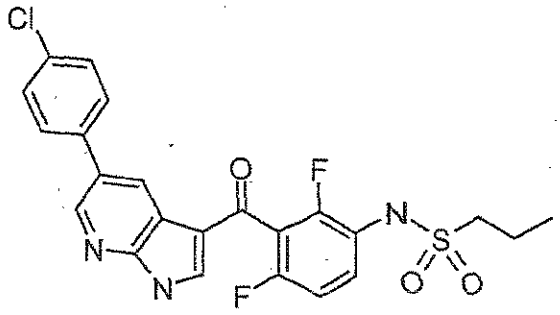
PROCESS FOR THE MANUFACTURE OF PHARMACEUTICALLY ACTIVE COMPOUNDS

The present invention is related to synthesis routes to obtain the compound Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (formula 1).



Formula (1)

The synthesis of the compound of formula (1) has been described before in WO 2007002433 and WO 2007002325.

However, the known synthesis routes may not be readily adapted for use on an industrial scale.

The present invention provides new and improved synthesis routes for the compound of formula (1), which employ reaction conditions which are particularly amenable to being carried out on an industrial scale. In particular, the process according to the present invention efficiently uses starting materials, avoids formation of high quantities of undesirable by-products, provides high throughput and good product yields and can safely be carried out in large scale production. It is also less expensive, and, due to the

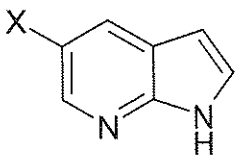
efficient use of starting materials, environmentally friendlier than processes disclosed in the prior art.

In another embodiment of the present invention there are identified specific compounds (compounds (A) and (B) as specified below) which are by-products of the present synthesis method. Trace amounts of compound (B), obtained by deprotection, i.e. cleavage of 2,6-dichlorobenzamide from compound (A) during the last step of the synthesis of the compound of formula (1), are typically found in the final product (formula (1)) as pharmaceutically acceptable impurity and in amounts of maximum 0.30%, but usually in about 0.02% to about 0.15%, as identified by HPLC, provided said compound of formula (1) had been synthesized according to the present method. Therefore, while the impurity/trace amounts of formula (B) will not affect the pharmacological- or toxicity profile of any potential, future medicament or pharmaceutical preparation containing the compound of formula (1), they may nevertheless serve as fingerprint in order to detect whether the present process has been used to manufacture the compound of formula (1). It will therefore allow for an unambiguous identification as to whether the present process has been used in the manufacture of the compound of formula (1).

Therefore, in another embodiment the present invention provides an analytical method for detecting whether the process according to the present invention has been used, characterized in that said analytical method detects the compound of formula (B) in a pharmaceutical preparation of the compound of formula (1).

Summary

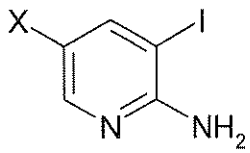
In a first aspect, there is provided a process for the manufacture of compound (I),



(I),

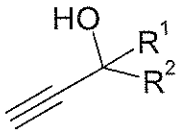
characterized in that

aa) the compound of formula (II)



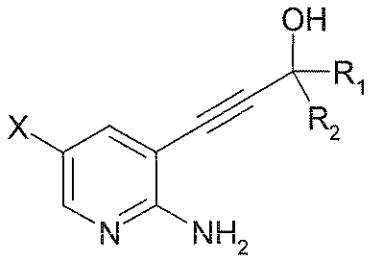
(II),

is reacted with the compound of formula (III)



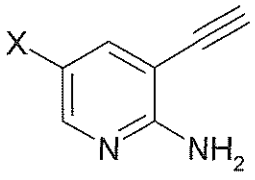
(III),

in the presence of a catalyst, copper(I)iodide and a base, to give the compound of formula (IV)



(IV), and

bb) said compound of formula (IV) is further reacted in the presence of aqueous alkali metal hydroxide at 50-90°C and under reduced pressure to give the compound of formula (V)



(V), and

cc) said compound of formula (V) is reacted in the presence of aqueous alkali metal hydroxide or a strong base to give the compound of formula (I);

wherein

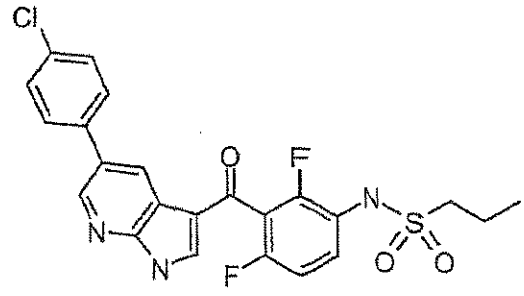
R^1 and R^2 are independently selected from a C1-C4 alkyl, and

X is -Br or -Cl.

In a second aspect, there is provided the compound of formula (IV) as defined herein.

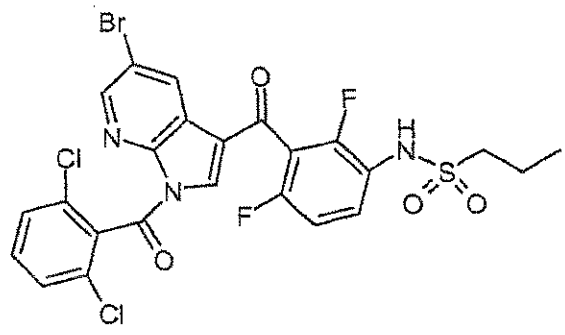
Detailed Description of the Invention

According to the present invention, there is provided a process for the manufacture of the compound of formula (1),



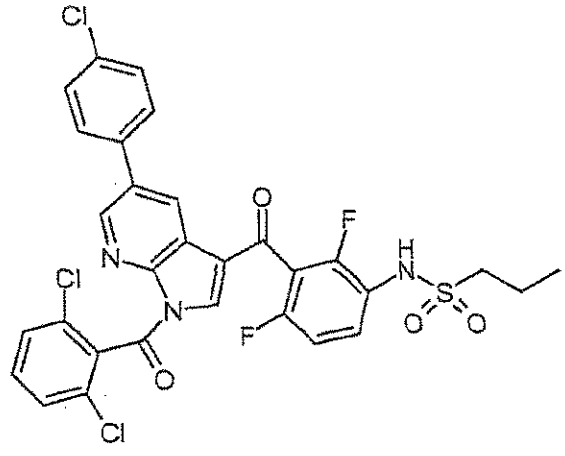
(1),

characterized in that the compound of formula (5)



(5)

is reacted in the presence of 4-Chlorophenylboronic acid (5a, scheme 1) and a Palladium Catalyst to give the compound of formula (6)

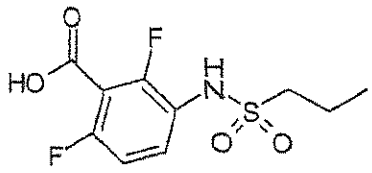


(6); and

the 2,6-Dichlorobenzamide group in said compound of formula (6) is cleaved using ammonia to give the compound of formula (1).

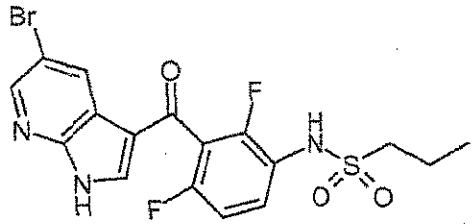
The term "Palladium Catalyst" as used herein means any suitable Palladium (Pd) Catalyst, preferably Bis(triphenylphosphin)palladium(II)dichloride ($(PPh_3)_2PdCl_2$) and Pd on charcoal. Preferably, the amount of $(PPh_3)_2PdCl_2$ is about 0.0025 equivalents with respect to compound of formula (5).

The compound of formula (5) can be obtained according to methods known to the person of skill in the art of organic chemistry. In a particularly preferred embodiment according to the present invention, the compound of formula (5) is obtained by reaction of a compound of formula (2)



(2)

in the presence of a suitable activating agent (e.g., oxalylchloride ($(COCl)_2$)) followed by the addition of 5-Bromo-7-azaindole (formula 3) and a suitable coupling agent (e.g., Aluminium trichloride) to give the compound of formula (4)

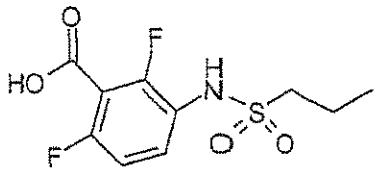


(4); and

said compound of formula (4) is further reacted in the presence of 2,6-Dichlorobenzoylchloride under conditions suitable to give the compound of formula (5).

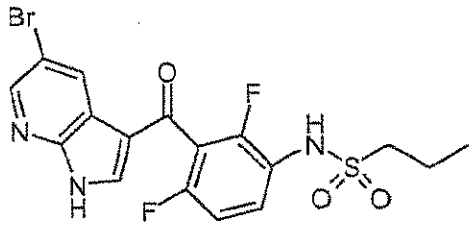
In another particularly preferred embodiment according to the present invention there is provided the process for the manufacture of the compound of formula (1), wherein

a) the compound of formula (2)



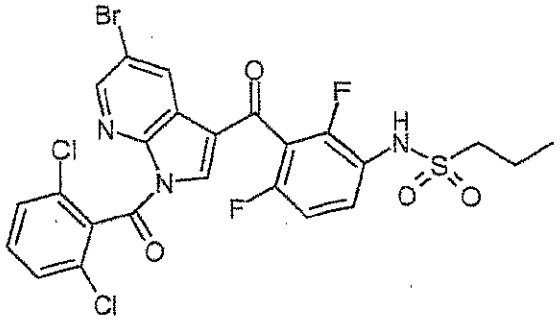
(2)

is reacted in a suitable solvent (e.g., methylenechloride (CH_2Cl_2)) in the presence of a suitable activating agent (e.g.,Vilsmeier's salt prepared in situ from oxalylchloride ($(COCl)_2$ and N,N-Dimethylformamide (DMF)) followed by the addition of 5-Bromo-7-azaindole (formula 3) and a suitable activating agent (e.g., Aluminium trichloride) to give the compound of formula (4)



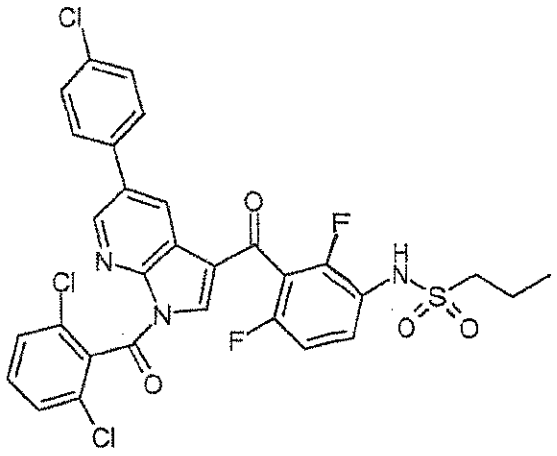
(4); and

b) said compound of formula (4) is further reacted with 2,6-Dichlorobenzoylchloride in the presence of a suitable base (e. g. n-Tripropylamine (n-Pr_3N)) and suitable catalyst (e. g. N,N-Dimethylaminopyridine (DMAP)) to give the compound of formula (5)



(5); and

c) said compound of formula (5) is further reacted in the presence of 4-Chlorophenylboronic acid and a suitable palladium catalyst (e.g., $(PPh_3)_2PdCl_2$) to give the compound of formula (6)



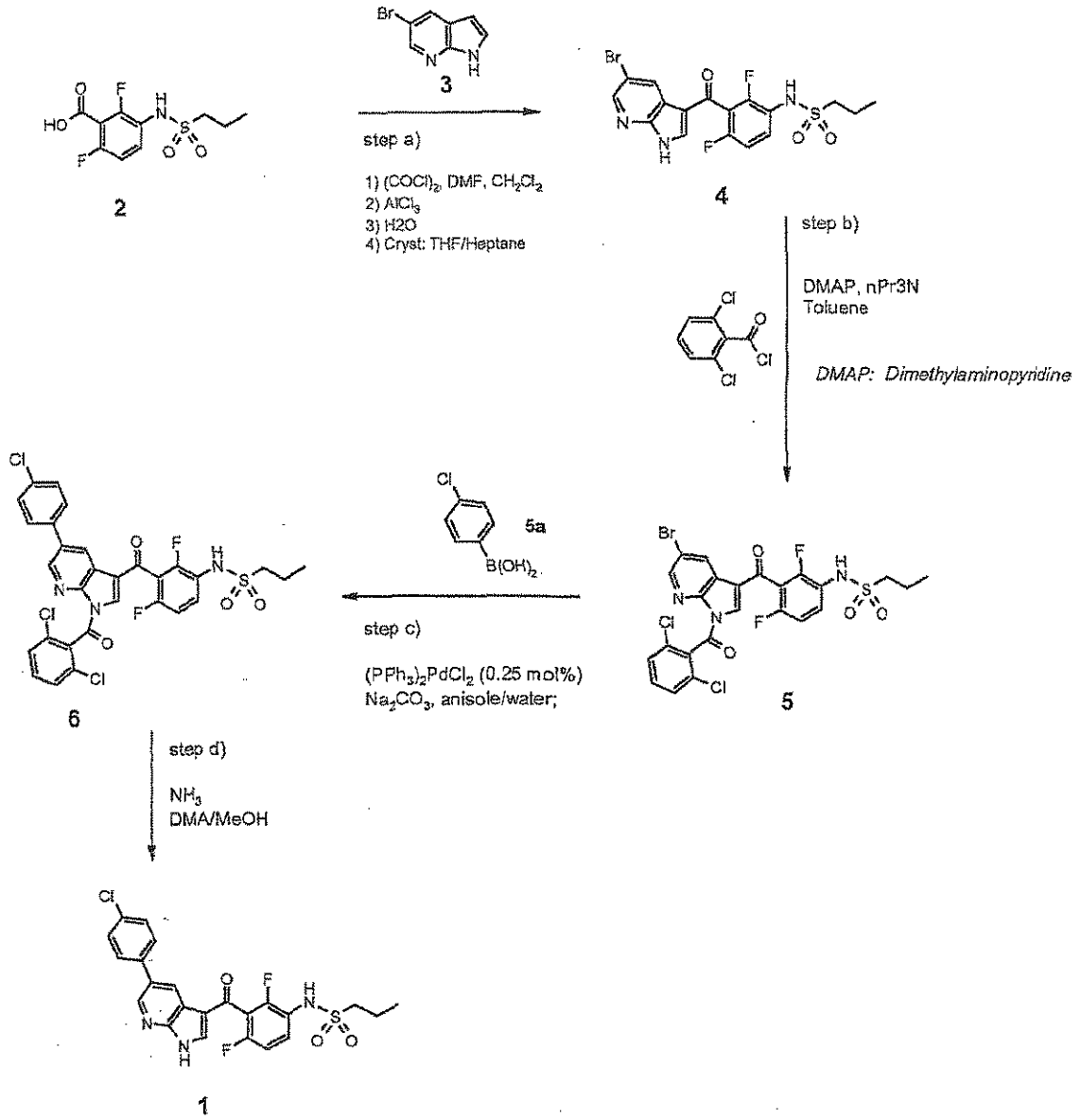
(6); and

d) said compound of formula (6) is finally reacted with ammonia (NH_3) or a primary or secondary amine (e. g. Dimethylamine) in an alcohol (methanol or ethanol) solution diluted with a polar aprotic solvent like DMA to give the compound of formula (1).

In a preferred embodiment according to the present invention, the above-mentioned reaction step c) is carried out in a 2 phase reaction mixture comprising an non-polar aprotic solvent such as anisole or toluene and aqueous sodium or potassium carbonate (Na_2CO_3, K_2CO_3).

The compounds (4), (5) and (6) are novel and form each another embodiment of the present invention.

The process according to the present invention can be summarized according to the following reaction scheme (scheme 1) wherein, unless explicitly otherwise stated, all abbreviations and expressions have the meanings well known to the person of skill in the art of organic chemistry. All reaction partners and auxiliary agents (like i.e. catalysts, solvents) are commercially available.



scheme 1

According to the present invention, the first reaction under step a) is the formation of an acid chloride of the carboxylic acid of formula (2). The reaction can be carried out employing a suspension of the compound of formula (2) in suitable medium, e.g., Methylenechloride (CH_2Cl_2) containing catalytic amounts of DMF, to which a solution of Oxalylchloride ($(COCl)_2$) in CH_2Cl_2 is slowly added. The addition is typically carried out at room temperature (RT) and the reaction mixture is further stirred at RT until reaction completion (ca 6h). The next reaction is a *Friedel-Crafts-Acylation*. The freshly obtained solution of acid chloride is added into a cooled (T = -12 to 5°C, preferably 0-5°C)

suspension of $AlCl_3$ and 5-Bromo-7-azaindole (3) in CH_2Cl_2. The reaction mixture is allowed to heat up till RT due to released heat of the exothermic reaction and stirred for about 8h to complete the reaction. The work-up and isolation procedure involves pouring of the reaction mixture into iced water, followed by extractive work-up and crystallization of the compound of formula (4) from THF/ Methylenchloride/Heptane. Compound of formula (4) can be further purified by washing with i.e. heptane.

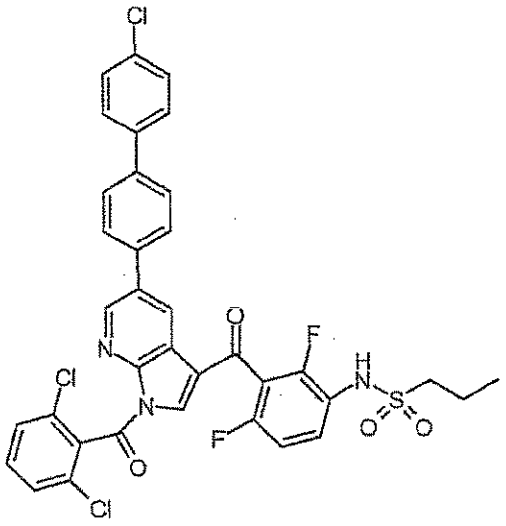
Reaction step b) starts with the preparation of a suspension of the compound of formula (4) in a suitable aprotic solvent (e.g., Toluene). Subsequently Dimethylaminopyridine (DMAP), n-Tripropylamine and 2,6-Dichlorobenzoylchloride are added at RT. The reaction mixture is stirred for about 60 minutes. After completion of the reaction an aqueous work-up is performed. Subsequently the toluene is slowly evaporated from the organic solution, leading to the crystallization of the compound of formula (5) which can finally be isolated and further purified through additional washing with e.g., cooled Toluene.

Reaction step c) is a Pd-catalyzed *Suzuki*-coupling reaction of the compound of formula (5) with 4-Chlorophenylboronic acid (5a). The reaction starts with the preparation of a suspension of the 4-Chlorophenylboronic acid (5a) and the compound of formula (5) in an aprotic solvent, such as anisole, to which an aqueous solution of Na_2CO_3 is added. The reaction mixture is heated slowly up to a temperature of about 85°C. During heating the Pd-catalyst is added at a temperature between RT and around 70°C,. Any suitable Pd-catalyst can be used, with Bis(triphenylphosphin) palladium(II)dichloride ($(PPh_3)_2PdCl_2$) being especially preferred. The reaction mixture is stirred for about 120 minutes at a temperature of about 85°C to complete the reaction. The hot bi-phasic reaction mixture is filtered to remove potentially precipitated Pd. After aqueous work-up the organic (Anisole) phase is concentrated by evaporation, diluted with methanol and cooled down to about 0°C in order to initiate crystallization of the compound of formula (6). The precipitate is isolated, washed several times with cooled methanol and subsequently dried in vacuum. If needed the compound of formula (6) can be further purified by re-crystallization from Toluene.

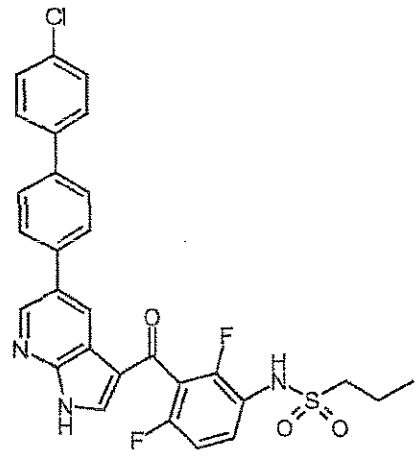
Reaction step d) is the removal of the 2,6-Dichlorobenzamide protection group. The reaction is carried out in a suspension/solution of the compound of formula (6) in

DMA / Methanol (about 1:1 - 2:1) by addition of about 3 - 7 equivalents of a saturated Ammonia solution (NH_3 in Methanol) at RT. The reaction mixture is stirred at about 55°C until the protection group is entirely cleaved (about 10h). The resulting solution is diluted with Methanol and subsequently the ammonia is removed via azeotropic distillation under reduced pressure. The residue is diluted with Methanol and cooled to RT in order to initiate crystallization of the compound of formula (1) which can then be isolated from the reaction mixture by filtration. Compound of formula (1) can be further purified by washing with e.g., methanol.

The process according to the present invention may lead to the formation of by-products of the formulae (A) and (B).



(A), and



(B).

In particular, the compound of formula (A) may be formed during the reaction of the compound of formula (5) with 4-Chlorophenylboronic acid (step c), scheme 1). The compound of formula (B) is the de-protected form of formula (A) as obtained during reaction step d) as defined above (see also scheme 1). These compounds, in particular the compound of formula (B), may be detected in amounts of about 0.02% to about 0.15% by weight in a composition which otherwise contains >99% by weight of the compound of formula (1) after completion of the process according to the present invention, and even involving conventional purification methods known to the person of skill in the art. Therefore, trace amounts of the compound of formula (B) may even be detectable in pharmaceutical preparations containing the compound of formula (1) when obtained according to the present process. These compounds, in particular the

compound of formula (B) can serve as characteristic fingerprints for the use of the present process. The compounds of formula (A) and (B) show the following NMR signals:

Compound A:

1H-NMR (500 MHz, d6-DMSO): δ 0.99 (t, J = 7.5 Hz, 3H), 1.72 – 1.82 (m, 2H), 3.15 – 3.21 (m, 2H), 7.37 (t, J = 9.0 Hz, 1H), 7.52 – 7.58 (m, 2H), 7.65 – 7.74 (m, 4H), 7.76 – 7.85 (m, 4H), 7.87 – 7.92 (m, 2H), 8.58 (br. s, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.90 (br. s, 1H), 9.85 (br. s, 1H).

Compound B:

1H-NMR (600 MHz, d6-DMSO): δ 0.97 (t, J = 7.5 Hz, 3H), 1.70 – 1.80 (m, 2H), 3.10 – 3.15 (m, 2H), 7.29 (t, J = 8.7 Hz, 1H), 7.54 – 7.63 (m, 3H), 7.78 – 7.82 (m, 2H), 7.83 – 7.90 (m, 4H), 8.25 (s, 1H), 8.70 (br. s, 1H), 8.79 (d, J = 1.8 Hz, 1H), 9.78 (br. s, 1H), 13.02 (br. s, 1H).

Therefore, as a further embodiment according to the present invention, there are provided the compounds of formulae (A) and (B) as such.

In yet another embodiment the present invention provides an analytical method for detecting whether the process according to the present invention has been used, characterized in that detectable levels of the compounds of formula (A) and/or (B) as disclosed herein are generally present in any commercial pharmaceutical preparation comprising primarily the compound of formula (1) prepared employing the synthetic process disclosed herein. Preferably the analytical method is used to detect the compound of formula (B). Any suitable analytical method known to the Organic Chemist may be applied, such as for example IR-spectroscopy, NMR-spectroscopy, Mass Spectrometry (MS) or High Performance Liquid Chromatography (HPLC). More preferably the analytical method is based on High Performance Liquid Chromatography (HPLC), which may optionally be combined with a second analytical method such as for example MS (HPLC-MS).

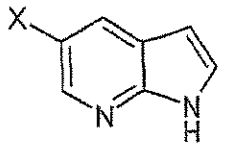
The compound of formula (1) shows potential as an active pharmaceutical ingredient, as inter alia described in WO 2007002433 and WO 2007002325. Consequently, in a

further embodiment of the present invention, there is provided a pharmaceutical preparation comprising the compound of formula (1) together with detectable amounts of at least compound of formula (B). More particularly there is provided a composition comprising the compound of formula (1) in an amount greater than 99% by weight and the compound of formula (B) in amounts from about 0.01% to about 0.15% by weight. Said composition may be further processed with pharmaceutically acceptable adjuvants to give any kind of pharmaceutical preparations as inter alia described in WO 2007002433 and WO 2007002325.

The starting materials, solvents, catalysts and auxiliary reagents used in the method according to the present invention (see i.e. scheme 1) are commercially available. However, when produced on a large industrial scale, there remains a need to also obtain large amounts of starting materials in good quality and high yields.

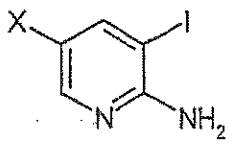
Consequently, according to the present invention, there are also provided improved methods of making azaindole derivatives which are halogenated at their 5-position, in particular 5-Bromo-7-azaindole ((3), CAS 183208-35-7) and 5-Chloro-7-azaindole (CAS 866546-07-8). The 5-Bromo-7-azaindole is a useful starting material in the above-mentioned process according to scheme 1.

Consequently, in a further embodiment according to the present invention there is provided a process for the manufacture of compound (I),

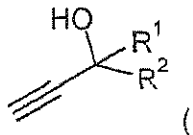

(I),

characterized in that

aa) the compound of formula (II)

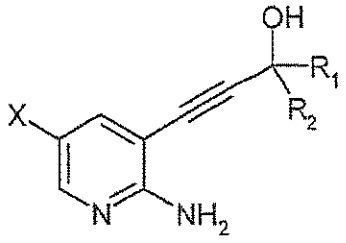

(II),

is reacted with the compound of formula (III)



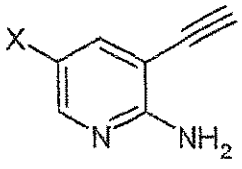
(III),

in the presence of a catalyst, copper(I)iodide and a base, to give the compound of formula (IV)



(IV), and

bb) said compound of formula (IV) is further reacted in the presence of aqueous alkali metal hydroxide at 50-90°C and under reduced pressure to give the compound of formula (V)



(V), and

cc) said compound of formula (V) is reacted in the presence of aqueous alkali metal hydroxide or a strong base to give the compound of formula (I);

wherein

R^1 and R^2 are independently selected from a C1-C4 alkyl, and

X is -Br or -Cl.

In one particularly preferred embodiment according to the present invention, the above process aa) to cc) is carried out with X being –Br leading to the compounds Ia, IIa, IVa, Va. The compounds 3 and Ia are thus identical and are both 5-Bromo-7-azaindole.

In another particularly preferred embodiment according to the present invention, the above process aa) to cc) is carried out with X being –Cl leading to the compounds Ib, IIb, IVb, Vb.

In still another preferred embodiment according to the present invention R_1 and R_2 are both methyl.

The synthesis of compounds of formula (I) as described above is a sequential process. After each reaction described in steps aa) to cc), aqueous work-up procedures are applied and the formed intermediate product is optionally being isolated. In an alternative setup it is also possible to carry out the reaction steps bb) and cc) almost simultaneously. This means the conversion of compound (V) into compound (I) starts as soon as compound (V) is formed, and before the reaction to obtain compound (V) (step bb)) is terminated. Therefore, the two reaction steps bb) and cc) may run under the same reaction conditions. Consequently, no work-up of compound (V) prior to its further reaction to compound (I) is required according to this alternative method.

Therefore, in yet another embodiment there is provided a method to obtain the compound of formula (I) directly from formula (IV) without the need to apply an aqueous work-up on the stage of the compound of formula (V). This can be achieved by adding to the compound of formula (IV), dissolved in an approximately 1:1 (w/w) mixture of water and *N*-methylpyrrolidone (NMP) 5 to 10 equivalents of aqueous sodium hydroxide at about 75 to about 85°C while applying a pressure of about 350 mbar, followed by stirring at about 75 to about 85°C and under reduced pressure (<400 mbar) for 15 to 20 hours. During the entire reaction time distilled acetone/water is continuously replaced by water. The termination of the reaction can be monitored by taking a sample out of the reaction mixture after 15 to 20 hours and analyzing said sample with HPLC. A specific procedure for this reaction is disclosed in Example 7b.

The term "C1-C4 alkyl" as used herein means a linear or branched saturated hydrocarbon, such as for example methyl, ethyl, propyl, i-propyl, n-butyl, 2-butyl, *tert*-butyl, with methyl being especially preferred.

The term "alkali metal hydroxide" as used herein means sodium-, lithium- or potassium hydroxide, with lithium- and sodium hydroxide being especially preferred.

The term "reduced pressure" as used herein means <500 mbar, preferably <400 mbar.

The term "catalyst" as used herein in step aa) means any Pd(II)- or Pd(0)-catalyst usually used in this type of *Sonogashira* reaction. Examples of such catalysts are $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ with bis-(triphenylphosphine)-palladium(II)-dichloride ($PdCl_2(PPh_3)_2$) being especially preferred .

The term "base" as used herein in step aa) means weak bases as for example N-methylmorpholine or trialkyl-amines, with triethylamine being especially preferred.

The term "strong base" as used herein in step cc) means alkali metal alcoholates, preferably potassium *tert.*-butylate.

In a particularly preferred embodiment according to the present invention, the above-mentioned reaction step aa) is carried out in the presence of bis-(triphenylphosphine)-palladium(II)-dichloride, copper(I)iodide and triethylamine, the reaction step bb) is carried out with aqueous lithium- or sodium hydroxide and the reaction step cc) is carried out in the presence of potassium *tert.*-butylate or aqueous sodium hydroxide. The elimination of acetone (step bb) and subsequent ring formation of step cc) are preferably carried out in *N*-methylpyrrolidone or in a mixture of *N*-methylpyrrolidone and water as solvent.

The process according to the reaction steps aa) to cc) is preferably carried out according to the specific conditions and parameters given in Example 7a) or b). Consequently, the specific process according to Example 7a) or b) form each another preferred embodiment according to the present invention.

The compounds of formula (II) can be obtained for example by iodination of the corresponding 5-halogenated 2-Amino-pyridines. Among the many iodination conditions known to the skilled in the art a mixture of iodine and periodic acid proved to be especially suitable for the mentioned transformation.

The above described synthesis route via the compound of formula (IV) is a novel, alternative method for the production of the otherwise well known compounds of formula (I), in particular the 5-Bromo-7-azaindole (3 or Ia). A particular advantage of this process is the use of the intermediate compound of formula (IV) which can be easily purified and isolated from the reaction mixture. In addition, the use of compound (IV) avoids the release of environmentally hazardous Si by-products upon cyclization, which are formed if the corresponding trimethylsilyl-ethynyl derivative is used, which is usually known for this type of reaction (*Sonogashira* reaction) as inter alia described in WO 2009/016460 and US 2006/0183758.

The compounds of formula (IV) are thus valuable and novel intermediates in the above-described synthesis to obtain 5-halogenated 7-azaindoles (I). Therefore, in yet another embodiment according to the present invention there is provided the compounds of formula (IV) as such.

The present invention is now illustrated by the following accompanying working examples. In some examples, the term "In-process control" is used. This term means that a sample is taken from the reaction mixture while the process is running, and said sample is being analyzed by standard techniques known to the skilled person, preferably by HPLC, in order to detect the degree of conversion of starting material into product.

Examples

Example 1 (step a))

Formation of Carboxylic Acid Chloride (step a) 1) according to scheme 1)

55.8	g	Sulfonamide Acid (2) was given into a dried 1st reaction vessel kept under nitrogen atmosphere, to which
280	mL	Methylenchloride were added. Then
619	µL	DMF were added to the obtained suspension and the resulting mixture was kept at a temperature between 18- 22 °C. Then,
25.4	g	Oxalylchloride were dissolved in
66	mL	Methylenchloride, and this solution was slowly added during approximately 30 minutes to the above-mentioned suspension whereby the temperature of said suspension was still kept between 18- 22 °C. The formation of CO_2 and CO could be observed during said addition. The reaction mixture was then further stirred for about 4 to 6 hours and further kept at a temperature between 18-22 °C until the suspension almost entirely turned into a solution and no gas formation could be observed any more.

Friedel-Crafts-Acylation

		In parallel to the above described formation of the acid-chloride, a 2nd reaction vessel was prepared, wherein
106.7	g	Aluminiumtrichloride were mixed together with
266	mL	Methylenchloride to give a suspension which was then cooled down to about -12 to 2°C. In parallel, a suspension of
39.4	g	5-Bromo-7-azaindole in
66	mL	Methylenchloride was prepared in a 3rd dried reaction vessel under nitrogen atmosphere. Said Bromoazaindole suspension was added to said Aluminiumtrichlorid-Suspension during approximately 30 minutes and at a temperature between -12 to 2°C. The obtained suspension was immediately further reacted by addition of the acid-chloride solution as obtained according to the procedure

described above during approximately 30 minutes, whereby the reaction mixture was allowed to warm up to about 20-25 °C using the spontaneous heat release observed upon addition of the said acid chloride solution. After addition of the acid-chloride solution, the reaction mixture was further stirred during approximately 8 to 10 hours; whereby the mixture was kept at a temperature between 20-25 °C. During this time a separation into 2 phases was observed.

Meanwhile, a 4th reaction vessel was prepared, containing

400 ml Water which was cooled to a temperature between 0-5 °C. The two phase reaction mixture as obtained according to the preceding steps was added slowly, during approximately 30 minutes, to said cooled water into said 4th reaction vessel whereby the resulting mixture was kept at a temperature between 0-20 °C. This resulted in an exothermic reaction and precipitation of the compound of formula (**4**) from the resulting biphasic reaction mixture.

Methylene chloride was widely removed by distillation under reduced pressure from the heterogeneous mixture. Then the aqueous suspension of the compound of formula (**4**) was diluted with methylene chloride and THF. A clear biphasic mixture was obtained by heating the reaction mixture to about 50 °C. After phase separation the organic phase was washed twice with 400 ml semi-saturated brine at about 50 °C. The organic phase was concentrated under reduced pressure at about 50 °C to a volume of about 400 ml whereby crystallization of the compound of formula (**4**) started.

600 ml Heptane was added within about 30 min at about 50 °C. The resulting suspension was cooled in about 3 – 5 h to ca. 0 °C. After stirring for at least one additional hour at ca. 0°C to complete the crystallization, the suspension was filtered and the wet precipitate was washed two times with

120 mL n-Heptan. The wet product was dried in vacuum and at a temperature between 50 – 60 °C.

Yield: 85 g (= 90 %) light beige colored, crystalline Azaindole (**4**).

Example 2 (step b))

Formation of compound (5)

45.8	g	of the compound (4) as obtained according to Example 1 were suspended in
600	ml	Toluene. Water as contained in the suspension was removed at a temperature between 60-80 °C and under reduced pressure of 450-400 mbar. Subsequently,
200	ml	Toluene were newly added and the suspension was cooled to 20-25 °C. Then, a solution of
1.22	g	Dimethylaminopyridin in
20	ml	Toluene was added, prior to the addition of
15.8	g	n-Tripropylamine. Subsequently,
22.0	g	2,6-Dichlorobenzoylchloride were slowly added via a dropping funnel during approximately 15 minutes while the mixture was kept between 20 and 25 °C.
		The reaction mixture was stirred for about 1-2 hours at a temperature between 20-25 °C, whereby the color of the mixture turned into brown.
		The brownish reaction mixture as obtained by the last step above, was diluted with
275	ml	water and subsequently with
29.6	g	hydrochloric acid (37%). The resulting two phase mixture was heated to 65-70 °C. The two phases were allowed to separate after about 10 minutes. The Toluene phase was washed at a temperature between 65 and 70 °C, first with
300	ml	of an aqueous solution containing 10% sodium hydrogencarbonate, and then with
300	ml	water. The organic (Toluene) phase was concentrated by evaporation at temperatures between 55 and 60 °C and at reduced pressure (200-80 mbar) to a volume of about 200

ml. During this procedure the crude product (5) precipitated due to crystallization. The resulting suspension was then slowly cooled down (within about 5 h) to -5 to 0 °C and further stirred at that temperature for 1 h. The crude product was separated by filtration, washed twice with

30 ml Toluene (0 °C), and was subsequently dried at 50-55 °C and 26-13 mbar.

Yield: 57 g (90%) of compound of formula (5).

Example 3 (step c))

*Formation of compound (**6**), Suzuki-Coupling*

23.16 g 4-Chlorphenylboronic acid (**5a**) were mixed with

85.00 g of comound (**5**) as obtained according to Example 2 in a dried 1st reaction vessel under nitrogen atmosphere, and to the resulting suspension were further added

395 ml Anisole.

The suspension was kept at room temperature (20-25 °C) and mixed with a solution of

57.08 g Sodium carbonate in

337 ml water. The reaction mixture was then heated to a temperature of 70 +/- 2 °C. At this temperature,

0.236 g Bis-(triphenylphosphin)-palladium(II)-dichloride together with

110 ml Anisole were given to the reaction mixture, which is subsequently slowly (within about 60 minutes) heated up to a temperature between 80-88 °C (Heating Temperature outside did not exceed 110°C) and stirred for about 2 h. Towards the end of the reaction the formation of a clear two phase reaction mixture with a dark red upper (organic) phase was obtained.

After completion of the reaction, the reaction mixture is cooled down to 60-80 °C and transferred via a filter into a 2nd reaction vessel. The 1st reaction vessel and the filter was washed with

110 ml warm Anisole which is added to the 2nd reaction vessel. The obtained two phases are separated and the organic phase is washed at 60-80 °C , first with

375 ml 0.1 N sulfuric acid containing 10 % (w/w) sodium sulfate, and subsequently with

375 ml water. During the last extraction reversal of the two phases was observed. The organic phase is now the lower phase. In order to obtain complete phase separation, the last extraction was carried out at a temperature of at least 70 °C. The obtained orange-yellow solution is concentrated at reduced pressure to about 225 mL (+/- 10 %), while the temperature of the solution was kept between 60-80 °C. Subsequently, the resulting suspension is cooled to about 60 °C. Then, over a period of about 30 minutes

628 ml methanol were continuously added. Subsequently, the suspension was slowly (within about 4 hours) cooled to 0 °C (+/- 2°C), and stirred for another 3 hours at that temperature until complete crystallization of the product of formula (**6**) occurred. The suspension was separated by filtration, and the wet solid residue was washed two times with

112 ml cold methanol.

The wet Chlorophenylbenzamide (**6**) was dried in a rotary evaporator under reduced pressure and at a water bath temperature between 70- 80 °C.

Yield: 74 – 76 g (82 - 85 %) almost colorless, crystalline Chlorophenylbenzamide (**6**). The product can be optionally re-crystallized from toluene for further purification.

1H-NMR (400 MHz, CDCl3): δ ppm 1.09 (t, J = 7.5 Hz, 3H), 1.86 – 1.99 (m, 2H), 3.10 – 3.19 (m, 2H), 6.53 (s, 1H), 7.11 (dt, J = 8.6, 1.5 Hz, 1H), 7.39 – 7.49 (m, 5H), 7.50 – 7.59 (m, 2H), 7.79 (td, J = 9.0, 5.6 Hz, 1H), 8.32 (br. s, 1H), 8.43 (br. s, 1H), 8.84 (d, J = 2.3 Hz, 1H).

Example 4 (step d))

Formation of compound (1)

70.0	g	Chlorphenylbenzamid (**6**),
175	ml	DMA and
88	ml	Methanol were given into a dried reaction vessel under nitrogen atmosphere.
		The resulting suspension was kept at 20 – 25 °C, and mixed with
48.0	g	of a solution of ammonia in methanol (15 %). The autoclave was then closed and the reaction mixture heated to 50 – 55 °C, which resulted in the formation of a clear solution. The temperature was maintained while stirring the reaction mixture for about 10 – 20 hours.
		Subsequently, the clear solution was transferred into a double jacket reaction vessel, and further diluted with
254	ml	Methanol. The reaction mixture was then concentrated to its original volume under reduced pressure and (600 – 500 mbar) at a jacket-temperature of maximum 60 °C. Subsequently,
508	ml	Methanol were newly added slowly over a period of about 20 – 30 minutes, whereby the temperature of the reaction mixture was kept between 45 – 55 °C. The resulting suspension was slowly cooled down (within about 2 hours) to 20 °C (± 3 °C) and subsequently was further stirred for at least 1 hour prior to separation of the solid reaction product (1) by filtration. The filter cake was washed two times with

120 mL Methanol. The wet product was dried in rotary evaporator under reduced pressure and applying a water bath temperature of 50 to 60 °C.

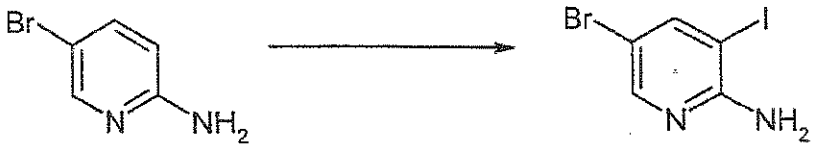
Yield: 49 g (95 %) of the white, crystalline compound formula (1).

1H-NMR (600 MHz, CDCl3): δ ppm 1.07 (t, J = 7.5 Hz, 3H), 1.84 – 1.98 (m, 2H), 3.07 – 3.17 (m, 2H), 6.41 (s, 1H), 7.06 (dt, J = 8.6 Hz, 1.5 Hz, 1H), 7.46 – 7.51 (m, 2H), 7.60 – 7.64 (m, 2H), 7.70 (td, J = 9.0, 5.5 Hz, 1H), 7.73 (d, J = 2.7 Hz, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.88 (d, J = 1.9 Hz, 1H), 9.55 (br. s, 1H).

Purity: ≥ 99 % (m/m, HPLC); Palladium content ≤ 5 ppm; compound (B): about 0.1%

Example 5

Preparation of 2-amino-5-bromo-3-iodopyridine (IIa)



IIa

In a 1000 mL double-jacket reactor (under a nitrogen atmosphere)

38.28 g Iodine is suspended in

21 g Acetic acid and

62 g Acetonitrile. To the brown mixture is added at 20 to 40°C

14.6 g Sulfuric acid 96%. The addition is strongly exothermic. The dropping funnel is rinsed with

20 g Water. The resulting mixture is heated with a jacket temperature of 90°C. When the temperature of the mixture is 70°C, the mixture is treated within 3 to 6 minutes with

45.20 g Periodic acid (50% in water). The addition is endothermic. The funnel is rinsed with

10 g Water. The solution is then treated at 65 to 75°C within 5 to 10 minutes with a previously prepared solution of

58.00 g 2-Amino-5-bromopyridine in

67 g Acetonitrile and

31.5 g Acetic acid. The dropping funnel is rinsed with

15 g Acetonitrile. The resulting solution is heated to 77 to 82°C and stirred under slightly reflux conditions for 3 to 4 hours (approx. 90°C jacket temperature). In-process control (proposed target value: <2.0 % starting material). Upon complete conversion the mixture is immediately cooled down and treated at 60 to 70°C drop wise with

66 g Sodium hydrogen sulfite (38-40% in water). Immediately after the addition, the mixture is diluted at 60 to 70°C within 30 to 60 minutes with

360 g Water. The mixture is then treated at 60 to 70°C within 50 to 90 minutes with approximately

~202 g Sodium hydroxide 28% to adjust the pH to 7.3 to 7.6. When the desired pH is reached the suspension is stirred at 60 to 70°C for 30 to 60 minutes. The suspension is cooled to 20 to 25°C within 2 to 5 hours and then stirred at this temperature for 2 to 5 hours. The crystals are filtered off and washed in two portions with a mixture of

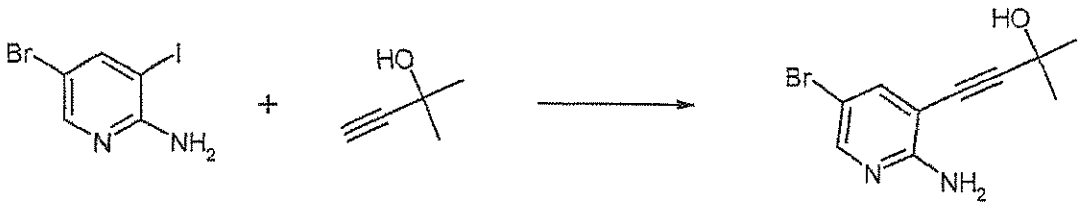
270 g Water and

23 g Acetonitrile. The wet crystals (approx. 120 g) are dried at 40 to 50°C / <30 mbar until constant weight.

Yield: 90.5 g of slightly brownish crystals with an assay of 95.0 %(m/m). This corresponds to a corrected yield of 86%.

Example 6

a) Preparation of 4-(2-Amino-5-bromo-pyridin-3-yl)-2-methyl-but-3-yn-2-ol.



A suspension of 2-amino-5-bromo-3-iodopyridine (10.0 g, 33.5 mmol), bis-(triphenyl-phosphine)-palladium(II)-dichloride (117 mg, 0.17 mmol), copper(I)iodide (79 mg, 0.41 mmol) and triethylamine (6.1 mL, 43.5 mmol) in dichloromethane (40 mL) was treated at 23 to 30°C within 1 to 2 hours with a solution of 1,1-dimethyl-2-propyn-1-ol (3.70 g, 44 mmol) in dichloromethane (10 mL) and the resulting mixture was stirred at 25°C for 3 hours. The mixture was diluted with dichloromethane (20 mL) and washed with water (2×50 mL). The organic phase was then treated with 1 M HCl (80 mL). The layers were separated and the organic layer was extracted with 1 M HCl (20 mL). The combined product containing aqueous layers were washed with dichloromethane (2×10 mL). The pH of the aqueous layer was adjusted to pH 7-9 by the drop wise addition of sodium hydroxide solution (28% in water, 18 g). The resulting suspension was stirred at 20°C for 2 hours and the crystals were then filtered off and washed with water (2×20 mL). The wet crystals were dried at 50°C / <30mbar affording 6.99 g (82%) of 4-(2-amino-5-bromo-pyridin-3-yl)-2-methyl-but-3-yn-2-ol as a melted mass with a purity of 99.5 % (HPLC, area%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.63 (s, 6H); 4.0 (br., 3H); 7.59 (d, J=2.4, 1H); 8.03 (d, J=2.4, 1H).

b) Alternative Preparation of 4-(2-Amino-5-bromo-pyridin-3-yl)-2-methyl-but-3-yn-2-ol.

In a 1000 mL double-jacket reactor (under a nitrogen atmosphere)

84.0 g 2-amino-5-bromo-3-iodopyridine (96.4 %(m/m)) is suspended in

900 g Dichloromethane. The Suspension is heated to reflux (45°C jacket temperature) and stirred at slightly reflux for 15 to 45 minutes. The

dimmish solution is cooled to 30 to 35°C and then polish-filtered (using a Zeta plus filter plate charged with Decalite Speedex). The first reactor and the transfer pipe are rinsed with

130 g Dichloromethane (pre-heated to 30 to 35°C). The clear filtrate is concentrated to a residual volume of 260 to 300 mL. The resulting suspension is treated at ca. 30°C with

600 mg Bis-(triphenylphosphine)-palladium(II)-dichloride,

400 mg Copper(I)-iodide and

38.0 g Triethylamine. The used receivers are rinsed with

10 g Dichloromethane. The brown suspension is treated at 30 to 34°C within 1 to 2 hours with a solution of

32.0 g 2-Methyl-3-butin-2-ol in

120 g Dichloromethane. The dropping funnel is rinsed with

15 g Dichloromethane. The mixture is stirred for 10 hours at 30 to 34°C. In-process control. Upon complete conversion the mixture is diluted at 30 to 34°C with

240 g Dichloromethane and

200 g Water and treated at 28 to 34°C within 10 to 20 minutes with

100 g Ammonium hydroxide solution (25% in water). The biphasic solution (ca. 950 mL) is stirred for 15 to 30 minutes at 28 to 34°C and the layers are then allowed to separate for 15 to 30 minutes. The organic layer is separated and the aqueous layer is extracted at 28 to 34°C with

80 g Dichloromethane. The combined organic layers are diluted at 30 to 34°C with

100 g Water and then treated at 28 to 34°C within 10 to 20 minutes with

50 g Ammonium hydroxide solution (25% in water). The biphasic solution is stirred for 15 to 30 minutes at 28 to 34°C and the layers are then allowed to separate for 15 to 30 minutes. The organic layer is separated and then washed at 28 to 34°C with

100 g Water. The organic layer is concentrated under reduced pressure and at a maximum temperature of 34°C to a volume of 550 to 600 mL. The organic layer is diluted at 25 to 32°C with

400 g Water and treated at 25 to 32°C within 15 to 30 minutes with

45 g Hydrochloric acid (37% in water). The biphasic solution (980 mL) is stir-

red for 15 to 30 minutes at 25 to 32°C and the layers are then allowed to separate for 30 to 60 minutes. The layers are separated and the organic layer is diluted with

225 g Water and then treated at 25 to 32°C within 15 to 30 minutes with

25 g Hydrochloric acid (37% in water). The combined product containing aqueous layers are washed at 25 to 32°C with

100 g Dichloromethane. From the aqueous layer dichloromethane is then azeotropically removed with water under reduced pressure and at a maximum internal temperature of 32°C. At the end of the distillation a volume of 550 to 600 mL is adjusted. The resulting aqueous solution is polish-filtered (using a Zeta plus filter plate). The first reactor and the transfer pipes are rinsed with

40 g Water. The clear solution is then treated at 22 to 30°C within 60 to 120 minutes with approximately

54 g Sodium hydroxide (28% in water) until the pH is adjusted to pH 7.5 to 9.5. This forces the product to precipitate. After the dosing the resulting suspension is stirred at 20 to 25°C for 4 to 16 hours. The crystals are filtered off and washed in two portions with

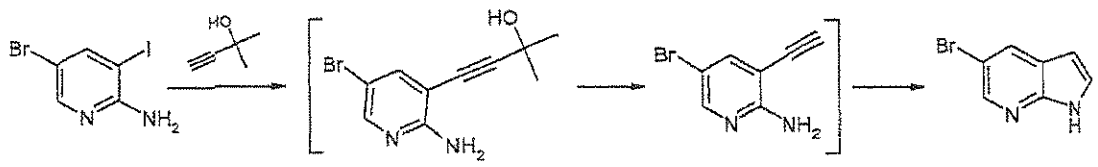
300 g Water. The wet crystals (ca. 73 g) are dried at 40 to 50°C and <30 mbar until constant weight.

Yield: 65.04 g (93%) of yellow crystals with a content of 98.6 %(m/m). This intermediate can optionally be re-crystallized from isopropanol/water for further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.61 (s, 6H); 2.3 (br., 1H); 4.9 (br., 2H); 7.57 (d, J=2.4, 1H); 8.01 (d, J=2.4, 1H).

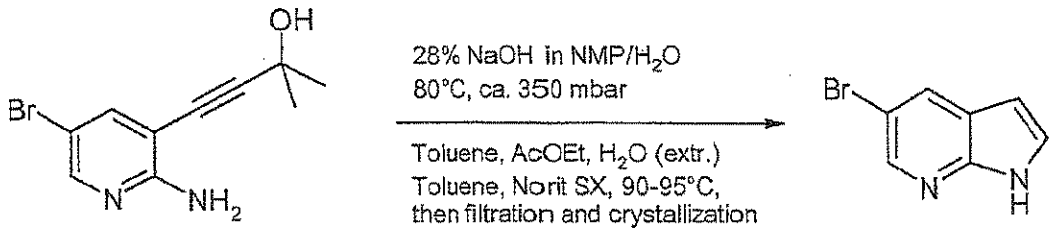
Example 7

*a) Preparation of 5-bromo-7-azaindole (**3** or **Ia**) from isolated 2-amino-5-bromo-3-iodopyridine*



A suspension of 2-amino-5-bromo-3-iodopyridine (5.0 g, 16.7 mmol), bis-(triphenyl-phosphine)-palladium(II)-dichloride (43 mg, 0.061 mmol), copper(I)iodide (29.4 mg, 0.15 mmol) and triethylamine (2.21 g, 21.8 mmol) in dichloromethane (20 mL) was treated at 23 to 30°C within 1 to 2 hours with a solution of 1,1-dimethyl-2-propyn-1-ol (1.85 g, 21.7 mmol) in dichloromethane (10 mL) and the resulting mixture was stirred at 25°C for 4 hours. The mixture was diluted with dichloromethane (10 mL) and washed with water (2×25 mL). The organic phase was then treated with 1 M HCl (40 mL). The layers were separated and the organic layer was extracted with 1 M HCl (15 mL). The combined product containing aqueous layers were washed with dichloromethane (2×8 mL). The pH of the aqueous layer was adjusted to pH 7-9 by the drop wise addition of sodium hydroxide solution (28% in water). The resulting suspension was stirred at 20°C over night and the crystals were then filtered off and washed with water (2×5 mL). The wet crystals were dissolved in *N*-methylpyrrolidone (50 mL) and treated within 2 hours at 60°C and 50-100 mbar with an aqueous solution of lithium hydroxide (2.4 M, 32 mL). The resulting mixture was heated to 75°C and stirred at this temperature and under reduced pressure (50-100 mbar) for 15-20 hours. Toluene (20 mL) and water (20 mL) were then added and the layers were separated. The aqueous layer was extracted with toluene (3x25 mL). The combined organic layers were washed with water (3x 10 mL) and then concentrated to dryness. The residue was dissolved in *N*-methylpyrrolidone (50 mL) and treated at 60°C with potassium *tert.*-butylate (3.52 g, 30.7 mmol). After stirring for 3 hours at 60°C, the mixture was cooled to ambient temperature and diluted with toluene (40 mL) and water (40 mL). The aqueous layer was separated and back extracted with toluene (3x50 mL). The combined toluene layers were washed with water (3x10 mL) and then concentrated to dryness. The residue was dissolved in a hot mixture of toluene and *n*-heptane (20 mL). The clear solution was cooled to -5°C within 4 to 6 hours whereupon crystals precipitated. The suspension was stirred at -5°C for 2-4 hours. The crystals were filtered off, washed with heptane and dried at 45°C /<30 mbars over night to afford 5-bromo-7-azaindole (2.05 g, 62% yield) as slightly yellow crystals with a purity of 99.6% (HPLC, area%).

b) Preparation of 5-bromo-7-azaindole from isolated 4-(2-Amino-5-bromo-pyridin-3-yl)-2-methyl-but-3-yn-2-ol.



A 1000 mL double-jacket reactor (under a nitrogen atmosphere) is charged with

80.0 g 4-(2-Amino-5-bromo-pyridin-3-yl)-2-methyl-but-3-yn-2-ol,

320 mL *N*-Methylpyrrolidone and

330 mL Water. The mixture is heated to 75 to 80°C and a vacuum of ca 350 mbar is applied. The solution is then treated at 75 to 80°C within 30 to 45 minutes with

181 mL Sodium hydroxide (28% in water). The dropping funnel is rinsed with

5 mL Water and the mixture stirred at 78 to 81°C for 15 to 20 hours. During stirring the jacket temperature and the vacuum have to be adjusted such that the internal temperature is 78 to 81°C and a slight steadily distillate flow is guaranteed. When the volume in the reactor has reached approx. 800 mL water is continuously added to keep the volume constant for the rest of the reaction time. In-process control. Upon complete conversion, the reaction mixture is concentrated to a volume of approx. 700 mL and then cooled to 50 to 55°C. The mixture is treated at this temperature with

200 mL Toluene. The biphasic mixture (ca. 900 mL) is stirred at 50 to 55°C for 15 to 30 minutes and the layers are then allowed to separate for 15 to 30 minutes. The aqueous layer is separated and then extracted at 50 to 55°C with 3×140 mL, totally with

420 mL Toluene. The combined toluene layers are washed at 50 to 55°C with 2x100 mL, totally with

200 mL Water. The toluene layer is concentrated under reduced pressure at 45 to 55°C until a residual volume of 450 to 500 mL is obtained. The residue is treated at 50 to 55°C with

225 g Ethyl acetate and the resulting solution is washed at 50 to 55°C with 3×150 mL, totally with

450 mL Water. From the organic layer water and ethyl acetate are azeotropically

distilled off with toluene under reduced pressure at 45 to 55°C. At the end of the distillation a volume of 600 to 700 mL is adjusted. The mixture is heated to 90 to 95°C and stirred until a clear solution is obtained. The solution is treated with

2.0 g Activated charcoal (Norit SX) and the resulting mixture stirred for 15 to 30 minutes at 90 to 95°C. The charcoal is removed by a hot filtration at 90 to 95°C. The first reactor, the filter and the transfer pipes are washed with 3x100 mL, totally with

300 mL Toluene. The filtrate is concentrated under reduced pressure to a volume of approx. 400 mL. The resulting suspension is heated to 90 to 100°C to obtain a clear solution. The solution is cooled to -5 to -10°C within 7 to 10 hours and the resulting suspension stirred at this temperature for additional 3 to 5 hours. The crystals are filtered off and washed in two portions with

120 mL Toluene (pre-cooled to <0°C). The wet crystals are dried at 55 to 65°C / <30 mbar until constant weight.

Yield: 46.5 g (75%) of slightly yellow crystals with an assay of 100.1 %(m/m).

Example 8

Preparation of 5-chloro-7-azaindol (Ib)

Step 1: Synthesis of 2-Amino-5-chloro-3-iodopyridine (IIb)



2-Amino-5-chloropyridine

2-Amino-5-chloro-3-iodopyridine (IIb)

In a 1000 mL double-jacket reactor under a nitrogen atmosphere

38.28 g Iodine is suspended in

21 g Acetic acid and

62 g Acetonitrile. To the brown mixture is added at 20 to 40°C

14.6 g Sulfuric acid 96%. The addition is strongly exothermic. The dropping funnel is rinsed with

20 g Water. The resulting mixture is heated with a jacket temperature of 90°C. When the temperature of the mixture is 70°C, the mixture is treated within 3 to 6 minutes with

45.20 g Periodic acid (50% in water). The addition is endothermic. The funnel is rinsed with

10 g Water. The solution is then treated at 65 to 75°C within 5 to 10 minutes with a previously prepared solution of

43.1 g 2-Amino-5-chloropyridine in

67 g Acetonitrile and

31.5 g Acetic acid. The dropping funnel is rinsed with

15 g Acetonitrile. The resulting solution is heated to 77 to 82°C and stirred under slightly reflux conditions for 4 hours (approx. 90°C jacket temperature). The mixture is then cooled 60-65°C and treated with

66 g Sodium hydrogen sulfite (39% in water). After the addition the mixture is diluted at 60 to 70°C within 10 to 20 minutes with

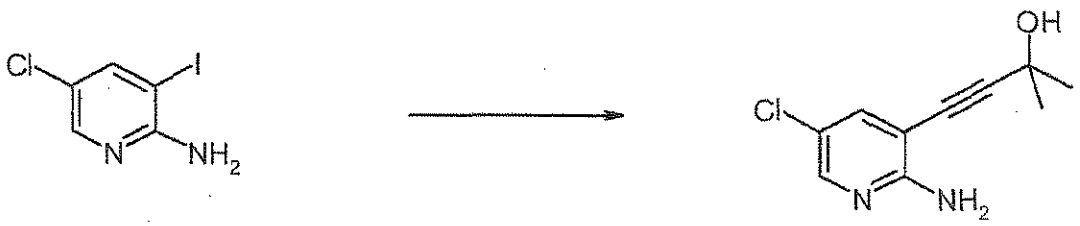
360 g Water. The mixture is then treated with

162 mL Sodium hydroxide 28% to adjust the pH to pH 7.4 and the resulting suspension is stirred at 50°C for 30 to 60 minutes. The suspension is cooled to 20 to 25°C within 2 hours and then stirred at this temperature over night. The crystals are filtered off and washed in two portions with a mixture of

270 g Water and

23 g Acetonitrile. The wet crystals (approx. 110 g) are dried at 40-50°C / <30 mbar to afford 72.5 g (85%) of slightly brownish crystals with a purity of 94.8 %(area).

Step 2: Synthesis of 4-(2-Amino-5-chloro-pyridin-3-yl)-2-methyl-but-3-yn-2-ol



In a 1000 mL double-jacket reactor

38.0 g 2-Amino-5-chloro-3-iodopyridine is suspended in

120 mL Dichloromethane. The suspension is treated at ca 30°C with

0.60 g Bis-(triphenylphosphine)-palladium(II)-dichloride,

0.41 g Copper(I)-iodide and

27.5 mL Triethylamine. The used receivers are rinsed with

10 g Dichloromethane. The brown suspension is treated at 30 to 34°C within 1 to 2 hours with a solution of

16.8 g 2-Methyl-3-butin-2-ol in

60 mL Dichloromethane. The dropping funnel is rinsed with

5 mL Dichloromethane. The mixture is stirred for 3 hours at 30 to 34°C and then treated at 30 to 34°C with

100 mL Dichloromethane and

150 mL Ammonium hydroxide solution (10% in water). The biphasic solution is stirred for 10 to 20 minutes at 30 to 34°C and the layers are then allowed to separate for 15 to 45 minutes. The organic layer is separated and the aqueous layer is extracted at 30 to 34°C with

40 mL Dichloromethane. The combined organic layers are washed at 28 to 34°C with

150 mL Ammonium hydroxide solution (10% in water) and then with

150 mL Water. The organic layer is then treated at 25 to 32°C with

300 mL Hydrochloric acid (1.0 M in water). The biphasic solution is stirred for 20 to 30 minutes at 25 to 32°C and the layers are then allowed to separate for 30 to 60 minutes. The organic layer is separated and extracted at 25 to 32°C with

100 mL Hydrochloric acid (1.0 M in water). The combined product containing aqueous layers are washed at 25 to 32°C with

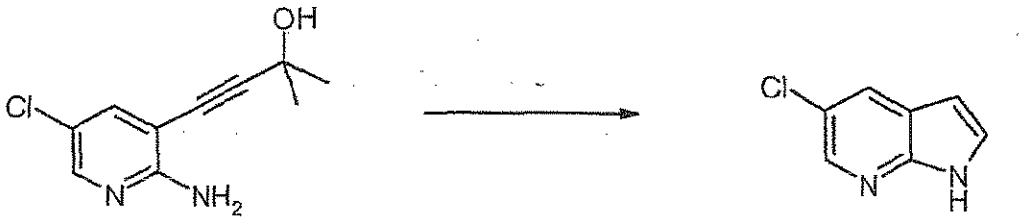
100 mL Dichloromethane. From the aqueous layer dichloromethane is then azeotropically removed with water under reduced pressure and at a

maximum internal temperature of 30°C. The aqueous solution is then treated at 22 to 30°C within 60 to 120 minutes with approximately

32 mL Sodium hydroxide (28% in water) until the pH is adjusted to pH 9. This forces the product to precipitate. After the dosing the resulting suspension is stirred at 20 to 25°C over night. The crystals are filtered off and washed in two portions with totally

150 g Water. The wet crystals (40.2 g) are dried at 40 to 50°C and <30 mbar until constant weight to afford 29.2 g (92%) of slightly brownish crystals with a purity of 98.7 %(area).

Step 3: Synthesis of 5-chloro-7-azaindol (Ib)



5-Chloro-7-azaindole (Ib)

A 500 mL double-jacket reactor (under a nitrogen atmosphere) is charged with

25.0 g 4-(2-Amino-5-chloro-pyridin-3-yl)-2-methyl-but-3-yn-2-ol

120 mL *N*-Methylpyrrolidone and

130 mL Water. The mixture is heated to 75 to 80°C (ca. 95°C jacket temperature) and a vacuum of ca. 350 mbar is applied. The solution is then treated at 75 to 80°C within 30 to 45 minutes with

85 mL Sodium hydroxide (28% in water). The dropping funnel is rinsed with

5 mL Water and the mixture stirred at 78 to 81°C over night. During stirring the jacket temperature and the vacuum have to be adjusted such that a slight steadily distillate flow is guaranteed. In a typical lab experiment approx. 50 mL of water/acetone are distilled off in 2 hours. During the reaction water is continuously added to keep the volume constant at approx. 270 mL. Upon complete conversion, the reaction mixture is cooled to 50 to

55°C. The mixture is treated at this temperature with

60 mL Toluene. The biphasic mixture is stirred at 50 to 55°C for 15 to 30 minutes and the layers are then allowed to separate for 15 to 30 minutes. The aqueous layer is separated and then extracted at 50 to 55°C with 3×50 mL, totally with

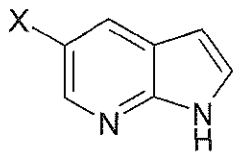
150 mL Toluene. The combined toluene layers are washed at 50 to 55°C with 5x40 mL, totally with

200 mL Water. The toluene layer is concentrated to dryness. The residue (17.3 g) is crystallized from

90 mL Toluene to afford 13.0 g (71%) of 5 chloro-7-azaindol (Ib) as slightly yellow crystals with a purity of 96.7 %(area).

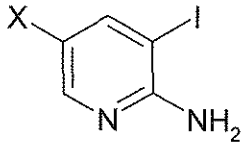
Claims

1. A process for the manufacture of compound (I),

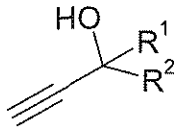

(I),

characterized in that

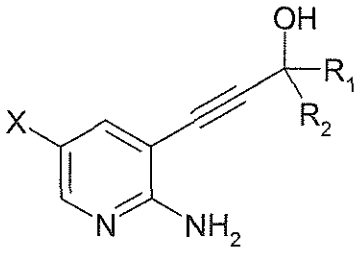
aa) the compound of formula (II)


(II),

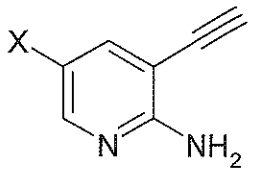
is reacted with the compound of formula (III)


(III),

in the presence of a catalyst, copper(I)iodide and a base, to give the compound of formula (IV)


(IV), and

bb) said compound of formula (IV) is further reacted in the presence of aqueous alkali metal hydroxide at 50-90°C and under reduced pressure to give the compound of formula (V)



(V), and

cc) said compound of formula (V) is reacted in the presence of aqueous alkali metal hydroxide or a strong base to give the compound of formula (I);

wherein

R^1 and R^2 are independently selected from a C1-C4 alkyl, and

X is -Br or -Cl.

2. The process according to claim 1, wherein X is –Br.

3. The process according to claims 1 or 2, wherein R^1 and R^2 are both methyl.

4. The process according to claim 2, wherein reaction step bb) is carried out in the presence of aqueous alkali metal hydroxide at 50-80°C and under reduced pressure below 100 mbar.

5. The process according to any one of claims 1 to 4, wherein the catalyst in step aa) is $PdCl_2(PPh_3)_2$ and the alkali metal hydroxide in step bb) is lithium- or sodium hydroxide.

5. The process according to claim 1, wherein the compound of formula (IV) is dissolved in a mixture of water and *N*-methylpyrrolidone, and is reacted in the presence of aqueous sodium hydroxide at about 75 to about 85°C and under reduced pressure for 15 to 20 hours to give directly the compound of formula (I) without the need to apply an aqueous work-up of the compound of formula (V).

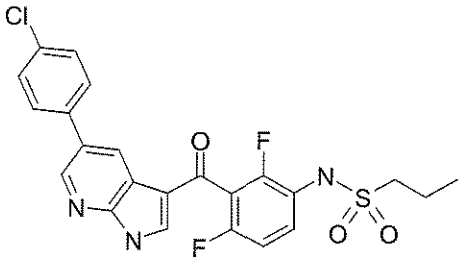
7. The compound of formula (IV) according to claim 1.

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PROCESS FOR THE MANUFACTURE OF PHARMACEUTICALLY ACTIVE COMPOUNDS

Abstract

According to the present invention there are provided novel processes for the manufacture of the compound of formula 1



(1),

as well as novel synthesis routes for key intermediates used in those processes.

(No suitable figure)