the use of the extremely expensive compound 3-(4-chlorophenyl)propyl methanesulphonate (**5**); the process involves the use of 3-(4-chlorophenyl)propan-1-ol (**11**), which is not only much less expensive, but used in the last step with excellent yields.

DETAILED DESCRIPTION OF THE INVENTION

The spiro derivative 4-azaspiro[3.5]nonan-4-ium bromide (**12**) is synthesised from piperidine (**2**) and 1-bromo-3-chloropropane (**8**) with a high yield. The product is recovered by a simple work-up.

The process is conducted in the presence of an inorganic base easily removed by filtration, preferably selected from hydroxides or carbonates such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, potassium carbonate, sodium carbonate, calcium carbonate, calcium bicarbonate, caesium carbonate, potassium bicarbonate and sodium bicarbonate, preferably potassium carbonate.

The process is conducted in an inert environment, preferably in a nitrogen or argon atmosphere, at temperatures ranging from 20°C to 120°C, preferably from 30 to 90°C.

The solvents used can be aprotic apolar solvents such as n-heptane, toluene and xylene, or polar aprotic solvents such as acetone, acetonitrile, methyl isobutyl ketone, methyl ethyl ketone, dimethylformamide, dimethylsulphoxide, dimethylacetamide, n-butyl acetate, isobutyl acetate, tert-butyl acetate and tetrahydrofuran, preferably acetonitrile and xylene.

Opening of the spiro ring 4-azaspiro[3.5]nonan-4-ium bromide (**12**) by 3-(4-chlorophenyl)propan-1-ol (**11**) is effected by means of a nucleophilic addition reaction.

The process is conducted in the presence of an easily removable inorganic and/or organic base, preferably selected from hydroxides or carbonates such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, sodium hydride, potassium tert-butoxide, sodium tert-butoxide, potassium carbonate, sodium carbonate, calcium carbonate, calcium bicarbonate, caesium carbonate, potassium bicarbonate and sodium bicarbonate, preferably potassium tert-butoxide.

The process is conducted in an inert environment, preferably in a nitrogen or argon atmosphere, at temperatures ranging from 5°C to 70°C, preferably from 15 to 50°C.

The solvents used can be aprotic apolar solvents such as n-heptane, toluene and xylene, or polar aprotic solvents such as acetone, acetonitrile, methyl isobutyl ketone, methyl ethyl ketone, dimethylformamide, dimethylsulphoxide, dimethylacetamide, n-butyl acetate, isobutyl acetate, tert-butyl acetate, tetrahydrofuran and 2-methyl-tetrahydrofuran, preferably tetrahydrofuran.

Typically, 1 mole of 1-bromo-3-chloropropane (**8**) is dissolved in 2-50 volumes, preferably 2-25 volumes, of a suitable aprotic apolar solvent, preferably acetonitrile. 0.8-6 equivalents, preferably 0.8-4 equivalents, of an inorganic base, preferably potassium carbonate, are added to the resulting solution. The mixture is left under stirring for a time ranging from 0.5 to 2.5 hours, preferably from 0.5 to 2 hours, at a temperature ranging from +10 to +100°C, preferably from +30 to +90°C.

0.8-2 Equivalents, preferably 1.0-1.75 equivalents, of piperidine (**2**) are added, and the mixture thus obtained is conditioned until the reaction is complete. The resulting mixture is filtered and concentrated under vacuum until 4-azaspiro[3.5]nonan-4-ium bromide (**12**) is obtained.

1 mole of 3-(4-chlorophenyl)propan-1-ol (**11**) is then dissolved in 2-50 volumes, preferably 2-30 volumes, of a suitable polar aprotic solvent, preferably tetrahydrofuran. 0.8-6 equivalents, preferably 0.8-4.5 equivalents, of a suitable organic base, preferably potassium tert-butoxide, are added to the resulting mixture, followed by 0.8-5 equivalents, preferably 1-3 equivalents, of 4-azaspiro[3.5]nonan-4-ium bromide (**12**). The resulting mixture is conditioned to a temperature ranging from +10 to +100°C, preferably from +15 to 50°C, until the reaction is complete. The mixture undergoes a mild acid work-up, and the organic phase is concentrated under vacuum to obtain crude pitolisant HCl, which is purified by known methods.

Pitolisant HCl (**I**) is prepared during the work-up steps, and the end product can be purified by known crystallisation or trituration procedures.

The process disclosed is advantageous because it enables pitolisant HCl (**I**) to be obtained in only two steps; the process is easily scaled-up to an industrial scale, and is preferable to the known processes in terms of cost-effectiveness.

The invention will now be illustrated in detail by the following examples.

The order of addition of the solvents and reagents may differ from that reported below.

Example 1 - 4-azaspiro[3.5]nonan-4-ium bromide (**12**)

25.0 g of 1-bromo-3-chloropropane (0.165 moles) is dissolved in acetonitrile (100 mL). 22.7 g of potassium carbonate (0.165 moles) is then added. The resulting mixture is heated to 60°C, and left under stirring for 10 minutes. 10 g of piperidine (0.117 moles) is then added, and the mixture is left under stirring until the reaction is complete. The mixture is cooled and filtered under vacuum, and the solid filtrate is washed with acetonitrile (100 mL).

The organic phase is concentrated under vacuum to give 22 g of 4-azaspiro[3.5]nonan-4-ium bromide (**12**) (orange oil; yield: 92%).

^{1}H NMR (DMSO-d6) δ: 4.31 - 4.12 (m, 4H, 7, 9), 3.50 (t, J = 5.7 Hz, 4H, 4, 6), 2.47 (p, J = 8.3 Hz, 2H, 8), 1.67 (p, J = 5.7 Hz, 4H, 1, 3), 1.46 (p, J = 6.0 Hz, 2H, 2)

^{13}NMR (DMSO-d6) δ: 62.1, 59.8, 26.0, 20.8, 13.8.

Example 2 - Pitolisant HCl (**I**)

1.0 g of 3-(4-chlorophenyl)propan-1-ol (**11**) (5.8 mmols) is dissolved in tetrahydrofuran (10 mL). 0.72 g of potassium tert-butoxide (6.4 mmols) is then added. The resulting solution is stirred for 30 minutes, after which 1.8 g of 4-azaspiro[3.5]nonan-4-ium bromide (**12**) (8.8 mmol) is added, and the mixture is left under stirring until the reaction is complete. The mixture is cooled and diluted with dichloromethane (50 mL). The organic phase is then washed three times with 1N aqueous hydrochloric acid. The organic phase is concentrated under vacuum to give 1.75 g of crude pitolisant HCl (**I**) (pale yellow solid; yield: 90%). The crude pitolisant HCl (**I**) is purified by known methods.

^{1}H (chloroform-d) δ: 11.93 (s, 1H), 7.26 – 7.20 (m, 2H), 7.13 – 7.06 (m, 2H), 3.55 – 3.45 (m, 4H), 3.39 (t, J = 6.3 Hz, 2H), 3.06 – 2.94 (m, 2H), 2.70 – 2.55 (m, 4H), 2.35 – 2.10 (m, 4H), 1.83 (dddd, J = 12.9, 8.8, 5.3, 2.5 Hz, 5H), 1.41 (qt, J = 11.4, 3.1 Hz, 1H).

^{13}NMR (chloroform-d) δ: 140.3, 131.4, 129.8, 128.4, 70.2, 7.5, 55.5, 53.3, 31.8, 30.9, 24.1, 22.5, 22.

CLAIMS

1. A process for the synthesis of pitolisant HCl (**I**) which comprises:

   a). reacting piperidine and 1-bromo-3-chloropropane in the presence of an inorganic base to give 4-azaspiro[3.5]nonan-4-ium bromide (**12**);

   b). reacting 4-azaspiro[3.5]nonan-4-ium bromide (**12**) with 3-(4-chlorophenyl)propan-1-ol in the presence of an inorganic base and treating with hydrochloric acid.

2. The process according to claim 1 wherein the inorganic base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, potassium carbonate, sodium carbonate, calcium carbonate, calcium bicarbonate, caesium carbonate, potassium bicarbonate and sodium bicarbonate, preferably potassium carbonate.

3. The process according to claim 1 or 2 wherein step a is effected under nitrogen or argon atmosphere at temperatures ranging from 20°C to 120°C, preferably from 30 to 90°C, in an apolar or polar aprotic solvent.

4. The process according to claim 3 wherein the solvents are selected from n-heptane, toluene, xylene, acetone, acetonitrile, methyl isobutyl ketone, methyl ethyl ketone, dimethylformamide, dimethylsulphoxide, dimethylacetamide, n-butyl acetate, isobutyl acetate, tert-butyl acetate and tetrahydrofuran, preferably acetonitrile and xylene.

5. The process according to any one of claims 1-4 wherein step b) is effected under nitrogen or argon atmosphere at temperatures ranging from 5°C to 70°C, preferably from 15 to 50°C, in an apolar or polar aprotic solvent.

6. The process according to claim 5 wherein the solvents are selected from n-heptane, toluene, xylene, acetone, acetonitrile, methyl isobutyl ketone, methyl ethyl ketone, dimethylformamide, dimethylsulphoxide, dimethylacetamide, n-butyl acetate, isobutyl acetate, tert-butyl acetate, tetrahydrofuran and 2-methyl-tetrahydrofuran, preferably tetrahydrofuran.

7. 4-Azaspiro[3.5]nonan-4-ium bromide (**12**).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/071581

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D295/088 C07D471/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/006708 A1 (FERRER INT [ES]; SALLARES JUAN [ES] ET AL.) 18 January 2007 (2007-01-18) cited in the application claim 1 -----	1-7
A	CN 104 447 620 A (REYOUNG PHARMACEUTICAL CO LTD) 25 March 2015 (2015-03-25) cited in the application paragraph [0022] -----	1-7
A	CN 103 435 575 A (INST PHARM & TOXICOLOGY AMMS) 11 December 2013 (2013-12-11) cited in the application paragraph [0052] -----	1-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search 14 October 2020	Date of mailing of the international search report 27/10/2020
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/071581

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007006708 A1	18-01-2007	AR 054530 A1	27-06-2007
		EP 1910323 A1	16-04-2008
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