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(54) Title: PREPARATION OF 1-BUTYL-4-PIPERIDINYLMETHYLAMINE

(57) Abstract

A process for the preparation of 1-butyl-4-piperidinylmethylamine, which process comprises: i) the reaction of isonipecotamide and 1-bromobutane to give the N-butyl derivative of isonipecotamide; followed by ii) reduction with $LiAlH_4$, characterised in that the reactions i) and ii) are carried out in toluene as solvent.

Preparation of 1-butyl-4-piperidinylmethylamine

This invention relates to a new synthetic process to an intermediate which is useful for the preparation of compounds having pharmacological activity.

WO 93/03725, WO 93/05038, WO 93/08187, WO 93/16072, WO 93/18027, WO 93/18036, WO 94/07859, WO 94/08965, WO 94/08994, WO 94/08995, WO 94/08998, WO 94/17071 (SmithKline Beecham plc) describe compounds having 5-HT_4 receptor antagonist activity.

WO 93/18036, Example 3 describes N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide SB 207266, (the hydrochloride salt is SB 207266-A) which is being developed by SmithKline Beecham plc as the active ingredient in a medicament for treatment of irritable bowel syndrome.

WO 93/18036 describes a method of preparation of SB 207266-A from N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide (i.e. the compound corresponding to SB 207266, without the oxazino moiety), by reacting with N-chlorosuccinimide and 3-bromo-1-propanol, followed by treatment with sodium carbonate. N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide is prepared by coupling 1-butyl-4-piperidinylmethylamine with indole-3-carboxylic acid. The 1-butyl-4-piperidinylmethylamine is prepared as in Description 7 of WO 93/05038 and Description 1 of WO 93/18036, in a three stage process from isonipecotamide and 1-bromobutane, by alkylation in ethanol, to give the N-butyl derivative of isonipecotamide which is dehydrated to the corresponding nitrile and then reduced with $LiAlH_4$ in ether.

An alternative process for preparing 1-butyl-4-piperidinylmethylamine has now been discovered which involves the use of a common solvent, allowing the two stages to be run without isolation of the N-butyl derivative of isonipecotamide.

Accordingly, the present invention provides a process for the preparation of 1-butyl-4-piperidinylmethylamine, which process comprises:

i) the reaction of 4-piperidinecarboxamide ("isonipecotamide") and 1-bromobutane to give the N-butyl derivative of 4-piperidinecarboxamide; followed by

ii) reduction with $LiAlH_4$,

characterised in that the reactions i) and ii) are carried out in toluene as solvent.

The advantages of this process as compared with that previously described are as follows:

1. Toluene does not contain any additives, whereas THF contains a stabiliser (di-*t*-butylcresol) which can only be removed from 1-butyl-4-piperidinylmethylamine by fractional distillation.

2. The overall process does not involve the preparation/isolation of the intermediate nitrile, and is therefore one step shorter.

3. The process does not involve the isolation of the N-butyl derivative of isonipecotamide.

4. The process uses a single solvent and eliminates the use of ethanol, chloroform and THF.

5. the special extractive work-up of the $LiAlH_4$ reaction reduces the usage of solvent and loss of product on solid alumina residues.

The following Examples illustrate the invention.

Example 1

4-Piperidinecarboxamide (*iso*-nipecotamide) and potassium carbonate (2 equivs.) were stirred in toluene and treated with 1-bromobutane (1 equiv.). The reaction mixture was heated at reflux (107-110°C) for 2 hours. After cooling to 80-85°C the mixture was washed with hot water followed by hot aqueous potassium carbonate solution. The resulting toluene solution of 1-butyl-*iso*-nipecotamide was dried by azeotropic distillation, maintaining the reaction volume by addition of fresh toluene.

The toluene solution was cooled to 0-5°C, under nitrogen. A solution of $LiAlH_4$.2THF in toluene (1.0 molar solution; 2.0 equivs.) was added over 1 hour, keeping the temperature <10°C. The mixture was allowed to warm to room temperature and was then heated to reflux for 1 hour. After cooling to 0-5°C, 32% w/w sodium hydroxide solution (1.5 equivs. wrt substrate) was added cautiously over 1 hour, keeping the temperature <10°C. The mixture was stirred for 30 minutes at ambient temperature and the precipitate filtered through celite, washing the bed thoroughly with toluene. The filtrate was evaporated *in vacuo* to give 1-butyl-4-piperidinylmethylamine as a pale yellow oil, containing ~13% by weight toluene, in 72% yield (after adjusting for toluene content).

Example 2

Alternatively the first part of the preparation may be carried out as follows:

4-Piperidinecarboxamide (*iso*-nipecotamide) and 5M aqueous potassium carbonate solution (2 equivs.) were stirred in toluene and treated with 1-bromobutane (1 equiv.). The reaction mixture was heated at reflux (107-110°C) for 2 hours. After cooling to 70-80°C the mixture was washed with hot water followed by hot aqueous potassium carbonate solution. The resulting toluene solution of 1-butyl-*iso*-nipecotamide was dried by azeotropic distillation, maintaining the reaction volume by addition of fresh toluene.

Example 3 A 3L vessel was purged with nitrogen and charged with *iso*-nipecotamide (112.1g 0.87mol) and dry toluene (785ml). The suspension was warmed to 50°C and potassium carbonate (248g, 1.79mol) and butyl bromide (119.8g,

0.87mol) were added in one portion. The resulting mixture was heated at reflux under Dean-Stark conditions for three hours and then cooled to 65°C and quenched by addition of water (875ml). The aqueous phase was separated at about 80°C and the organic layer dried by azeotropic distillation of toluene (200ml). Fresh toluene (200ml) was added to maintain a constant volume.

The reaction mixture was cooled to about 5°C and treated, dropwise, with a solution of lithium aluminium hydride.2THF in toluene (500ml, 3.5M, 1.75mol). The mixture was stirred at ambient temperature for one hour and then at about 55°C for a further two hours. The reaction was then quenched by cautious addition of sodium hydroxide solution (1200ml, 10.8M) and heated to about 70°C. The aqueous phase was separated and washed twice with toluene (300ml each wash). The combined organic washes were concentrated under reduced pressure and the product 1-butyl-4-piperidinylmethylamine (SB-211156) (127g) was isolated as a pale yellow oil in 85% yield by vacuum distillation (bp 106°C at 20mm Hg approx.).

Example 4

N-[(1-^{n}Butyl-4-piperidyl)methyl] indole-3-carboxamide

To a stirring solution of indole-3-carboxylic acid (1g) in dichloromethane (20 ml) at 0°C under nitrogen was added oxalyl chloride (0.81 ml) and dry dimethylformamide (3 drops). After 3 hours, the solvents were evaporated under reduced pressure. a portion of the residual acid chloride (420 mg) was dissolved in dichloromethane (12 ml) and added dropwise to a solution of N-(1-^{n}butyl-4-piperidinyl)methylamine (400 mg) in dichloromethane (12 ml) followed by triethylamine (0.36 ml). After stirring at ambient temperature overnight, the reaction mixture was washed with saturated $NaHCO_3$, and the organic phase was dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue recrystallised from ethyl acetate to give the title compound (D1) (467 mg, 64%).

^{1}H NMR ($CDCl_3$) 250 MHz

δ: 9.29 (br s,1H), 8.05-7.9 (m,1H), 7.81 (d,1H), 7.55-7.4 (m,1H), 7.39-7.2 (m, 2H), 6.28 (br s, 1H), 3.39 (t,2H), 3.0 (br d, 2H), 2.45-2.25 (m,2H), 2.1-1.1 (m11H), 0.9 (t,3H).

Example 5

N-[(1-^{n}Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (SB 207266)

Method 1:- A stirred solution of N-chlorosuccinimide (57 mg, 0.48 mmole) in chloroform (3ml) was treated with a solution of N-[(1-^{n}butyl-4-piperidyl)methyl] indole-3-carboxamide, from Example 4, (100 mg, 0.32 mmole) in chloroform (8 ml) and kept at room temperature for 2h, then treated with 3-bromo-1-propanol (0.03 ml, 0.32 mmole). After stirring for 16h, more 3-bromo-1-propanol (0.03 ml, 0.32 mmole) was added. The mixture was stirred at room temperature for a further 3h, then treated with excess 10% Na_2CO_3 solution and extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil, which was dissolved in acetone (10 ml), treated with anhydrous potassium carbonate (130 mg, 0.96 mmole) and stirred at room temperature for 16h. The mixture was concentrated *in vacuo*, the residue treated with 10% Na_2CO_3 solution (10 ml) and extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil, which was chromatographed, initially on silica gel eluting with chloroform/methanol (19:1), then on basic alumina eluting with ethyl acetate. The colourless oil obtained crystallised from ether to afford the title compound (E3) as a white solid (20 mg, 17%) mp 110-113°C.

^{1}H NMR ($CDCl_3$)

δ: 8.34 (d,1H), 7.05-7.30 (m,3H), 6.55 (t,1H), 4.53 (t,2H), 4.10 (t,2H), 3.33 (t,2H), 2.90-3.05 (m,2H), 2.25-2.45 (m,4H), 1.90-2.25 (m,2H), 1.20-1.85 (m,9H), 0.92 (t,3H).

MS (Cl) MH^+ 370.

Method 2:- A stirred suspension of N-[(1-^{n}butyl-4-piperidyl)methyl] indole-3-carboxamide, from Example 4, (120 g, 0.38 mole) in chloroform (2 L) under nitrogen at room temperature was treated with freshly distilled 3-bromo-1-propanol (69 ml, 0.77 mole) followed by the portionwise addition of dry N-chlorosuccinimide (55 g, 0.42 mole) over 5 minutes. The resulting yellow solution was stirred for 2.5h, then treated with 1M HCl in ether (15 ml, 0.015 mole). A moderate exotherm occurred and the reaction colour changed to orange. After a further 2h the mixture was treated with 10% Na_2CO_3 solution (700 ml) and the chloroform layer separated, dried (Na_2SO_4) and concentrated *in vacuo* to leave a thick red oil. This was treated with acetone (1.5 L) and anhydrous potassium carbonate (130 g, 0.95 mole), then stirred at room temperature for 18h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (1 L) and extracted with ethyl acetate (1 L). On standing a solid began crystallising from the ethyl acetate extract. After 2h at 8°C this was filtered off and dried to afford 51.7 g of the title compound (E3) as a beige solid. The mother liquors were extracted with 1M HCl acid (800 ml), the acid extract then basified with K_2CO_3 and extracted with chloroform (2 x 700 ml). The combined chloroform extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with chloroform/methanol (96:4). A yellow oil was obtained which upon trituration with ether gave a further 21.3g of title compound (E3) as a white solid. Conversion to the hydrochloride salt and recrystallisation from ethanol/60-80 petrol gave a white solid mp 254-256°C dec.

HCl salt - ^{1}H NMR (D_2O)

δ: 7.90 (d,1H), 6.88-7.20 (m,3H), 4.35 (br t,2H), 3.70 (br t,2H), 3.40 (br d,2H), 3.20 (br d,2H), 2.9 (br t,2H), 2.65(br t,2H), 2.12 (br t,2H), 1.20-1.90 (m,9H), 0.87 (t,3H).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the preparation of 1-butyl-4-piperidinylmethylamine, which process comprises:

i) the reaction of 4-piperidinecarboxamide and 1-bromobutane to give the N-butyl derivative of 4-piperidinecarboxamide; followed by

ii) reduction with $LiAlH_4$,

characterised in that the reactions i) and ii) are carried out in toluene as solvent.

2. A process according to claim 1 wherein the process is run without isolation of the N-butyl derivative of 4-piperidinecarboxamide.

3. A process according to claim 1 or 2 wherein in reaction i) potassium carbonate is added and the mixture is heated at reflux under Dean-Stark conditions.

4. A process according to Claim 1, 2 or 3 in which the reaction mixture after the reduction is treated with hot sodium hydroxide solution and the mixture is extracted with an organic solvent.

5. A process according to claim 1 substantially as hereinbefore described with reference to any one of examples 1 to 3.

6. 1-butyl-4-piperidinylmethylamine whenever prepared by the process of any one of claims 1 to 5.

7. A process for the preparation of N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide ("SB 207266"), or a pharmaceutically acceptable salt thereof, which process comprises preparing 1-butyl-4-piperidinylmethylamine according to the process of any one of claims 1 to 5, followed by coupling with a derivative of the carboxylic acid function of an indole 3-carboxylic acid, and thereafter as necessary converting the indole and/or substituents, including cyclisation to N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.

8. A process according to claim 7 substantially as hereinbefore described with reference to example 4 and/or 5.

9. N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide whenever prepared by the process of Claim 7 or 8.

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