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(12) (19) (CA) **Demande-Application**

(21) (A1) **2,314,988**
(86) 1998/12/15
(87) 1999/07/01

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(51) Int.Cl.[6] C07C 217/20, A61K 31/135
(30) 1997/12/22 (9704834-2) SE

(54) **PROCEDE DE PREPARATION D'ISOPROPYLMETHYL-[2-(3-N-PROPOXYPHENOXY)ETHYL]AMINE**

(54) **PROCESS FOR THE PREPARATION OF ISOPROPYL-METHYL-[2-(3-N-PROPOXYPHENOXY)ETHYL]AMINE**

(57) La présente invention concerne un nouveau procédé de synthèse d'isopropylméthyl-[2-(3-n-propoxyphénoxy)éthyl]amine. En outre, la présente invention concerne un nouvel intermédiaire et une étape de purification facultative faisant partie du nouveau procédé. La présente invention concerne également la production d'une composition pharmaceutique contenant de l'isopropylméthyl-[2-(3-n-propoxyphénoxy)éthyl]amine et l'utilisation d'isopropylméthyl-[2-(3-n-propoxyphénoxy)éthyl]amine purifiée en médecine.

(57) The present invention relates to a novel process for the synthesis of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. Moreover, the present invention also relates to a novel intermediate and an optional purification step in the novel process. Additionally, the present invention also relates to the manufacture of a pharmaceutical formulation containing isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine and the use of purified isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in medicine.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 217/20, A61K 31/135 — **A1**

(11) International Publication Number: WO 99/32430

(43) International Publication Date: 1 July 1999 (01.07.99)

(21) International Application Number: PCT/SE98/02315

(22) International Filing Date: 15 December 1998 (15.12.98)

(30) Priority Data:
9704834-2 22 December 1997 (22.12.97) SE

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF ISOPROPYL–METHYL–[2–(3–N–PROPOXYPHENOXY)ETHYL]AMINE

(57) Abstract

The present invention relates to a novel process for the synthesis of isopropyl–methyl–[2–(3–n–propoxyphenoxy)ethyl]amine. Moreover, the present invention also relates to a novel intermediate and an optional purification step in the novel process. Additionally, the present invention also relates to the manufacture of a pharmaceutical formulation containing isopropyl–methyl–[2–(3–n–propoxyphenoxy)ethyl]amine and the use of purified isopropyl–methyl–[2–(3–n–propoxyphenoxy)ethyl]amine in medicine.

PROCESS FOR THE PREPARATION OF ISOPROPYL-METHYL-[2-(3-N-PROPOXYPHENOXY)ETHYL]AMINE

Field of the invention

The present invention relates to a novel process for the synthesis of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. Moreover, the present invention also relates to a novel intermediate and an optional purification step in said process. Additionally, the present invention also relates to the manufacture of a pharmaceutical formulation containing isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine and the use of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in medicine.

Background of the invention and prior art

Isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is a compound with anaesthetic properties. It is useful as a topical local anaesthetic for the treatment of pain, including localised pain, and especially on intact skin.

WO 9715548 discloses a process for the preparation of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. Said process comprises a couple of reaction steps starting with reacting 3-n-propoxyphenol with 1,2-dibromoethane resulting in 1-(2-bromoethoxy)-3-n-propoxybenzene. Further, 1-(2-bromoethoxy)-3-n-propoxybenzene is reacted with N-methylisopropylamine in an autoclave. The product, isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, was thereafter further purified by distillation *in vacuo*.

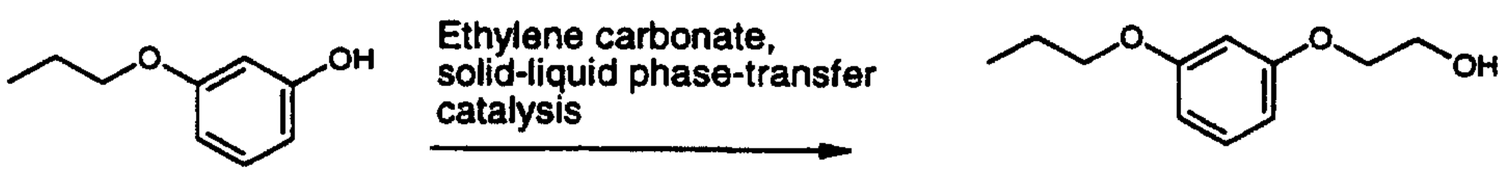
Summary of the Invention

The object of the present invention is to provide a new process for the preparation of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine suitable for full scale production.

Scheme 1 below describes the main reaction steps in the manufacture of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine starting from 3-propoxyphenol. The starting material as well as the reactants used, are readily available through processes known in the art.

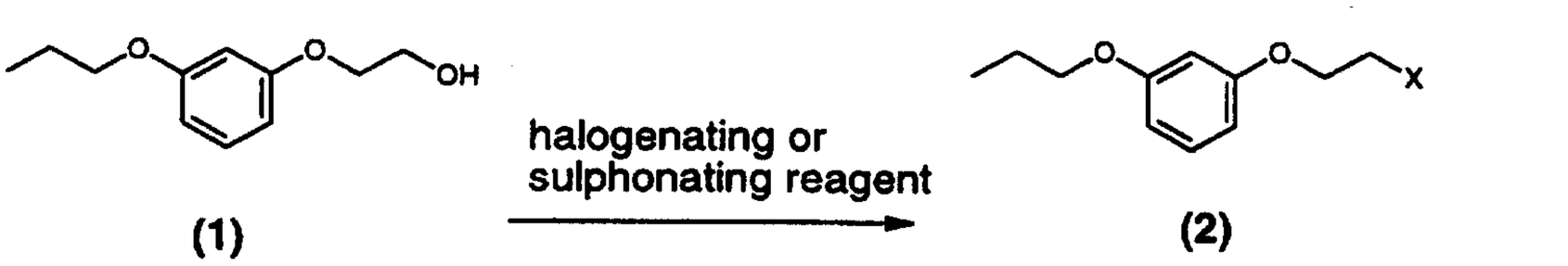
Scheme 1

Step 1



(1)

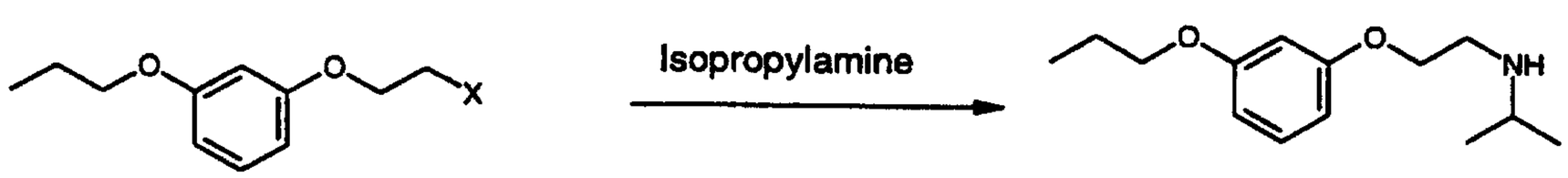
Step 2



(1) (2)

X = halogen or sulphonate ester

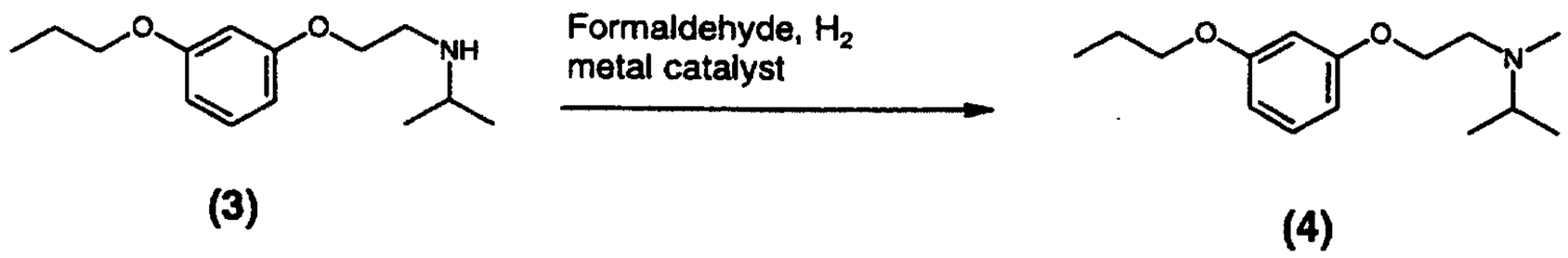
Step 3



(2) (3)

X = halogen or sulphonate ester

Step 4



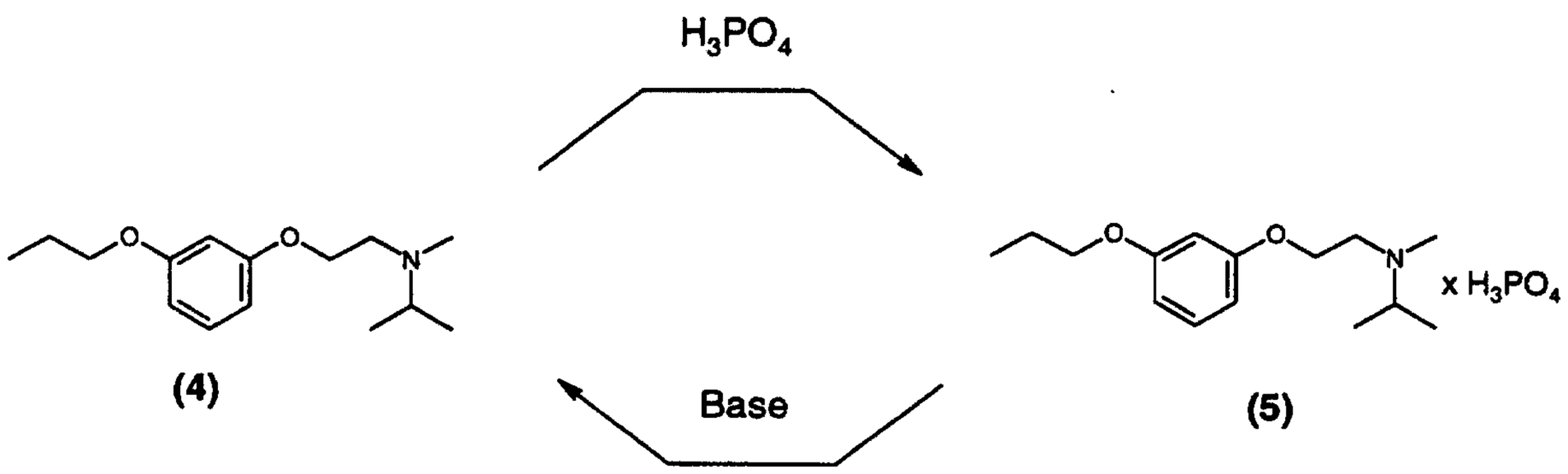
(3) (4)

Advantages of the improved process of the present invention are disclosed in the following paragraphs.

Another object of the present invention is to provide a process utilizing reagents and solvents that are environmentally friendly. There is a general interest from environmental groups both inside and outside the pharmaceutical industry that the industry shall develop and use environmentally friendly processes. The process of the present invention does not use any mutagenic alkylating agents, such as 1,2-dibromoethane, which is used in processes according to prior art. One object of the present invention is therefore to provide a process for the manufacture of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine wherein the use of 1,2-dibromoethane is avoided. 1,2-dibromoethane is a known mutagenic compound and its use should therefore, if possible, be limited. This is especially true in full scale production.

Another object of the present invention is to provide a new and optional purification of crude isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. We have surprisingly found that the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is a crystalline compound. The optional purifaction step is shown in Scheme 2.

Scheme 2



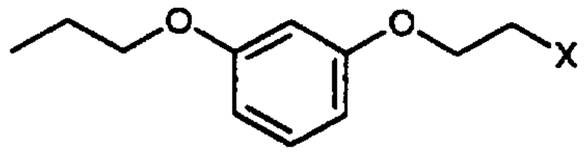
In Step 1, 3-propoxy-phenol is reacted with ethylene carbonate using solid-liquid phase-transfer catalysis conditions. The reaction is preferably carried out at 60-120°C and for a prolonged period of time. The reaction is preferably carried out in an organic solvent, such as an aprotic organic solvent or xylene. Examples of such aprotic organic solvents include, but are not limited to, DMF, and 1-methyl-2-pyrrolidinone. 1-Metyl-2-pyrrolidinone is the preferred aprotic organic solvent. Optionally, the reaction is carried out without any additional organic solvent. The amount of ethylene carbonate used is 1-4 molar equivalents, preferably 2-3 equivalents. The solid-liquid phase-transfer catalysis conditions are created using a solid, non-soluble base and a phase-transfer catalyst. The amount of base and phase-transfer catalyst are not crucial and can therefore be varied according to procedures known in the art. The base and the phase-transfer catalyst can be any suitable base and phase-transfer catalyst known in the art to create solid-liquid phase-transfer catalysis conditions. Examples of suitable bases include, but are not limited to, sodium carbonate, sodium hydrogencarbonate, potassium carbonate and potassium hydrogencarbonate. Potassium carbonate is the preferred base. Examples of suitable phase-transfer catalysts include, but are not limited to, tetrabutyl ammonium iodide, tetrabutyl ammonium hydrogensulphate, and tetrabutyl ammonium bromide. Tetrabutyl ammonium bromide is the preferred phase-transfer catalyst.

The phase-transfer catalyst used in step 1, can be replaced by a compound which has as an intrinsic property to function as a phase-transfer catalysts under the conditions used in Step

1. . Examples of such compounds include, but are not limited to, polyethyleneglycol (PEG), e.g. PEG 6000.

After complete reaction, the reaction mixture is cooled, diluted with water and extracted with a suitable organic solvent, such as xylene or methyl tert-butyl ether. The organic phase is concentrated and the crude 2-(3-propoxy-phenoxy)-ethanol is purified by means of distillation.

In step 2, the 2-(3-propoxy-phenoxy)-ethanol formed in Step 1 above, is further reacted with a suitable reagent to produce a compound of formula 2,



(2)

wherein X is a bromine, chlorine, iodine or a sulphonate ester group. Examples of sulphonate esters include, but are not limited to, alkane- and arylsulphonate ester, e.g. methanesulphonate, ethanesulphonate, p-toluenesulphonate, p-bromophenylsulphonate. Preferred compounds of formula 2 are sulphonate esters. Examples of reagents capable of producing preferred compounds of formula 2 include, but are not limited to, methanesulphonyl chloride, ethanesulphonyl chloride, p-toluenesulphonyl chloride and p-bromosulphonyl chloride.

In Step 3, the compound of formula 2 in an organic solvent, such as methyl tert-butyl ether or toluene, is further reacted with isopropylamine in the presence of water. The reaction is performed at elevated temperature, preferably 60-110°C, for a prolonged period of time and under increased pressure, preferably 1-10 atmospheres. Isopropylamine should be added at an excess, such as 2 to 6 equivalents, preferably 3-4 equivalents. Optionally an additional and non-nucleophilic base, such as potassium or sodium carbonate, can be added to the reaction mixture. The amount of water present in the reaction mixture is not crucial

and can optionally be omitted. The reaction mixture is thereafter cooled and aqueous acid is added under vigorous stirring until the pH of the aqueous phase reaches a constant value of 3-5, preferably 3-3.5. The aqueous phase is separated, washed with methyl tert-butyl ether or toluene and thereafter used without any further purification in the subsequent step.

In Step 4, the acidic aqueous solution of isopropyl-[2-(3-propoxy-phenoxy)-ethyl]-amine prepared in Step 3 above, is reacted with formaldehyde in the presence of palladium on charcoal. The reaction mixture is hydrogenated at atmospheric pressure or above, such as 1-6 bars, for several hours. The amount of formaldehyde is not crucial, but can be between 1-10 equivalents, by weight. The amount of palladium on charcoal used is 0.01 to 0.5 molar equivalents, preferably 0.05-0.2. The reaction mixture is thereafter treated with aqueous base, such as sodium hydroxide, to pH ~12 and extracted with methyl tert-butyl ether. The organic phase is separated and distillation gives pure isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine.

Surprisingly, we have been able to crystallize isopropyl-methyl-[2-(3-n-propoxyphenoxy)-ethyl]amine from the reaction mixture in step 4, by converting it to the corresponding monophosphate salt. The monophosphate salt of isopropyl-methyl-[2-(3-n-propoxy-phenoxy)ethyl]amine is a crystalline and stable salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine and therefore has advantageous properties. The introduction of a crystalline intermediate in the process for the preparation of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is advantageous. It introduces a simple and convenient optional and additional purification step in a reaction sequence where all intermediates are syrups. Thereby, the time and energy consuming distillation used in processes according to prior art is avoided. The crystallization of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine results in an intermediate of a high purity that can be further converted to the corresponding isopropyl-methyl-[2-(3-n-propoxy-phenoxy)ethyl]amine by a simple alkalization step.

In the optional purification step, the content of crude isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in ethyl acetate is first assayed and adjusted to 6-10 ml ethyl acetate per gram of crude isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, prepared in Step 4 above. The content of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in ethyl acetate is preferably 7-9 ml ethyl acetate per gram of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. To the assayed solution of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, methanol and a solution of phosphoric acid in methanol are added. The amount of phosphoric acid should be around 0.9 to 1.0 molar equivalents, preferably 0.95 equivalents. The total amount of methanol added to the assayed solution should be adjusted to the amount of phosphoric acid used. The concentration of phosphoric acid in the resulting solution of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in a mixture of methanol and ethyl acetate should be around 5-15%, by volume, preferably 9-11%, by volume. The precipitated salt is collected, for example by filtration or centrifugation, and thereafter washed with ethyl acetate.

The monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, prepared above, is thereafter mixed with water and aqueous sodium hydroxide is added to pH ~11.5. Methyl tert-butyl ether, or other suitable solvent, is added and the two phases are separated. The organic phase is washed with water and concentrated yielding pure isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine.

The final distillation of crude isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, prepared by step 4 above, may be replaced by the optional purification step, *i.e.* the preparation of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. Under those circumstances the alkaline aqueous phase containing the crude isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine will preferably be extracted with ethyl acetate instead of methyl tert-butyl ether. The prepared monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine can thereafter be converted to the corresponding isopropyl-methyl-[2-(3-n-propoxy-

phenoxy)ethyl]amine by a simple alkalization step. The mode of procedure can easily be made by a technician.

The present invention is described in more detail in the following non-limiting examples. Roman numerals are referring to Scheme 1 and 2.

Examples

Example 1

2-(3-Propoxy-phenoxy)-ethanol (1)

To 3-propoxyphenol (17.9 kg, 117.4 mol) was added ethylene carbonate (20.7 kg, 234.8 mol), K_2CO_3 (17.9 kg, 126.7 mol), tetrabutylammonium bromide (3.8 kg, 11.5 mol) and 1-methyl-2-pyrrolidinone (56.5 L). The mixture is heated to ca 90°C for about 10 hours, then cooled to 45°C where water (132 L) followed by methyl tert-butyl ether (82 L) are added. The phases are separated and the organic phase is washed with 0.5 M HCl (aq) followed by 0.5 M $NaHCO_3$ (aq). The organic phase is concentrated under reduced pressure and the crude **1** is purified by means of distillation, 150°C/0.95 mbar, yielding **1** (17.9 kg) as an oil with a chromatographic purity over 97 %.

MS (EI): 196 (34), 153 (13), 152 (7), 135 (4), 111 (67), 110 (100). ^{1}H NMR (200 MHz): δ 7.15 (t, 1 H), 6.5 (m, 3 H), 4.0 (m, 2 H), 3.9 (m, 4 H), 2.5 (s, 1 H), 1.79 (m, 2 H), 1.0 (t, 3 H). ^{13}C NMR (50 MHz): δ 160.4, 159.8, 129.9, 107.2, 106.7, 101.6, 69.5, 69.2, 61.4, 22.6, 10.5.

Methanesulphonic acid 3-propoxy-phenoxyethyl ester (2)

1 (17.9 kg, 91.0 mol) dissolved in methyl tert-butyl ether (83 L) and triethylamine (15.2 L, 108.1 mol) is allowed to react with MsCl (7.7 L, 99.12 mol). The resulting slurry is

allowed to stand at ambient temperature for about 2 hours, water is added, the phases are separated and the organic phase is used as is in the subsequent step.

MS (EI): 274 (55), 232 (7), 195 (1), 153 (6), 135 (16), 123 (100), 110 (66), 79 (64).

Isopropyl-[2-(3-propoxy-phenoxy)-ethyl]-amine (3)

To the solution of **2** are added K_2CO_3 (14.0 kg, 98.1 mol), isopropylamine (36.2 L, 455.9 mol) and water (31 L). The mixture is heated to 90°C for 16 hours with the reactor sealed resulting in a pressure of about 2 bar. The reaction mixture is cooled to ambient temperature, the aqueous phase is discarded and the organic phase is washed with water. To the organic phase is then added 0.5 M H_2SO_4 (aq) to pH~3.5 and the phases are separated. The aqueous phase is washed with methyl tert-butyl ether and used as is in the subsequent step.

MS (EI): 237 (7), 222 (34), 194 (1), 135 (7), 85 (80), 72 (100). ^{1}H NMR (200 MHz): δ 7.1 (m, 1 H), 6.5 (m, 3 H), 4.1 (t, 2 H), 3.9 (t, 2 H), 3.0 (t, 2 H), 2.9 (m, 2 H), 1.9 (m, 2 H), 1.6 (m, 1 H), 1.0 (d + t, 9 H). ^{13}C NMR (50 MHz): δ 160.4, 160.1, 129.8, 107.0, 106.6, 101.5, 69.5, 67.6, 48.5, 46.5, 23.0, 22.6, 10.5.

Isopropyl-methyl-[2-(3-propoxy-phenoxy)-ethyl]-amine (4)

To the acidic aqueous solution of **3** are added wet 10 % palladium on charcoal (5.2 kg, 41.1 % Pd/C) and 37% formaldehyde (20.3 L, 270.2 mol). The mixture is hydrogenated at 3 bar for about 4 hours. The reaction mixture is treated with conc. NaOH to pH~12, The solids are filtered off and the resulting two phase system is extracted with EtOAc. The phases are separated and the organic phase is washed with water and thereafter concentrated. The residue is distilled at 128-130°C/0.3 mbar to yield pure isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine (18.1 kg, 72.1 mol).

Optional purification of crude isopropyl-methyl-[2-(3-propoxy-phenoxy)-ethyl]-amine.

To a solution of crude **4** (19.0 kg, 75.7 mol) in ethyl acetate (8 ml ethyl acetate per gram **4**) is added MeOH (9.6 L) followed by H_3PO_4 (4.85 L, 72.5 mol) dissolved in MeOH (19.2 L) over 3 hours at ambient temperature. The resulting slurry of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is then isolated by filtration and the solid material is washed with EtOAc. The wet product (41.8 kg, 67.6 mol, 89 % yield) with a chromatographic purity over 99 % is used as is in the subsequent step.

Mp: 131-134°C.

The content of H_3PO_4 is 27.8 % (w/w) which corresponds to a 1:1 molar ratio between **5** and H_3PO_4 (28.0 % w/w theoretical value).

The wet product (41.8 kg, 67.6 mol) is mixed with water purified (66 L) and conc. NaOH is added to pH~11.5 and the resulting two phase mixture is extracted with methyl tert-butyl ether. The phases are separated, the organic phase is washed with water purified and then concentrated under reduced pressure. The residual solvents are finally stripped off using a thin film evaporator, affording isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine (14.28 kg, 56.67 mol) as an oil with a chromatographic purity over 99 %.

MS (EI): 251 (10), 236 (9), 86 (100). ^{1}H NMR (400 MHz): δ 7.1 (m, 1 H), 6.5 (m, 3H), 4.0 (t, 2 H), 3.9 (t, 2 H), 2.9 (m, 1 H), 2.8 (t, 2 H), 2.3 (s, 3 H), 1.8 (m, 2 H), 1.0 (d + t, 9 H).

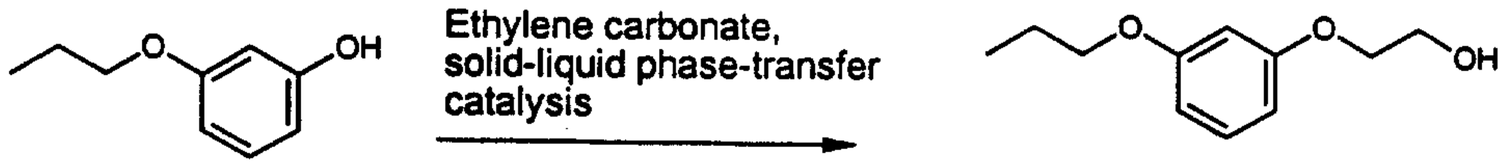
^{13}C NMR (50 MHz): δ 160.3, 160.1, 129.7, 106.9, 106.5, 101.4, 69.4, 66.8, 54.0, 51.7, 38.2, 22.5, 17.9, 10.5.

Found %: C, 71.5; H, 10.3; N, 5.7; O, 12.5. Calculated %: C, 71.67; H, 10.02; N, 5.57; O, 12.73.

Claims

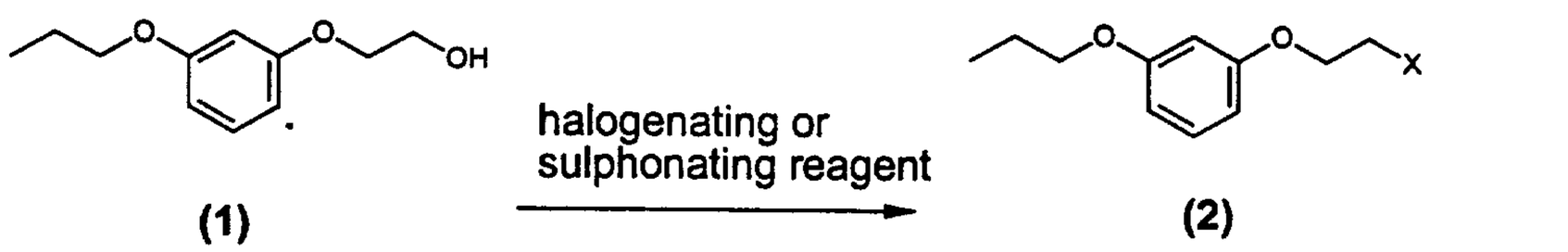
1. A process for the preparation of isopropyl-methyl-[2-(3-propoxy-phenoxy)-ethyl]-amine comprising the following reaction steps;

Step 1



(1)

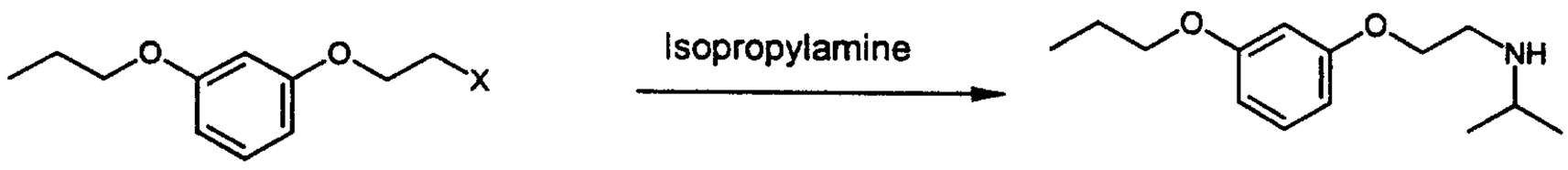
Step 2



(1) (2)

X = halogen or sulphonate ester

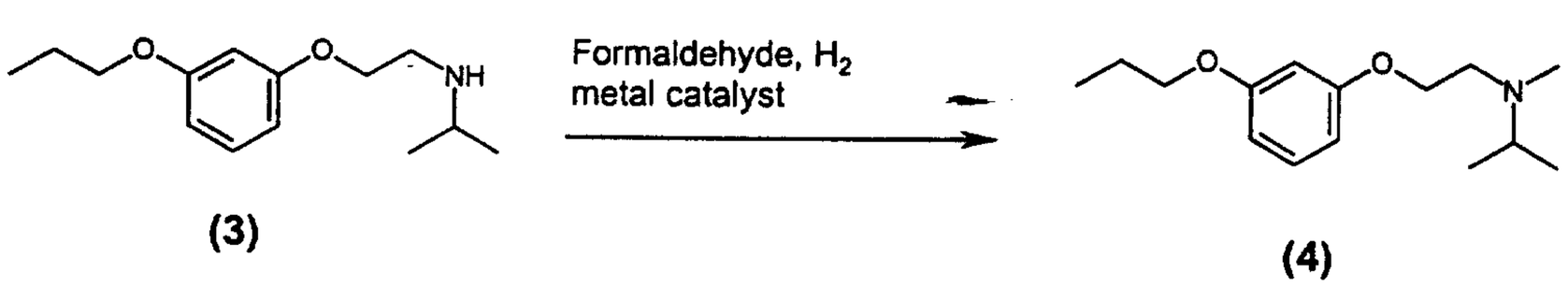
Step 3



(2) (3)

X = halogen or sulphonate ester

Step 4



(3) (4)

2. A process according to claim 1 characterized in that a solid insoluble base and a phase-transfer catalyst is used in Step 1.

3. A process according to claim 2, characterized in that the base is sodium carbonate, potassium carbonate, sodium hydrogen carbonate, or potassium hydrogencarbonate.

4. A process according to claim 2, characterized in that the phase-transfer catalyst is PEG 6000, tetrabutyl ammonium bromide, tetrabutyl ammonium hydrogen sulphate, or tetrabutyl ammonium iodide.

5. A process according to claim 1, characterized in that Step 1 is performed in an aprotic organic solvent.

6. A process according to claim 5, characterized in that aprotic organic solvent is 1-metyl-2-pyrrolidinone.

7. A process according to claim 1, characterized in that X is a bromine, chlorine, iodine, methanesulphonate, p-toluenesulphonate or p-bromophenylsulphonate group.

8. A process according to claim 1, characterized in that Step 3 is performed at a pressure above atmospheric pressure.

9. A process according to claim 1, characterized in that Step 3 is performed at a pressure between 1-10 bar.

10. A process according to claim 1, characterized in that Step 3 is performed at elevated temperature.

11. A process according to claim 1, characterized in that Step 3 is performed at 60-110°C.

12. A process according to claim 1, characterized in that Step 3 is performed with an additional base present in the reaction mixture.

13. A process according to claim 1, characterized in that Step 3 in performed with water present as a solvent.

14. A process according to claim 1, characterized in that the metal catalyst in Step 4 is palladium.

15. A process according to claim 10, characterized in that the palladium is supported on charcoal.

16. A process according to claim 1, characterized in that the formaldehyde in Step 4 is added as an aqueous solution of formaldhyde.

17. Isopropyl-[2-(3-propoxy-phenoxy)-ethyl]-amine.