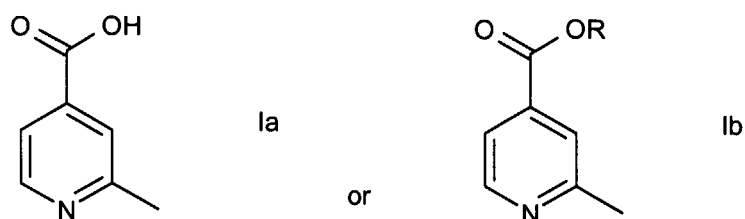


Process for preparation of isonicotinic acid derivatives

The present invention relates to a process for the manufacture of compounds of formula Ia or Ib



and pharmaceutically acceptable additional salts thereof,

5 wherein

R is lower Alkyl.

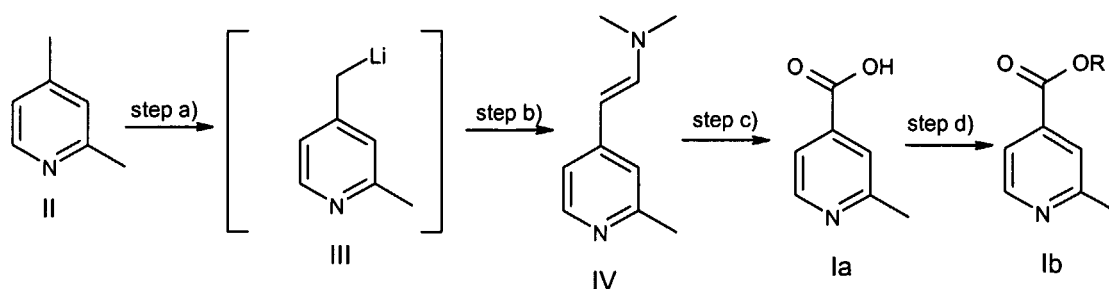
The compounds of formula Ia or Ib are valuable intermediate products for the manufacture of compounds which are pharmaceutically active as adenosine A2a receptor antagonist or metabotropic Glutamate receptor 2 antagonist. They are important in the regulation of many aspects of cellular metabolism and in the modulation of different central nervous system activities (WO 01/97786, WO 03/043636, and WO 02/083665).

The object of the present invention is to provide a new process for preparing isonicotinic acid derivatives of formula Ia or Ib from inexpensive starting compounds.

This object is surprisingly achieved by the process as shown in scheme 1:

15

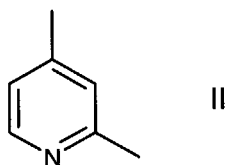
Scheme 1



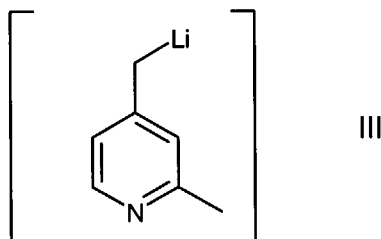
The new process has the advantage that it is simple, cheap and efficient comparing with the process known in the art (R. Johnson, T. Lovet and T. Stevens, Journal of the Chemical Society 796, 1970; J. Bardhan, Journal of the Chemical Society 2223, 1929; J. LoCicero and R. Johnson, Journal of the American Chemical Society, 74, 2094-7; 1952).

5 The new process comprises the step of

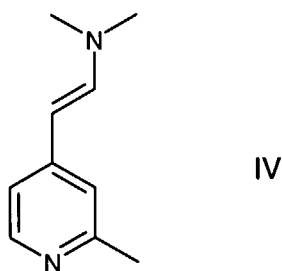
a) lithiating of compound of formula II



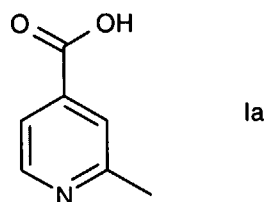
with lithium diethylamide to a lithiated compound of formula III;



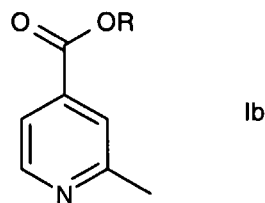
10 b) reacting the compound of formula III with DMF to produce the compound of formula IV;



c) oxidizing the compound of formula IV with O₃ and H₂O₂ to produce compound of formula Ia;



d) if desired, esterifying compound of formula Ia with an alcohol of the formula ROH to produce compound of formula Ib;



5 wherein R is as defined above.

The term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred lower alkyl groups are groups with 1-4 carbon atoms. More preferred lower alkyl group is methyl.

10 The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Step a)

15 Step a) comprises lithiating 2,4-dimethyl-pyridine of formula II with a lithiating agent, such as lithium diethylamide to a lithiated compound of formula III.

Typically, the reaction is performed in an organic solvent, such as ether, hydrocarbon or THF, preferably THF.

20 The reaction temperature is typically in the range of -70 °C to 0 °C, preferably between -70 °C to -50 °C.

The reaction time is as a rule 0.5 to 3 hours, preferably 1 hour.

Step b)

Step b) comprises reacting compound of formula III with DMF to produce the compound of formula IV

25 Typically the reaction is performed in an organic solution of compound of formula III and DMF is added.

The reaction temperature is typically in the range of -70 to 0 °C, preferably -60 °C to -40 °C.

The reaction is as a rule finished after 0.5 to 3 hours, preferably 1 hour.

The general principle of reaction steps a) and b) are described in J. Ragan, B. Jones, 5 C. Meltz and J. Teixeira, Synthesis, 483 (4) 2002.

Step c)

Step c) comprises oxidizing the compound of formula IV with O₃ and H₂O₂ to produce compound of formula Ia;

10 The reaction of step c) is typically performed in an organic solvent, such as an organic acid, an alcohol, chlorinated hydrocarbon or an ester, containing small amounts of water, such as 1-10%, preferably acetic acid containing 5% of water. The inclusion of water avoids the build-up of dangerous peroxides in the reaction mixture, especially in the presence of a protic solvent. The ozonolysis is performed at the temperature range of 0 °C to 50 °C, preferably 15 °C to 20 °C for typically 0.5- 3 hours, preferably 1 hour.

15 The reaction mixture is further oxidized with H₂O₂, typically for a time range of 0.5- 3 hours.

In the absence of an additional acid, the oxidation with H₂O₂ requires heating to a temperature range of 30 to 100 °C, preferably 50 °C.

20 In the presence of an additional acid, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, methanesulfonic acid, p-toluenesulfonic acid, preferably hydrochloric acid, sulfuric acid or formic acid, the subsequent oxidation with H₂O₂ may be achieved at ambient temperature. H₂O₂ may be added from the start or after the ozonolysis reaction. Hereby, the added water is substituted by aqueous H₂O₂, (preferably ca. 1 equ. constituting also ~5% water content) which provides both the water 25 presence and the additional oxidant for the second stage from the outset.

Step d)

Step d) comprises esterifying compound of formula Ia with an alcohol of formula ROH to produce compound of formula Ib.

30 Esterifying with an alcohol of formula ROH to produce compound of formula Ib is typically performed in an alcohol, such as methanol, ethanol, n-propanol, i-propanol, n-

butanol, i-butanol, 2-butanol or t-butanol, preferably methanol in the presence of a mineral acid or a substance generating a mineral acid *in situ*, e.g. SOCl₂.

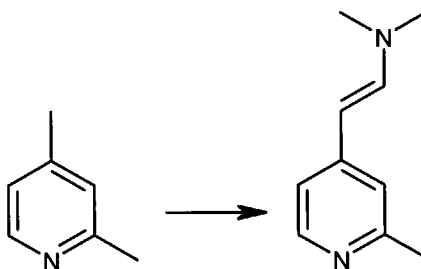
The reaction temperature as mainly depends on the boiling temperature of the alcohol used, as a rule lies in the range of 60 °C to 150 °C.

5 The reaction time is as a rule finished after 1 to 24 hours, preferably 1 hour.

The following examples shall illustrate the invention in more detail without limiting it.

Example 1

Preparation of dimethyl-[2-(2-methyl-pyridin-4-yl)-vinyl]-amine



11.05 g 2,4 -Lutidine (0.1 mol) were dissolved in 50 ml THF. The solution was cooled and stirred, maintaining the temperature at between -70 to -50 °C. 81.25 ml nBuLi (0.13 mol) was added over 0.25 hour. The dark red solution was stirred for a further 0.5 hour, then 15.14 ml diethylamine (0.145 mol) was added in one portion producing an orange suspension. After a 0.5 hour, 15.5 ml DMF (0.2 mol) was added. The brown-red solution was stirred for 1 hour then quenched with 50 ml 50% saturated aqueous ammonium chloride solution. Upon warming to ambient temperature, the reaction mixture was extracted with tert. butyl methyl ether (TBME) (3x 100 ml) and the combined organic phases were washed with 50 ml H₂O, dried over Na₂SO₄, filtered and concentrated under reduced pressure (45 °C/450-20 mbar) providing an orange-red oil (14.8 g, 91%) which was sufficiently pure (Gas Liquid Chromatography (GLC) 98 area%) to be used directly in the next step.

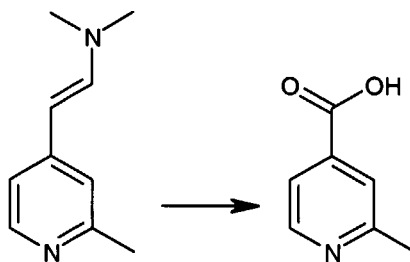
15

20

Example 2

i) Preparation of 2-methyl-isonicotinic acid (no additional acid, 50 °C)

- 6 -



1.63 g Dimethyl-[2-(2-methyl-pyridin-4-yl)-vinyl]-amine (10 mmol) were dissolved in 19 ml acetic acid containing 1 ml H₂O. To the red solution maintained and stirred at ca. 15-20 °C was passed O₃ (~85 mmol/hour) for 1 hour. The reaction was

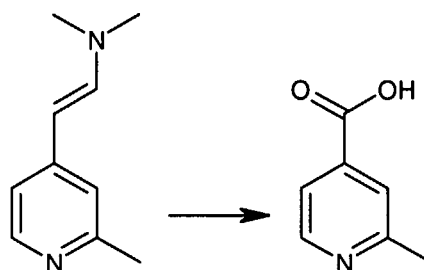
5 mildly exothermic, changing in appearance from an orange (10 min) to a yellow solution (15 min) then from a yellow (20 min) to a white suspension (30 min). Excess ozone was purged with argon until a peroxide test was essentially negative. 1.02 ml 30% aqueous H₂O₂ (10 mmol) was added in one portion and the resulting yellow suspension was stirred at 50 °C for 2 hours during which time a white suspension was formed. With

10 the aid of toluene, the aqueous acetic acid solvent was removed under reduced pressure (45 °C/100-50 mbar). The white residue was briefly digested in 25 ml tert. butyl methyl ether (TBME) at 40 °C then at ambient temperature for 30 min. The product was filtered, washed with TBME and dried for 2 hours at 45 °C/25 mbar: 1.17 g (85 %) beige crystals (GLC 98 area%, as trimethylsilylester).

15

¹H-NMR: (400 MHz, D₆ DMSO): δ = 2.54 (s, 3H), 7.59 (dd, 1H), 7.70 (s, 1H), 8.60 (dd, 1H)

ii) Preparation of 2-methyl-isonicotinic acid (additional acid, ambient temperature)



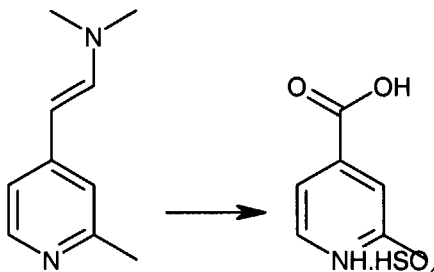
20

The reaction procedure was performed according to i). After purging with argon, 1.16 ml 98 % aqueous formic acid (30 mmol) and 1.02 ml 30 % aqueous H₂O₂ (10 mmol) were added in one portion and the suspension was stirred at ambient temperature for 3 hours. The solvent was removed with the aid of toluene under reduced pressure (45

25 °C/80-20 mbar). The residue was briefly digested in 25 ml tert. butyl methyl ether

(TBME) at 40 °C then at ambient temperature for 30 min. The product was filtered, washed with TBME and dried for 2 hours at 45 °C/25 mbar: 1.17 g pale orange crystals (GLC 99 area%, as trimethylsilylester).

iii) Preparation of 2-Methyl-isonicotinic acid.H₂SO₄

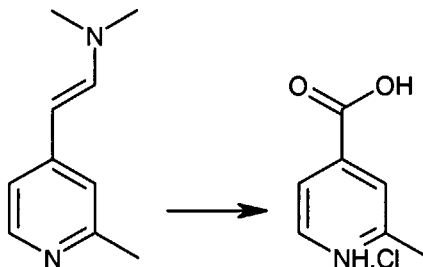


5

The ozonolysis procedure was performed as according to i) in the presence of 1 eq. 30% aqueous H₂O₂ on a 2 mmol scale. After purging with argon, 0.12 ml concentrated H₂SO₄ (2.1 mmol) was added in one portion and the yellow suspension was stirred at ambient temperature for 1 hour. The solvent was removed with the aid of toluene under reduced pressure (45 °C/80-20 mbar). The residue was briefly digested in 5 ml THF at 50 °C then at ambient temperature for 30 min. The product was filtered, washed with THF and dried for 1 hour at 45 °C/20 mbar: 0.43 g (92%) pale yellow crystals (HPLC 82 area%).

10

iv) Preparation of 2-methyl-isonicotinic acid.HCl



15

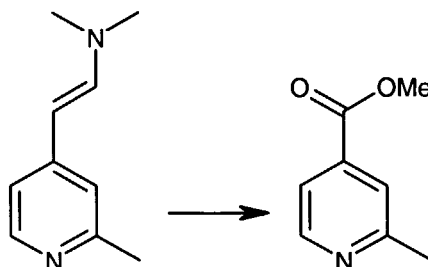
The reaction procedure was performed as according to iii) on a 2 mmol scale. After purging with argon, 1.1 ml 37% aqueous HCl (2 eq.) was added in one portion and the suspension was stirred at ambient temperature for 1 hour. The solvent was removed with the aid of toluene under reduced pressure (45 °C/80-20 mbar). The residue was briefly digested in 5 ml THF at 50 °C then at ambient temperature for 30 min. The product was filtered, washed with THF and dried for 1 hour at 45 °C/20mbar: 0.33 g (94%) pink crystals (HPLC 88 area%, GLC 98 area% as trimethylsilylester).

20

¹H-NMR: (400 MHz, D₆ DMSO): δ = 2.77 (s, 3H), 8.03 (dd, 1H), 8.017 (s, 1H), 8.83 (dd, 1H)

Example 3

Preparation of methyl 2-methyl-isonicotinate



5

The reaction procedure was performed as according to Example 2 iv) on a 10 mmol scale but with the addition of 37% aqueous HCl (2 eq.) and 30% aqueous H₂O₂ (1 eq.) after the initial ozonolysis step. The crude product was taken in 10 ml MeOH, the suspension cooled to ca. 5 °C and 1.62 ml thionyl chloride (SOCl₂) (22 mmol) were added cautiously. The reaction mixture was heated at 65 °C for 1 hour during which a yellow suspension transformed into an orange solution. The solvent was removed under reduced pressure (45 °C/200-20 mbar) and the residue was distributed between 20 ml ethyl acetate (EtOAc) and 20 ml saturated aqueous NaHCO₃. The aqueous phase was separated and extracted with EtOAc (2x 20 ml). The combined organic phases were washed with 20 ml saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered and concentrated under reduced pressure (45 °C/150-20 mbar) providing an orange-red oil (1.19 g, 79%, GLC 100 area%).

10

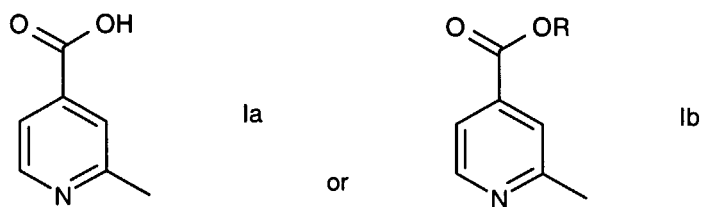
15

¹H-NMR: (400 MHz, CDCl₃): δ = 2.63 (s, 3H), 3.95 (s, 3H), 7.63 (dd, 1H), 7.71 (s, 1H), 8.65 (dd, 1H)

20 MS: 151.0 (M⁺)

Claims

1. A process for the manufacture of compounds of formula Ia or Ib



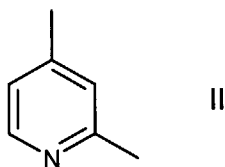
and pharmaceutically acceptable additional salts thereof,

- 5 wherein

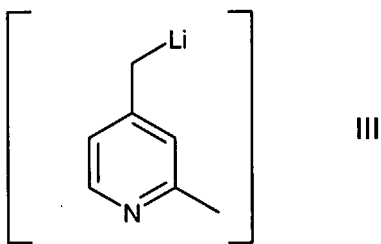
R is lower Alkyl;

comprises the step of

- a) lithiating compound of formula II

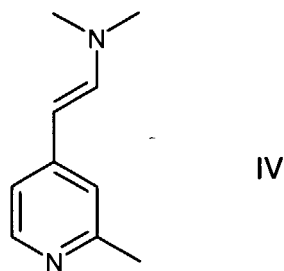


- 10 with a lithiating agent to a lithiated compound of formula III

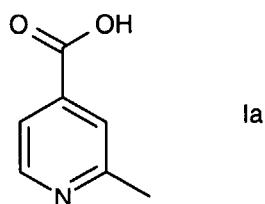


- b) reacting of the compound of formula III with DMF to produce the compound of formula IV

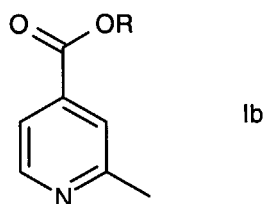
- 10 -



c) oxidizing the compound of formula IV with O_3 and H_2O_2 to produce compound of formula Ia;



5 d) if desired, esterifying compound of formula Ia with an alcohol of formula ROH to produce compound of formula Ib;



wherein R is as defined above.

2. Process of claim 1 characterized in that R is methyl.
- 10 3. Process of claim 1 characterized in that lithiating agent is lithium diethylamide.
4. Process of claim 1 characterized in that step a) is performed in an organic solvent at a temperature of $-70\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$.
5. Process of claim 3 characterized in that the organic solvent is THF, and the temperature is $-70\text{ }^{\circ}\text{C}$ to $-50\text{ }^{\circ}\text{C}$.
- 15 6. Process of claim 1 characterized in that step b) comprises reacting compound of formula II with DMF at a temperature of $-70\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$.
7. Process of claim 5 characterized in that the temperature is $-60\text{ }^{\circ}\text{C}$ to $-40\text{ }^{\circ}\text{C}$.

8. Process of claim 1 characterized in that in step c) the ozonolysis is performed in an organic solvent containing 1-10 % of water at a temperature of 0 °C to 50 °C.
9. Process of claim 7 characterized in that the organic solvent is acetic acid, the water content is 5 % and the temperature is 15 °C to 20 °C.
- 5 10. Process of claim 1 characterized in that in step c) the oxidation with H₂O₂ is performed in the absence of an additional acid at a temperature of 30 °C to 100 °C.
11. Process of claim 9 characterized in that the temperature is 40 °C to 60 °C.
12. Process of claim 1 characterized in that in step c) the oxidation with H₂O₂ is performed in the presence of an additional acid at ambient temperature.
- 10 13. Process of claim 11 characterized in that the additional acid is hydrochloric acid, sulfuric acid or formic acid.
14. Process of claim 1 characterized in that the step d) is performed in an alcohol in the presence of a mineral acid or a substance generating a mineral acid at a temperature of 60 °C to 150 °C.
- 15 15. Process of claim 13 characterized in that the alcohol is methanol, the substance generating a mineral acid is SOCl₂ and the temperature is 60 °C to 70 °C.
16. The invention as herein before described.