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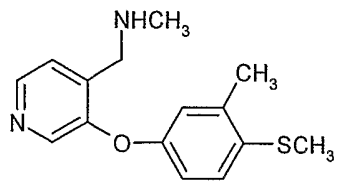
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(54) Title: PROCESS FOR THE PREPARATION OF A 3-PHENOXY-PYRIDINE DERIVATIVE



(I)

.$HO_2CCH(OH)CH(OH)CO_2H$

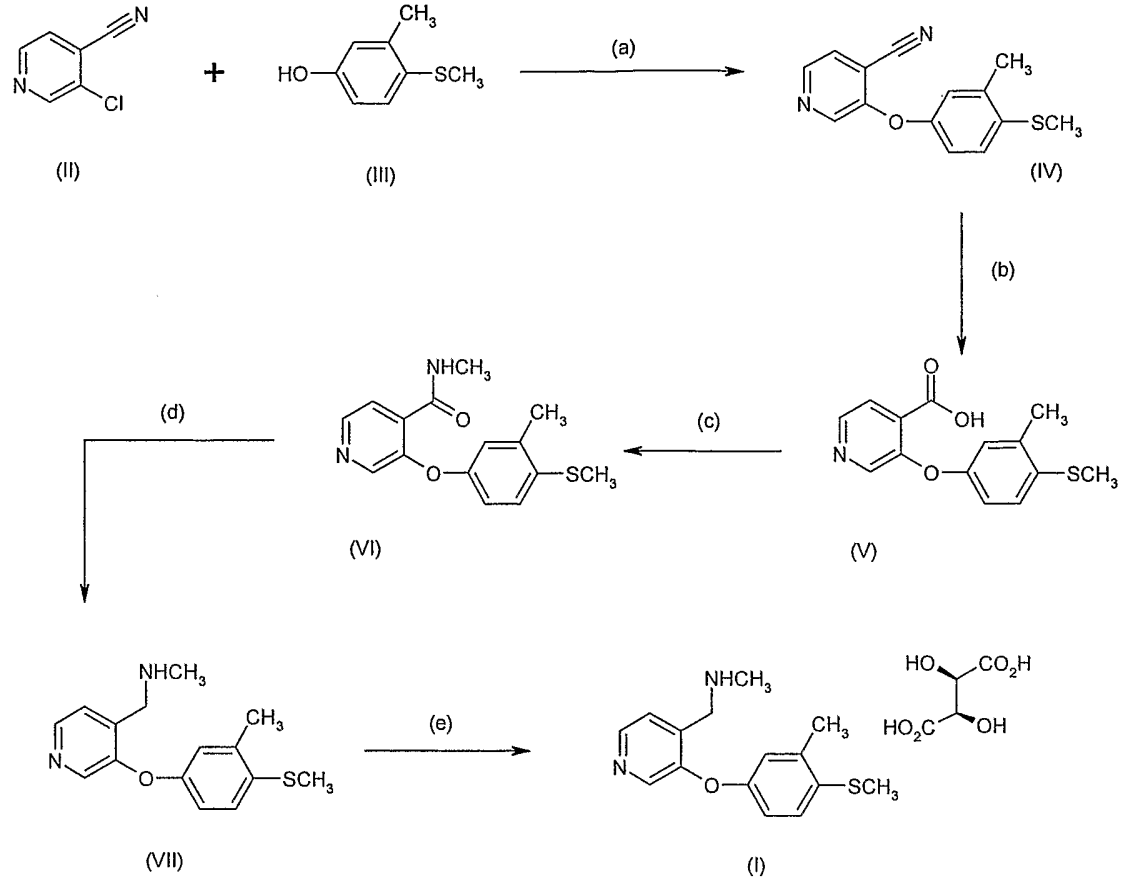
(57) Abstract: The present invention is concerned with an improved process for the preparation of the selective serotonin reuptake inhibitor N-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine (L) or (D) tartrate (I) and with intermediate products therein. Formula (I)

PROCESS FOR THE PREPARATION OF A 3-PHENOXY-PYRIDINE DERIVATIVE

The present invention is concerned with an improved process for the preparation of the selective serotonin reuptake inhibitor *N*-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine (*L*) or (*D*) tartrate and with intermediate products therein.

WO 02/083643 describes the preparation of *N*-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine (*L*) tartrate (I), in which the compound is prepared by (a) reaction of 3-chloroisonicotinonitrile (II) with 3-methyl-4-(methylthio)phenol (III) in the presence of potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide (DMF), at elevated temperature; (b) carrying out a hydrolysis of 3-[3-methyl-4-(methylthio)phenoxy]isonicotinonitrile (IV) with 6M sodium hydroxide solution in a suitable solvent such as ethanol, at elevated temperature, followed by quenching with a suitable acid such as conc. $HCl_{(aq)}$; (c) reaction of crude 3-[3-methyl-4-(methylthio)phenoxy]isonicotininc acid (V) (obtained from step (b)) with carbonyldiimidazole (CDI) in a suitable solvent such as tetrahydrofuran (THF), followed by treatment with a 2M solution of methylamine in a suitable solvent such as THF; (d) reduction of the amide (VI) with BH_3.THF,in a suitable solvent such as THF, to form *N*-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine (VII); (e) the corresponding *L*-tartrate salt was prepared by dissolving amine (VII) in isopropyl alcohol, adding *L*-tartaric acid, allowing the mixture to cool and then recrystallising the resulting solid twice from EtOH.

The complete sequence may be represented as follows:



Scheme 1

There are a number of problems with this route, when applied to bulk scale synthesis, namely:

(i) Reaction times for process step (a) are slow when carried out on a large scale, typically 18 to 24 hours. Additionally, the work-up procedure for process step (a) requires large volumes of solvent. This is impractical on an industrial scale, as it is time consuming (a significant economic disadvantage), and most notably because a large amount of waste solvent must be disposed of after the product has been isolated. Also, the product obtained must be purified by column chromatography; again this is not desirable when preparing large amounts of product.

(ii) Again for process step (b) large volumes of solvent are required for the work-up, this leads to the same difficulties as outlined above. Furthermore the by-product, NH_4Cl was difficult to remove when this step was carried out on

scale. Additionally it was found that residual amounts of the NH_4Cl by-product, when carried through to process step (c), unexpectedly led to the formation of a by-product, the primary carboxamide derivative of compound (V).

(iii) The product of process step (c) is obtained, after work-up and without further purification, as a foam. Such a product is not easily handled in bulk, and accordingly this work-up procedure is ill suited to an industrial process.

(iv) The reaction quench in process step (d) involves addition of methanol followed by 6M $HCl_{(aq)}$. Such a two-step process involving large volumes of solvent is undesirable on a large scale.

(v) In process step (e), the formation of salt (I) is carried out using a large volume of isopropyl alcohol. The isolation of salt (I) is then achieved *via* two recrystallisations from ethanol. Such an inefficient process is economically costly on an industrial scale.

In summary, whilst this reaction sequence provides an adequate route for the production of the compound of formula (I) on a laboratory scale, there is a clear requirement for a robust process that would be more applicable to industrial scale generation of these compounds.

As a result the synthetic process depicted in scheme 1 has been improved according to the following embodiments of the invention:

1. In process step (a), compounds of formula (IV) are prepared by reaction of 3-chloroisonicotinonitrile (II) with 3-methyl-4-(methylthio)phenol (III) in a suitable solvent, at elevated temperature; followed by a work-up; characterised by performing the reaction in the presence of a base having particle size D_{90}<900 microns and VMD <500 microns.

Preferably the base is potassium carbonate of particle size D_{90}<900 microns and VMD <500 microns.

Following completion of the reaction, preferably the work-up consists of the slow addition of water to the stirred reaction mixture at 60°C, followed by collection of the crystallised product, compound (IV).

Other suitable bases include carbonate bases such as sodium carbonate, caesium carbonate; butoxide bases such as potassium t-butoxide, lithium t-butoxide, sodium t-butoxide; hydroxide bases such as sodium hydroxide; and organic bases such as pyridine and morpholine.

Suitable reaction solvents include polar aprotic solvents such as *N*-methyl-2-pyrrolidinone (NMP), tetrahydrofuran, dimethylsulfoxide, dioxan, acetonitrile and ethers.

2. Compounds of formula (V) are prepared by process step (b), hydrolysis of a compound of formula (IV). The reaction is carried out using a suitable base in a suitable solvent, at elevated temperature, followed by quenching with a suitable acid; characterised by the purification of the crude product by slurrying in water, at 40-70°C, followed by filtration and drying.

Suitable bases include $KOH_{(aq)}$, and $LiOH_{(aq)}$.

Suitable solvents include methanol, isopropyl alcohol, n-butanol, t-butanol, 2-butanol, t-amyl alcohol and tetrahydrofuran.

Suitable acids include concentrated $H_2SO_{4\ (aq)}$, $HBr_{(aq)}$, and aqueous acetic acid.

The preferred base is 1M-2.5M $NaOH_{(aq)}$.

After the quench, the solid material is isolated prior to purification.

3. The amide (VI) is generated by process step (c), reaction of acid (V) with carbonyldiimidazole (CDI) in a suitable solvent, followed by addition of a suitable methylamine source; characterised by the distillation and replacement of the

reaction solvent with *tert*-butyl methyl ether (TBME), and the isolation of the product by crystallisation.

Suitable solvents include DCM, *t*-BuOMe, and ethyl acetate.

Suitable sources of methylamine include methylamine gas, and salts of methylamine in the presence of a base (a suitable salt would include hydrochloride, suitable bases would include triethylamine and DMAP).

The preferred solvent is DCM.

The product containing TBME solution may be washed with $NaOH_{(aq)}$, $NH_4Cl_{(aq)}$ and water, prior to the isolation of the product by crystallisation.

4. Compound (VII) is prepared by process step (d), reduction of amide (VI) using a suitable reducing agent in a suitable solvent; characterised by the direct quenching of the reaction by the addition of a solution of a suitable acid in a suitable solvent.

Upon completion of the quench, the THF is preferably distilled and replaced with water. This solution is adjusted to pH12 by the addition of 40% $NaOH_{(aq)}$, and then extracted with *t*-BuOMe.

Suitable solutions of acids include $HCl_{(aq)}$, $H_2SO_{4\ (aq)}$, $HBr_{(aq)}$, and aqueous acetic acid, in a suitable solvent such as THF.

The preferred acid solution is 6M $HCl_{(aq)}$/THF

Suitable reaction solvents include dioxan, and methyl THF ethers.

Suitable reducing agents include $LiAlH_4$, solutions of AlH_3, DIBAL-H, catalytic hydrogenation, $NaBH_4/BF_3$.THF, and $BF_3.Et_2O$.

The preferred reducing agent is $NaBH_4/BF_3$.THF.

5. Compound (I) is prepared by process step (e), addition of *D* or *L* tartaric acid to compound (VII), in a suitable solvent optionally at elevated temperature.

Suitable solvents include aqueous ethanol, methanol, methyl ethyl ketone, acetone, n-butanol, t-butanol, 2-butanol, t-amyl alcohol, and THF (all as aqueous mixtures).

The preferred solvent is aqueous ethanol.

Preferably the *L* form of tartaric acid is used.

Following salt formation, compound (I) is obtained by recrystallisation from a suitable solvent, such as aqueous ethanol, methanol, methyl ethyl ketone, acetone, n-butanol, t-butanol, 2-butanol, t-amyl alcohol, and THF (all as aqueous mixtures).

Preferably compound (I) is recrystallised from aqueous ethanol.

6. In a particularly preferred embodiment, process steps (d) and (e) are combined to avoid the isolation of compound (VII).

In this embodiment, preferred conditions for process step (d) are THF as solvent and $NaBH_4/BF_3$.THF as reducing agent.

Following completion of process step (d), including quench and work-up, compound (VII) is isolated as a solution in TBME, by extraction with TBME. This solvent is then preferably distilled and replaced with ethanol.

In this embodiment, preferred conditions for process step (e) are aqueous ethanol as solvent, and use of the L form of tartaric acid.

The advantages of the embodiments described above may be summarised as follows:

(i) The use of potassium carbonate of particle size D_{90}<900 microns and VMD <500 microns, in process step (a), led to a surprising reduction in reaction time, from 24 hours to 12 hours. Furthermore, following completion of reaction, slow addition of water to the reaction mixture allows the isolation of compound (IV) by crystallisation. This procedure can be completed in two hours; whereas using the procedure described in WO 02/083643, it would take two days. Additionally, far less waste solvent is generated in the improved route. All these advantages bring significant environmental and economic benefits.

(ii) In process step (b), the development of a slurrying process for the work up, has the advantage of reducing the volume of solvent required. This process also facilitates the removal of the NH_4Cl by-product, thus preventing the formation of the carboxamide by-product in process step (c).

(iii) For process step (c), the procedure described in WO 02/083643 does not provide compound (VI) in physical from that is amenable to industrial scale processing. The high solubility of amide (VI) renders it less susceptible to crystallisation techniques. In the improved process, the use of DCM as reaction solvent allows its replacement with TBME at the end of the reaction. This in turn allows the compound to be isolated by crystallisation, following washing with $NH_4Cl_{(aq)}$ to remove imidazole. This inventive choice of solvent would not be obvious to one skilled in the art.

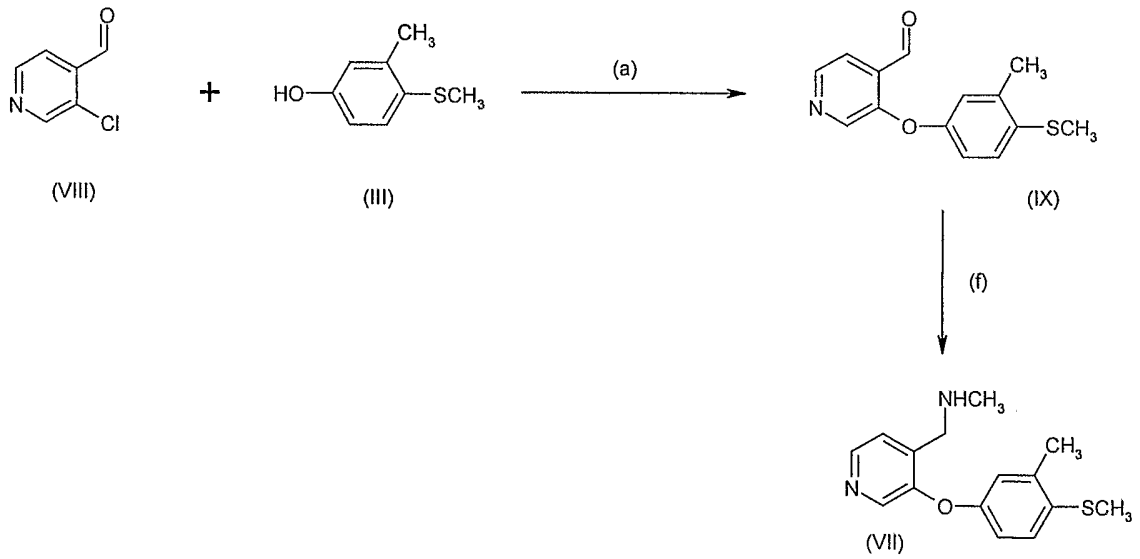
(iv) The reaction quench in process step (d) involves addition of a 6M $HCl_{(aq)}$/THF mixture. This allows the resultant hydrogen evolution to be controlled, thus making it a safer procedure. This improved method is highly advantageous on a large scale as only one quench need be carried out, and as a result, far less solvent is used.

(v) The use of aqueous ethanol for both salt formation and recrystallisation in process step (e) is far more efficient than the process described in WO 02/083643, and further more gives a higher yield of compound (I).

(vi) Compound (VII) is an oil, and as such is difficult to remove from large reaction vessels. The improved route allows the combination of process steps (d) and (e), thus avoiding the isolation of amine (VII). When process steps (d) and (e) are combined as described, the yield is 68%. When process steps (d) and (e) are carried out according to the procedure of WO 02/083643, the yield is only 48%.

(vii) This improved process is suitable for producing quantities of compound (I) on an industrial scale.

The invention also encompasses a further embodiment that provides an alternative synthesis of compound (VII). This embodiment is illustrated by the following reaction scheme:

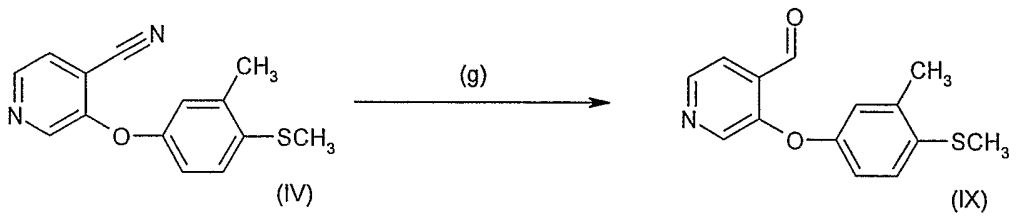


Scheme 2

Aldehyde (IX) can be prepared by process step (a), reaction of 3-chloronicotinaldehyde (VIII; prepared by reaction of 3-chloropyridine with Lithium diisopropylamide in DMF at –78°C) with phenol (III), in the presence of potassium carbonate in a suitable solvent such as DMF.

Compound (VII) is then prepared from aldehyde (IX) by process step (f), reductive amination. Methylamine is the amine source and $NaBH_4$ is the reducing agent. The reaction is carried out in a suitable solvent such as THF.

Alternatively, aldehyde (IX) can be prepared by process step (g), reduction of nitrile (IV) with DIBAL (diisobutylaluminium hydride) in a suitable solvent such as THF; as illustrated by scheme 3 below.



Scheme 3

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

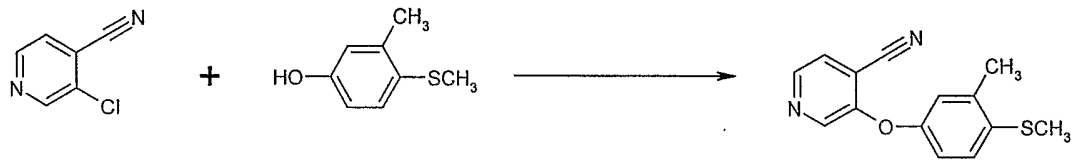
CDI	carbonyldiimidazole
MEK	methylethyl ketone
DMF	*N,N*-dimethylformamide
TBME / *t*-BuOMe	*tertiary*-butyl methyl ether
DMSO	dimethylsulfoxide
DCM	dichloromethane
DMSO	dimethylsulfoxide
m/z	mass spectrum peak
HPLC	High Pressure Liquid Chromatography
MS	mass spectrum
NMR	nuclear magnetic resonance
q	quartet

s	singlet
t	triplet
br	broad
THF	tetrahydrofuran
Kg	Kilograms
L	Litre
mL	millilitre
g	grams
$CDCl_3$	deuterated chloroform

NMR spectra were obtained using a Varian Inova 300 MHz spectrometer by dissolving the sample in an appropriate solvent.

Mass spectra were obtained using a LC/MS system consisting of an 1100 series Hewlett Packard LC in combination with a Micromass ZMD mass spectrometer.

1) 3-[3-methyl-4-(methylthio)phenoxy]isonicotinonitrile



DMF (120ml) was charged to the vessel and stirred at 22°C under a nitrogen atmosphere. 3-Methyl-4-(methylthio)phenol (17.5g; commercially available) was charged to the vessel, a yellow solution was formed. K_2CO_3 (22.4g) was then charged to the vessel, a yellow suspension was produced. Finally, 3-chloro-isonicotinonitrile (15g; WO 02/083643, preparation 71) was charged to the vessel, and a yellow/orange suspension was formed. This suspension was heated to 100°C for 6 hours, and was then cooled to 60°C. Water (300ml) was added over 1 hour. The suspension was cooled to 22°C over 2 hours and stirred for a minimum of 6 hours. The solid was collected by filtration and pulled dry. The solid cake was washed with water (15ml) and pulled dry. The product was dried under vacuum at 50°C for 12 hours.

Yield = 85%

^{1}HNMR δ_H ($CDCl_3$, 300 MHz) 2.36 (3H, s), 2.48 (3H, s), 6.97(2H, m), 7.21 (1H, d), 7.51 (1H, d), 8.31(1H, s), 8.45(1H, d);

MS *m/z* (ES+) 257 (MH^+).

2) 3-[3-methyl-4-(methylthio)phenoxy]isonicotinic acid



Ethanol (200ml) was charged to the vessel and stirred at 22°C under a nitrogen atmosphere. 3-[3-methyl-4-(methylthio)phenoxy]isonicotinonitrile (20g) was charged to the vessel, a cream suspension was formed. Sodium hydroxide (9.36g), dissolved in 200 ml of water, was added to the vessel. The resulting suspension was heated to reflux 85°C, after 30mins a brown solution was formed. After 3 hours the solution was cooled to 22°C. The resulting solution was pH adjusted to 1-1.5 by the addition of c.HCl. A thick suspension was formed, which was stirred for 2 hours at 22°C. The solid was collected by filtration, washed with 2 x water (20ml) and pulled dry. The product was dried under vacuum at 70°C.

Yield = 115%.

The product can be further purified by the following method:

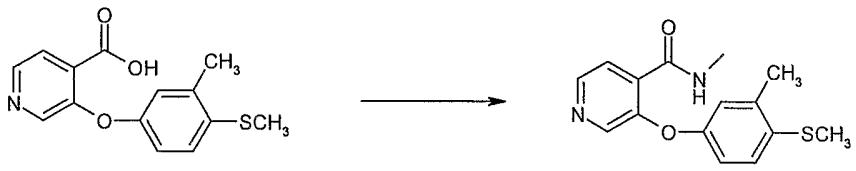
Water (100ml) was charged to the vessel and stirred at 22°C under a nitrogen atmosphere. 3-[3-methyl-4-(methylthio)phenoxy]isonicotinic acid (10g) was charged to the vessel, a cream suspension was formed. The suspension was heated 70°C for 2 hours, and then the solid was collected by filtration and pulled dry. The solid cake was washed with 2x water (20ml) and pulled dry. The product was dried under vacuum at 70°C for 12 hours.

Yield = 7.5g

^{1}HNMR δ_H (DMSO-d_6, 300 MHz) 2.23 (3H, s), 2.42 (3H, s), 6.78 (1H, d), 6.87 (1H, m), 7.18 (1H, d), 7.70 (1H, d), 8.34 (1H, s), 8.50 (1H, d);

MS *m/z* (ES^-) 274 (MH^-).

3) *N*-methyl-3-[3-methyl-4-(methylthio)phenoxy]isonicotinamide

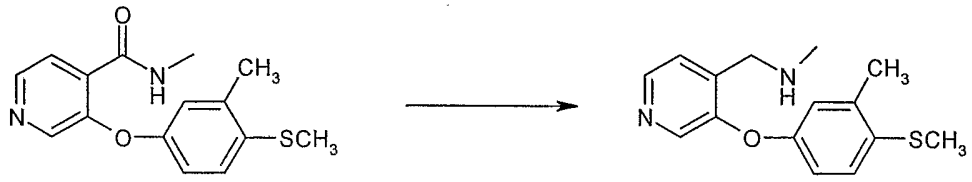


To a clean dry vessel DCM (500ml) was charged and stirred at 22°C under a nitrogen atmosphere. 3-[3-methyl-4-(methylthio)phenoxy]isonicotinic acid (50g) was charged to the vessel, a cream suspension was formed. CDI (30.92g) was added portionwise over 10 minutes. The resulting suspension was stirred at 22°C for 2 hours. After 2 hours a clear solution was formed and methylamine (2M) in THF (108.7ml) was added slowly maintaining the temperature range of 20- 30°C. The resulting suspension was stirred at 22°C. After 3 hours the DCM was stripped to minimum stir volume and replaced with *t*-BuOMe to give a final volume of 1000ml (20ml/g *t*-BuOMe). The solution was cooled to 22°C. The organic phase was washed with 1N NaOH (150ml) and the organic phase held. The aqueous NaOH was extracted with *t*-BuOMe (200ml) and the organic phases combined. The organic phase was washed with saturated ammonium chloride (2x 125ml), and then with water (100ml). The organic phase was collected and the solvent level was reduced to approx 3ml/g. The solution was cooled to 22°C and stirred for at least 4 hours. The resulting white suspension was cooled to 0 to -5°C and stirred for at least 2 hours. The product was collected by filtration, washed with the mother liquors and pulled dry.

Yield = 71%.

^{1}HNMR δ_H ($CDCl_3$, 300 MHz) 2.35 (3H, s), 2.47 (3H, s), 3.01(3H, d), 6.91 (2H, m), 7.20 (1H, d), 7.61 (1H, br, s), 8.07(1H, s), 8.21(1H, s), 8.46(1H, d);
MS *m/z* (ES+) 289 (MH^+)

4) *N*-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine



To a clean dry vessel was charged THF (340ml) and stirred at 22°C under a nitrogen atmosphere. *N*-methyl-3-[3-methyl-4-(methylthio)phenoxy]isonicotinamide (20g) was charged to the vessel. The reaction was stirred for 30 minutes to give a clear solution. Sodium borohydride (7.87g) was added, resulting in a white suspension. This suspension was cooled to -10°C and stirred for 30minutes. Borontrifluoride.THF (30.61ml) was added slowly to the suspension, maintaining the temperature in the range of –10 to 5°C. The reaction was heated to 60°C over 90 minutes. After 9 hours the reaction was cooled to 22°C and stirred. A 6N $HCl_{(aq)}$/THF mixture was prepared from 37% HCl (27.4g), de-ionised water (23.6ml) and THF (92ml). The reaction mixture was cooled to -10°C and the 6N HCl solution was added slowly keeping the temperature <10°C. The suspension was heated at 50°C for 90 mins then cooled to 22°C. The solvent was reduced to minimum volume to remove THF and replaced with de-ionised water to leave a final water volume of 300ml. The reaction was cooled to 22°C, charged with TBME (120ml) and the mixture stirred for 10 mins.

The organic phase was removed and discarded.

The aqueous phase was recharged to the vessel along with TBME (200ml).

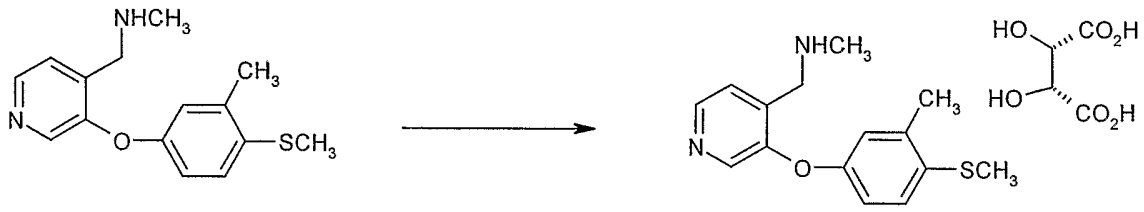
The 2-phase mixture was stirred and the pH adjusted to pH 11-12 with 32% NaOH.

The phases were separated and the aqueous extracted with TBME (1 x 120ml).

The organic phases were combined and the solvent removed under vacuum to leave a pale pink oil (18.2g, 96%)

^{1}HNMR δ_H (DMSO-d_6, 300 MHz) 2.23(6H, d), 2.41 (3H, s), 3.63 (2H, s), 6.78 (1H, d), 6.85 (1H, m), 7.19 (1H, d), 7.52 (1H, d), 8.12 (1H, s), 8.35 (1H, d);
MS *m/z* (ES+) 275 (MH^+)

5) *N*-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine - (*L*)-tartrate



A solution of *N*-Methyl{3-[3-methyl-4-(methylthio)phenoxy]-4-pyridyl}methylamine in TBME (450ml) was charged to a clean spec free vessel *via* an inline filter. The solution was stirred at 22°C under a nitrogen atmosphere. The *t*-BuOMe was stripped to minimum stir volume and replaced with ethanol to give a final volume of 187ml (6.5ml/g ethanol). The resulting solution was cooled to 22°C over 1 hour. *L*-tartaric acid (15.82g) was charged to a vessel containing purified water (15ml) and ethanol (56.6ml); this was stirred at 22°C until a clear solution was formed. This was added in one portion to the solution of the amine *via* an in-line filter. The vessel was rinsed with ethanol (14.4ml) and the contents were added to the amine solution *via* an in-line filter. After 1 hour a white suspension was formed. The suspension was cooled to 0°C over 3 hours. The suspension was stirred for a least 1 hour. The product was collected by filtration, washed with ethanol (1ml/g) and pulled dry. The product was dried under vacuum at 50°C for 12 hours.

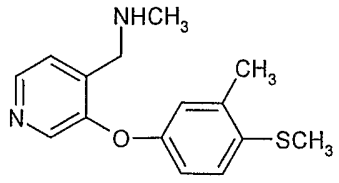
Yield = 84%

^{1}HNMR δ_H (DMSO-d_6, 300 MHz) 2.25 (3H, s), 2.43 (3H, s), 2.48(3H, m), 3.98 (2H, s), 4.04 (2H, s), 6.83 (1H, d), 6.94 (1H, s), 7.23 (1H, d), 7.56 (1H, d), 8.13 (1H, s), 8.38(1H, d);

MS *m/z* (ES+) 275 (MH^+)

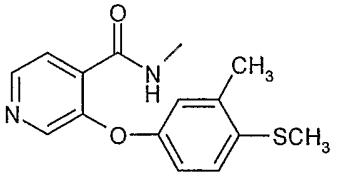
Claims

1 A process for the preparation of a compound of formula (VII):



(VII)

comprising the reaction of a compound of formula (VI)



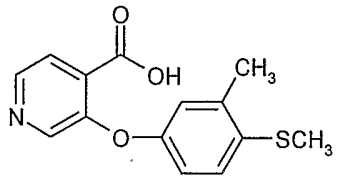
(VI)

with a suitable reducing agent in a suitable solvent;

characterised by the direct quenching of the reaction by the addition of a solution of a suitable acid in a suitable solvent.

2 A process according to claim 1 wherein the reducing agent is $NaBH_4/BF_3$.THF and the acid solution is 6M $HCl_{(aq)}$/THF.

3 A process according to claims 1 and 2 which further comprises the preparation of a compound of formula (VI) by the reaction of a compound of formula (V)



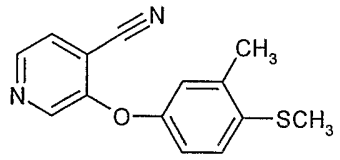
(V)

with carbonyldiimidazole in a suitable solvent, followed by the addition of a suitable methylamine source;

characterised by the distillation and replacement of the reaction solvent with TBME upon completion of the reaction, and the isolation of the product by crystallisation.

4 A process according to claim 3 wherein the reaction solvent is DCM.

5 A process according to claims 3 and 4 which further comprises the preparation of a compound of formula (V) by the hydrolysis of a compound of formula (IV)

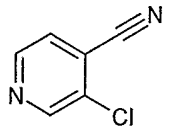


(IV)

with a suitable base, in a suitable solvent followed by quenching with a suitable acid;

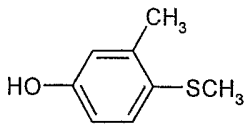
Charaterised by the purification of the crude product *via* a water slurry at elevated temperature.

6 A process according to claims 5 which further comprises the preparation of a compound of formula (IV) by the reaction of a compound of formula (II)



(II)

with a compound of formula (III)



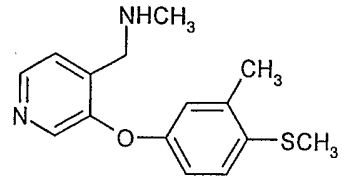
(III)

in a suitable solvent at elevated temperature;

charaterised by performing the reaction in the presence of a base having a particle size D_{90}<900 microns and VMD<500 microns.

7 A process according to claim 6 wherein the base is K_2CO_3 of particle size D_{90}<900 microns and VMD<500 microns.

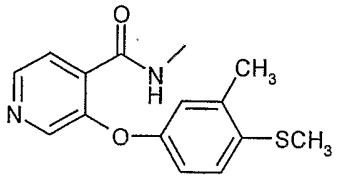
8 A process for the preparation of a compound of formula (I),



$.HO_2CCH(OH)CH(OH)CO_2H$ (I)

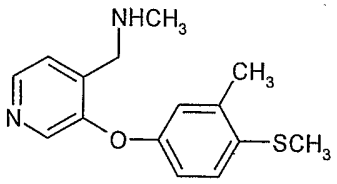
comprising the consecutive steps of:

(a) the reaction of a compound of formula (VI)



(VI)

with a suitable reducing agent in a suitable solvent, followed by quenching and work-up, and subsequent extraction with TBME; to obtain the crude compound of formula (VII)



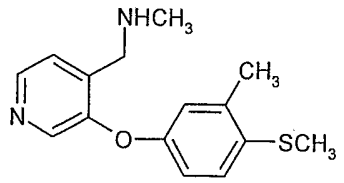
(VII)

as a solution in TBME;

(b) distillation and replacement of the TBME with ethanol;

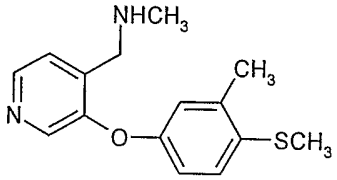
(c) treatment of the resulting ethanolic solution of compound (VII) with a solution of tartaric acid in aqueous ethanol, to form the desired salt.

9 A process for the preparation of a compound of formula (I):



$.HO_2CCH(OH)CH(OH)CO_2H$ (I)

comprising the reaction of a compound of formula (VII)



(VII)

with tartaric acid;

characterised in that the reaction and purification are carried out in a suitable aqueous solvent.

10 A process according to claim 9 wherein the solvent is aqueous ethanol.

INTERNATIONAL SEARCH REPORT

Inter I Application No
PCT/IB2005/002037

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/62

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)
IPC 7 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 practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/083643 A (PFIZER LIMITED; ADAM, MAVIS, DIANE; ANDREWS, MARK, DAVID; GYMER, GEOFF) 24 October 2002 (2002-10-24) cited in the application preparations 47, 64 page 38, line 1 - page 39, line 19	1-10

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 2005	05/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Usuelli, A

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/IB2005/002037

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02083643 A	24-10-2002	AT 281435 T	15-11-2004
		BG 108204 A	30-12-2004
		BR 0208812 A	09-03-2004
		CA 2443699 A1	24-10-2002
		CZ 20032677 A3	16-06-2004
		DE 60201819 D1	09-12-2004
		EE 200300498 A	16-02-2004
		EP 1377550 A1	07-01-2004
		ES 2227448 T3	01-04-2005
		HU 0303880 A2	28-04-2004
		WO 02083643 A1	24-10-2002
		JP 2005504728 T	17-02-2005
		MX PA03009383 A	29-01-2004
		NO 20034525 A	08-12-2003
		PT 1377550 T	31-01-2005
		SI 1377550 T1	28-02-2005
		SK 12452003 A3	03-08-2004
		US 2003207857 A1	06-11-2003
		US 2004106594 A1	03-06-2004
		ZA 200307507 A	19-11-2004