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(54) **PROCESS FOR PREPARING A SUBSTITUTED IMIDAZOPYRIDINE COMPOUND**

VERFAHREN ZUR HERSTELLUNG EINER SUBSTITUIERTEN IMIDAZOPYRIDINVERBINDUNG
PROCEDE DE PREPARATION D'UN COMPOSE D'IMIDAZOPYRIDINE SUBSTITUE

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EP-A1- 0 033 094 **EP-A2- 0 308 917**
WO-A1-99/55706
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specification

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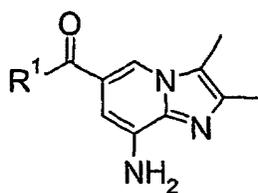
Description

FIELD OF THE INVENTION

5 **[0001]** The present invention relates to a new process for the preparation of a substituted imidazopyridine compound, more specifically a new process for the preparation of a 2,3-dimethylimidazo[1,2-a]pyridine substituted in the 6-position by a carboxamido or a carboxyalkyl group. In further aspects, the present invention also relates to new intermediates used in the process.

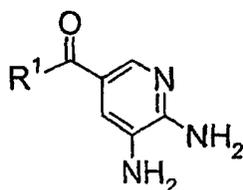
10 BACKGROUND AND PRIOR ART

[0002] The present invention relates to a new process suitable for large-scale preparation of a substituted imidazopyridine compound of formula (1),



25 (1)

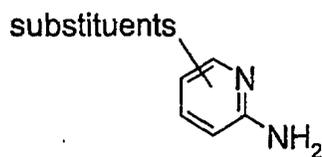
wherein R¹ is a C₁-C₆ alkoxy or NH₂ group, comprising the step of reacting a compound of the formula (2)



40 (2)

wherein R¹ is a C₁-C₆ alkoxy or NH₂ group, with a 3-halo-2-butanone compound in cyclohexanone.

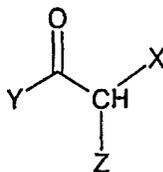
[0003] A similar reaction is described in EP 33094, EP 204 285, EP 228 006, EP 308 917, and WO 99/55706 wherein a substituted aminopyridine compound of the general formula (X)



55 (X)

is reacted with a compound of formula

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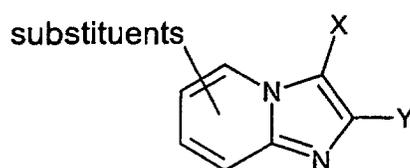
wherein X is i.a. H, CH₃ or an ester group, such as COOCH₃ or COOC₂H₅,

Y is i.a. CH₃, CH₂CH₃, and

Z is a leaving group, such as halogen, mesyl or tosyl,

15 to give a compound of the general structure

20



25 wherein X and Y are as described above.

[0004] The reaction is carried out in an inert solvent, such as acetone, alcohols, benzene, N,N-dimethylformamide, tetrahydrofuran, chloroform, or diethyl ether, preferably at elevated temperature, and optionally in the presence of an inorganic or organic base.

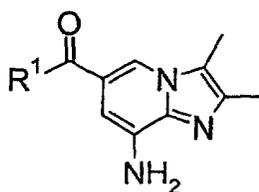
30 **[0005]** The reaction is characterized by long reaction times, e.g. 16 to 84 hours, high reaction temperatures and relatively low yields, e.g. 22% to 55%. The reaction is thereby not suitable for large-scale preparation of substituted imidazopyridine compounds.

[0006] We have surprisingly found that if the process of the present invention is carried out as described herein the reaction time can be shortened, the reaction temperature can be lowered and the yield is increased.

35 OUTLINE OF THE INVENTION

[0007] The present invention provides a new process for large-scale preparation of substituted imidazopyridine compound of formula (1)

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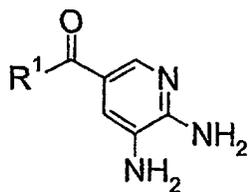
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50 **(1)**

wherein R¹ is a C₁-C₆ alkoxy or NH₂ group, comprising the step of reacting a compound of the formula (2)

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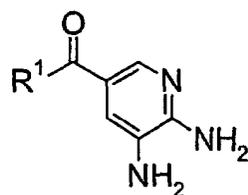
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(2)

with a 3-halo-2-butanone compound in cyclohexanone.

In a first embodiment of the present invention a compound of the formula (2)

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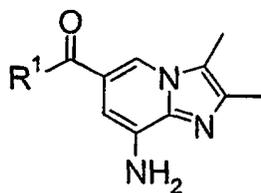
20

(2)

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wherein R¹ is a C₁-C₆ alkoxy group, is reacted with a 3-halo-2-butanone compound in cyclohexanone to give a compound of the formula (1)

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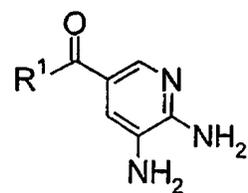
(1)

40

wherein R¹ is a C₁-C₆ alkoxy group.

[0008] In a second embodiment of the present invention a compound of the formula (2)

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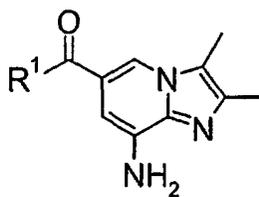
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(2)

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wherein R¹ is a NH₂ group, is reacted with a 3-halo-2-butanone compound in cyclohexanone to give a compound of the formula (1)

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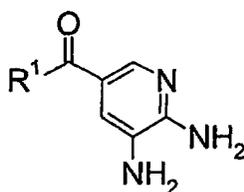
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(1)

wherein R¹ is NH₂ group.

15 **[0009]** The process of the present invention is performed by solving or suspending a compound of formula (2)

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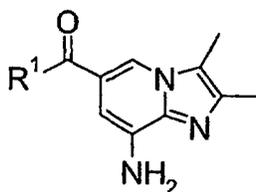
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(2)

wherein R¹ is a C₁-C₆ alkoxy or NH₂ group, in cyclohexanone and adding a 3-halo-2-butanone compound, heat the reaction for a few hours and thereafter isolate a compound of formula (1)

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35



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(1)

45 wherein R¹ is a C₁-C₆ alkoxy or NH₂ group, in high yields.

[0010] The amount of cyclohexanone is not crucial for carrying out the present invention, and can therefore in practical circumstances be adjusted according to needs and equipment used. It is also possible to mix cyclohexanone with inert solvents, such as ethers. Example of suitable inert solvents comprises, but is not limited to, tetrahydrofuran (THF). The amount of inert solvent can be up to around 50%, by volume, without causing a decrease in yield.

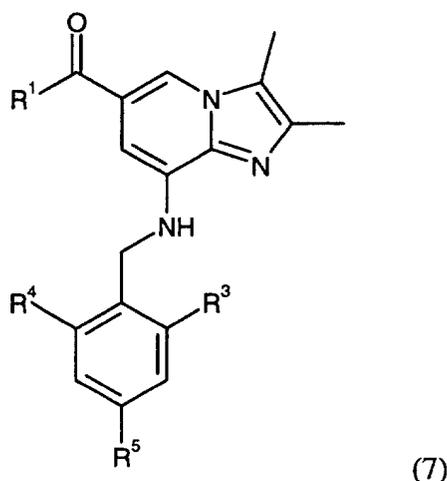
50 **[0011]** The amount of 3-halo-2-butanone compound is not critical for carrying out the present invention. It is for practical and economical reasons preferred to add 1.1 to 5 molar equivalents, preferably 1.1 to 2 equivalents. Example of suitable 3-halo-2-butanone compounds comprises, but is not limited to, 3-bromo-2-butanone and 3-chloro-2-butanone, of which the latter is preferred.

[0012] Reaction temperatures and reaction times can be varied to meet the actual need. It is preferred to have a reaction temperature from 80°C to 100°C. This reaction temperature gives a complete reaction within a few hours, e. g. 1 to 4 hours. Conversion is usually above 95% and the isolated yield is usually above 70%.

55 **[0013]** The starting material to be used in the present invention can be prepared as disclosed in WO 99/55706 or alternatively as is described below in Scheme 1.

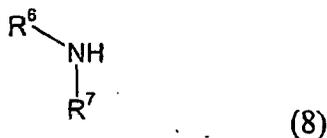
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wherein R³ is H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl or halogen; R⁴ is H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl or halogen; R⁵ is H, or halogen; and Y is a leaving group, such as a halide, tosyl or mesyl group, to give a compound of Formula (7).



wherein R¹, R³, R⁴, and R⁵ are as defined above. It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

[0018] Compounds of the Formula (7) wherein R¹ is C₁-C₆ alkoxy can thereafter be further reacted with an amino compound of the general Formula (8)



wherein R⁶ and R⁷ are the same or different and chosen from a group consisting of H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl, C₁-C₆ alkoxy-substituted C₁-C₆ alkyl, hydroxylated C₁-C₆ alkoxy-substituted C₁-C₆ alkyl, aryl, to give the corresponding amide compound.

[0019] R⁶ and R⁷ may together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms thereby forming e.g. morpholine, piperazine, pyrrolidine, or piperidine.

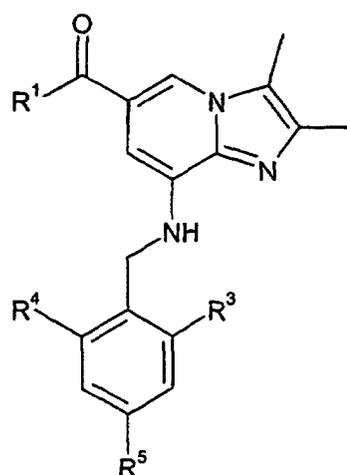
[0020] The reaction can be carried out by heating the reactants in the neat amino compound or dissolved in an inert solvent under standard conditions.

[0021] Alternatively can compounds of the Formula (7)

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(7)

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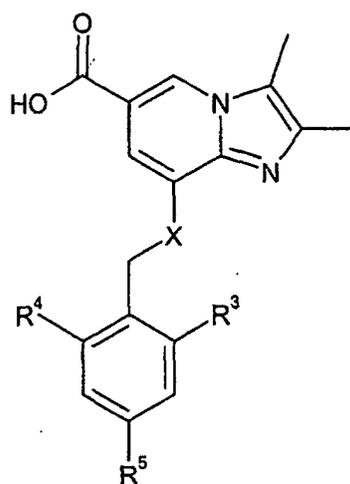
wherein R³, R⁴, and R⁵ are as defined above and R¹ is an NH₂ group, be hydrolyzed under standard conditions to the corresponding carboxylic acid compounds of Formula (9)

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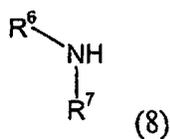


(9)

wherein R³, R⁴, and R⁵ are as defined above.

[0022] Compounds of the Formula (9) can thereafter be reacted with amino compounds of Formula (8)

50



(8)

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wherein R⁶ and R⁷ are as defined above, in the presence of a coupling reagent to give the corresponding amide compound. The reaction can be carried out in an inert solvent under standard conditions.

EXAMPLES

Example 1.1

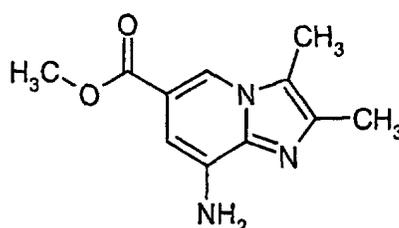
5 Preparation of Bromobutanone

[0023] In a reactor, sodium bromide (84 kg) is suspended in dimethylformamide (125 l). 3-Chloro-2-butanone (85 kg) is added at 15°C-30°C. Stirring is continued for 4 hours and then filtered: The filtercake is washed with cyclohexanone (38 l). The bromobutanone thereby prepared is ready to be used in the cyclisation step.

10 Example 1.2

Synthesis of methyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

15 [0024]

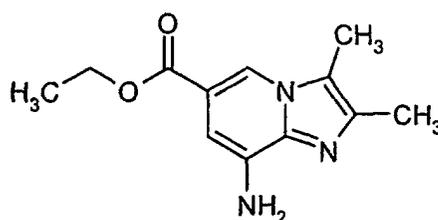


[0025] To a suspension of 5,6-diamino-nicotinic acid methyl ester (1 eq., 5.1 g) in cyclohexanone (50 ml) bromobutanone (1.2 equiv., 3.9 ml) was added over 10 min. The mixture was heated to 100°C (inner temperature) and stirred 2.5 h at this temperature. The mixture was cooled to room temperature and the pale solid was filtered off and was washed with TBME (3x10ml). Drying under reduced pressure at 45°C. Yield: 6.53 g (75%).

Example 1.3

35 Synthesis of ethyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

[0026]

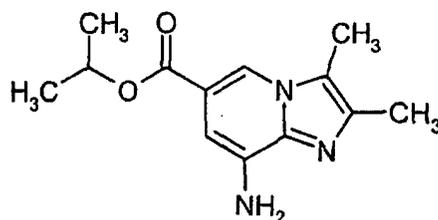


[0027] To a suspension of 5,6-diamino-nicotinic acid ethyl ester (1 eq., 5.0 g) in cyclohexanone (50 ml) bromobutanone (1.4 equiv., 5.95 g) was added over 15 min. The dark brown mixture was heated to 100°C (inner temperature) and stirred 1.5 h at this temperature. The mixture was cooled to room temperature and the light brown solid was filtered off and was washed with TBME (20 ml). Drying under reduced pressure at 45°C. Yield: 5.06 g (65%).

Example 1.4

Synthesis of isopropyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

5 [0028]



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[0029] To a suspension of 5,6-diamino-nicotinic acid isopropyl ester (1 eq., 5.1 g) in cyclohexanone (50 ml) bromobutanone (1.2 equiv., 3.4 ml) was added over 10 min. The dark brown mixture was heated to 100°C (inner temperature) and stirred 1.5h at this temperature. The suspension was cooled to room temperature and the pale yellow solid was filtered off and was washed with TBME (3x10ml). Drying under reduced pressure at 45°C. Yield: 6.0 g (74%).

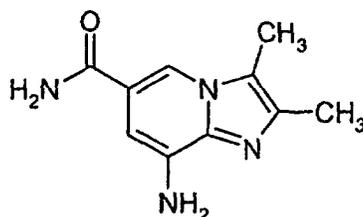
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Example 1.5

Synthesis of 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

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[0030]



30

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[0031] 5,6-Diamino-nicotinamide (50 g, 0.313 mol (assay: 95.4%), 1.0 equiv.) was suspended in cyclohexanone (250 mL). The suspension was heated to 100°C. The filtrate (bromobutanone in cyclohexanone) was added at 100°C over 1 h 10 min. Heating was continued for 3 h and the heating source was thereafter removed. The reaction mixture was allowed to cool to 20°C and stirred at this temperature for another 2 h. The solid was filtered off, washed carefully with TBME (2 x 330 mL) and dried to yield 70.3 g of title compound. Yield: 70%.

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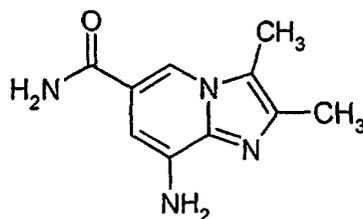
Example 1.6

Synthesis of 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

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[0032]

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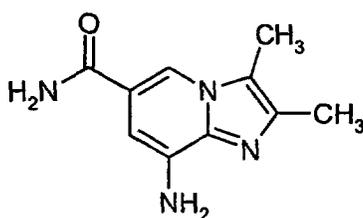
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[0033] NaBr (27.0 g; 0.259 mol; 1.33 equiv) was suspended in cyclohexanone (220 mL) and 3-chloro-2-butanone (25.7 mL; 0.242 mol; 1.24 equiv) was added in one portion. The mixture was heated to 80°C and stirred for 3 h. The mixture was cooled to 50°C, the white solid was filtered off and washed with cyclohexanone (60 mL). 5,6-Diamino-nicotinamide (30 g; 0.1946 mol; 1.0 equiv) was added to the filtrate and the mixture was heated to 100°C for 4 h, after which 98% conversion was determined by HPLC. The reaction mixture was cooled to 20°C, stirring was continued for 2 h at 20°C. The solid was filtered off, washed with TBME (220 mL) and dried to yield 46.6 g of the title compound. Yield: 73%.

Example 1.7

Synthesis of 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

[0034]

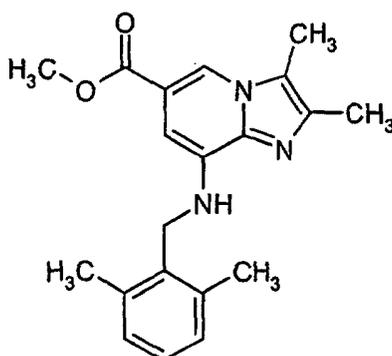


[0035] 5,6-Diamino-nicotinamide (30.0 g; 0.183 mol; 1.0 equiv) was suspended in cyclohexanone (280 mL). 3-Bromo-2-butanone (24 mL; 0.22 mol; 1.2 equiv) was added and the mixture was heated for 4 h to 100°C. The reaction mixture was cooled to 20°C and allowed to stir for another 2 h. The solid was filtered off, washed with TBME (200 mL) and dried to yield 48.4 g of the title compound. Yield: 78%.

Example 1.8

Synthesis of methyl 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate

[0036]



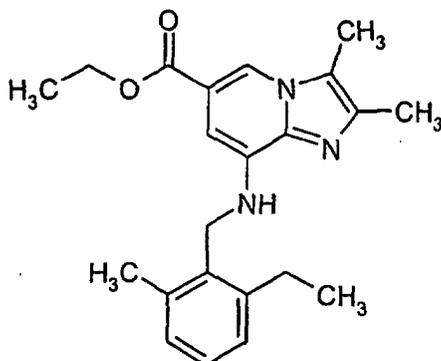
[0037] Methyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (0.8 g, 3.6 mmol), 2,6-dimethylbenzylchloride (0.57 g, 3.7 mmol), sodium carbonate (1.0 g, 9.4 mmol) and a catalytic amount of potassium iodide were added to acetonitrile (10 ml) and were refluxed for 20 h. Following filtration, the salts were washed with methylene chloride and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: ethyl acetate (75:25) as eluent. The yellow residue was treated with hexane to give 0.23 g (19%) of the title product.

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Example 1.9

Synthesis of ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate

5 [0038]



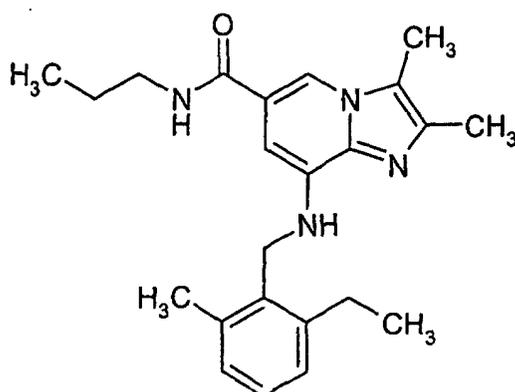
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[0039] Ethyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (0.7 g, 3.0 mmol), 2-ethyl-6-methylbenzylchloride (0.5 g, 3.0 mmol), sodium carbonate (0.64 g, 6.0 mmol) and a catalytic amount of potassium iodide were added to acetone (50 ml) and were refluxed for 20 h. Following filtration, the acetone was evaporated under reduced pressure to give an oil. The oily product was purified by column chromatography on silica gel using diethyl ether : petroleum ether (1:1) as eluent to give 0.12 g (9%) of the title product. ¹H-NMR (500 MHz, CDCl₃): δ 1.25 (t, 3H), 1.5 (t, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 2.75 (q, 2H), 4.45-4.5 (m, 4H), 4.9 (bs, 1H), 6.8 (s, 1H), 7.05-7.2 (m, 3H), 8.1 (s, 1H)

30 Example 1.10

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-carboxamide

35 [0040]



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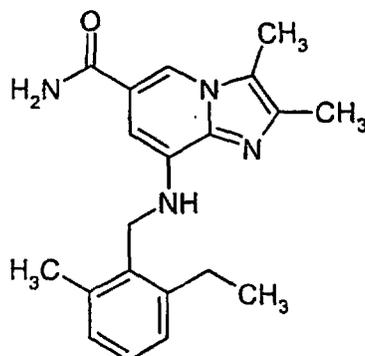
[0041] Ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), propylamine (1.0 g, 17 mmol) and a catalytic amount of sodium cyanide were refluxed in methanol (20 ml) for 24 h. An additional amount of propylamine (1.0 g, 17 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using diethyl ether as eluent. Crystallization from diethyl ether gave 0.053 g (42%) of the title compound. ¹H-NMR (300 MHz, CDCl₃): δ 1.0 (t, 3H), 1.2 (t, 3H), 1.65-1.75 (m, 2H), 2.3 (s, 3H), 2.35 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.4-3.5 (m, 2H), 4.35 (d, 2H), 4.9 (bs, 1H), 6.2 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 4H), 7.85 (s, 1H).

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Example 1.11

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

[0042]

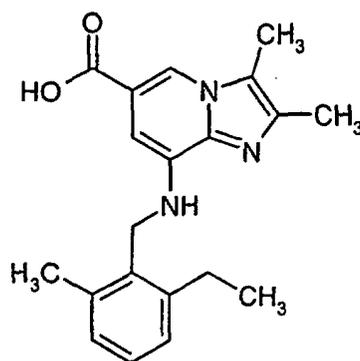


[0043] 8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (3.3 g, 16.2 mmol), 2-ethyl-6-methylbenzylchloride (2.73 g, 16.2 mmol), potassium carbonate (8.0 g, 58 mmol) and potassium iodide (1.1 g, 6.6 mmol) were added to acetone (150 ml) and refluxed for 20 h. An additional amount of 2-ethyl-6-methylbenzylchloride (1.0 g, 5.9 mmol) was added and the reaction mixture was refluxed for 7 h. Methylene chloride (60 ml) and methanol (30 ml) were added. The reaction mixture was filtered and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: methanol (100:7) as eluent. Crystallization from ethyl acetate gave 2.8 g (50%) of the title compound. ¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 4.4 (d, 2H), 4.9 (bs, 1H), 6.0 (bs, 2H), 6.45 (s, 1H), 7.0-7.2 (m, 3H), 7.9 (s, 1H).

Example 1.12

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid

[0044]



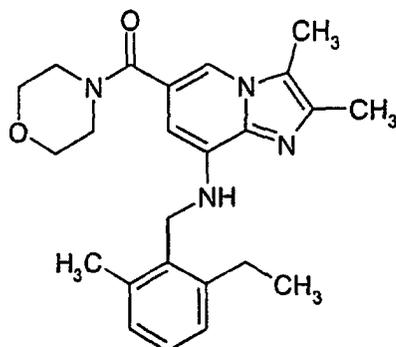
[0045] 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate (11.0 g, 0.025 mol) and sodium hydroxide (7.0 g, 0.17 mol) were solved in ethanol (95 %) (120 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (150 ml). The pH was adjusted to 5 by addition of conc. HCl and acetic acid and the solid that precipitated was isolated by filtration, washed with water and acetone, and dried to give 7.6 g (88 %) of the title compound. ¹H-NMR (500 MHz, DMSO-d₆): δ 1.15 (t, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 2.69 (q, 2H), 4.38 (d, 2H), 5.2 (bs, 1H), 6.73 (s, 1H), 7.07-7.2 (m, 3H), 8.12 (s, 1H)

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Example 1.13

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine

5 [0046]

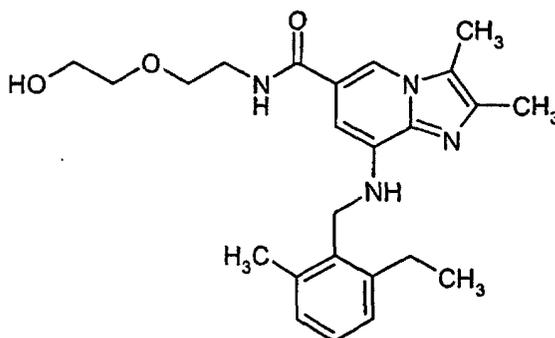


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[0047] 2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). Morpholine (0.12 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was added to a column with silica gel and purification by chromatography using ethyl acetate : methylene chloride (1:1) as eluent gave 0.12 g (66%) of the desired product. ¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 2.7 (q, 2H), 3.7 (s, 8H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.15 (s, 1H), 7.0-7.2 (m, 3H), 7.4 (s, 1H)

Example 1.14

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Synthesis of (2-ethyl-6 methylbenzylamino)-N(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

40 [0048]

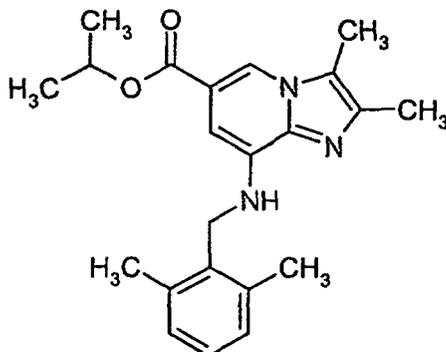


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[0049] 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.29 g, 0.90 mmol) were added to methylene chloride (10 ml). 2-(2-aminoethoxy)ethanol (0.2 g, 1.9 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent. Crystallization from diethyl ether gave 0.24 g (80%) of the desired product. ¹H-NMR (500 MHz, CDCl₃): δ 1.25 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 3.4-3.45 (m, 2H), 3.55-3.7 (m, 6H), 4.35 (d, 2H), 5.05 (t, 1H), 6.45 (s, 1H), 7.0-7.2 (m, 4H), 7.5 (s, 1H)

Example 1.15

Synthesis of isopropyl 8-[(2,6-dimethylbenzyl)amino]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

5 [0050]



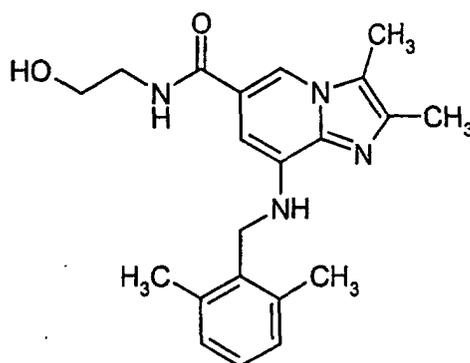
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[0051] Isopropyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (9.85 kg, 1.0 equiv., 29.71 mol) was suspended in isopropanol (59 L); NaI (0.6 equiv., 2.68 kg, 17.88 mol) and K₂CO₃ (2.5 equiv, 10.29 kg, 74.48 mol) were added and the mixture was heated to about 70°C. 2,6-Dimethylbenzyl chloride (1.1 equiv, 5.22 kg, 32.77 mol) was dissolved in isopropanol (-60 L) and this solution was added to the reaction mixture. After the addition was complete, the temperature was kept at 60°C for additional 1.5 hours. Additional K₂CO₃ was added (9.15 kg) and the resulting suspension was stirred for further 2h at 60°C. Additional 2,6-dimethylbenzyl chloride (2.76 kg) in isopropanol (22L) was added slowly at an temperature of 60°C; after the addition the reaction mixture was stirred for further 4 hours at this temperature. The suspension was diluted with water (124L), cooled, stirred and filtered. The filtercake was washed with water and then with cold isopropanol, dried under reduced pressure at 40°C to give 11.37 kg wet material, yield: 90%.

Example 1.16

35 Synthesis of 8-[(2,6-dimethylbenzyl)amino]-N-(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

[0052]



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[0053] A reactor was charged with isopropyl 8-[(2,6-dimethylbenzyl)amino]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (11.30 kg, 1 equiv., 27.02 mol) and THF (45 L), ethanolamine (18.97 kg, 11 equiv., 309.2 mol) was added at about 20°C. The suspension was heated to about 100°C. Some solvent was distilled off and then THF (35 L) was added and the distillation was continued. The procedure of adding THF and distilling it off was repeated until complete conversion. To the suspension ethanol (140L) was added and the suspension was heated to reflux. To obtain a clear

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solution additional ethanol (13L) was added. The hot solution was filtered and then cooled. The white solid was filtered off, washed with ethanol and dried to yield the product as a white powder. (8271 g).

2. PREPARATION OF STARTING MATERIALS

Example 2.1

Synthesis of 6-amino-5-nitro-nicotinamide

[0054] 100 g of 6-hydroxy-5-nitro-nicotinic acid (0.54 mol; HPLC > 98% area) was suspended in toluene (750 mL). DMF (1 mL, 0.013 mol, 0.024 equiv.) was added and the mixture was heated to 110°C (inner temperature). Thionylchloride (99 mL, 2.5 equiv.) was added over 120 min. Heating was continued for 4h at 110°C. The reaction mixture was concentrated to half the volume (400 mL of solvent were distilled off), and toluene (400 mL) was added. This procedure was repeated once again (410 mL of toluene were distilled off and fresh toluene (410 mL) was added again). The solution was then cooled to 20°C and slowly added to aqueous ammonia (25%, 440 mL, 12 equiv.) over 40 min. Precipitation started immediately. During the addition the temperature was maintained below 15°C. After the addition had been completed the reaction mixture was allowed to warm up to room temperature and stirring was continued for 16h. The solid was filtered off, washed with water (500 mL), ethanol (250 mL), TBME (250 mL) and dried (50-10 mbar, 40°C bath temperature, 16 h) to yield 91.3 g of the title compound (0.501 mol, 87%).

Example 2.2

Synthesis of 5,6-diamino-nicotinamide

[0055] 44.5 g of 6-amino-5-nitro-nicotinamide (0.24 mol; HPLC: 93% area) were suspended in methanol/water 1:1 (500 mL), 5.0 g of catalyst [Pd(4%)-Ru(1%)/C paste (62% H₂O type: 485; Johnson Matthey); type: 485; Johnson Matthey] was added. Hydrogenation was carried out at 5 bar and 30°C for 5h. After completion the catalyst was filtered off and washed with methanol/water 1/1 (50 mL). 480 mL of the solvent was distilled off. The resulting suspension was cooled to 20°C and filtered off. The solid was washed with methanol (20 mL) and TBME (30 mL). After drying (200-10 mbar; 40°C bath temperature, 16 h) 27.3 g of the title compound (0.18 mol, 73%) were obtained.

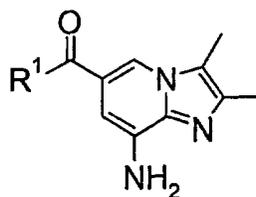
Example 2.3

Synthesis of 5,6-diamino-nicotinamide

[0056] 42.3 g of 6-amino-5-nitro-nicotinamide (0.23 mol, HPLC: 93% area) was suspended in methanol/water 1:1 (500 mL). 5.2g of catalyst [Pd(5%)/C (57.8% H₂O); type: 39, Johnson Matthey] was added. Hydrogenation was carried out at 5 bar and 30°C for 4h. After completion the catalyst was filtered off and washed with methanol/water 1/1 (100 mL). 550 mL of the solvent was distilled off. The resulting suspension was cooled to 20°C and filtered off. The solid was washed with methanol (20 mL) and TBME (30 mL). After drying (200-10 mbar; 40°C bath temperature, 16 h) 28.5 g of the title compound (0.18 mol, 78%) was obtained.

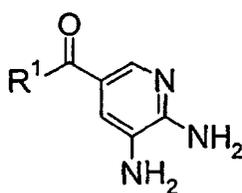
Claims

1. A process for preparing a substituted imidazopyridine compound of formula (1)



(1)

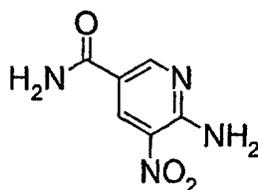
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15 wherein R¹ is C₁-C₆ alkoxy or NH₂,
comprising the step of reacting a compound of the formula (2)



(2)

25 with a 3-halo-2-butanone compound in cyclohexanone.

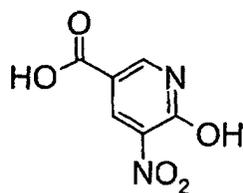
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2. A process according to claim 1, wherein the 3-halo-2-butanone compound is 3-bromo-2-butanone or 3-chloro-2-butanone.
 3. A process according to claim 1 or 2, wherein the amount of the 3-halo-2-butanone compound is 1.1 to 5 molar equivalents.
 - 35 4. A process according to claim 1, wherein the reaction temperature is 80°C to 100°C.
 5. A process according to claim 1, wherein cyclohexanone is diluted with an inert solvent.
 - 40 6. A process according to claim 1, wherein R¹ is C₁-C₆ alkoxy.
 7. A process according to claim 1, wherein R¹ is NH₂.
 - 45 8. A process according to claim 1, **characterized in that** compound (2) is prepared by a process comprising the step of hydrogenating a compound of formula (4)



(4)

55 in an aqueous alcoholic solution using a catalyst.

9. A process according to claim 8, wherein the catalyst is a Pd-Ru/C paste.
10. A process according to any of claim 8 or 9, **characterized in that** compound (4) is prepared by a process comprising the step of reacting a compound of formula (3)

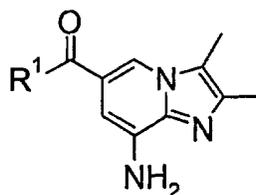


(3)

with thionyl chloride to give the corresponding chloride compound, which is thereafter treated with ammonia.

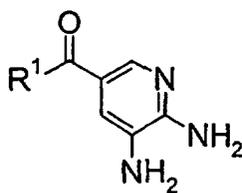
Patentansprüche

1. Verfahren zur Herstellung einer substituierten Imidazopyridinverbindung der Formel (1)



(1)

worin R¹ für C₁-C₆-Alkoxy oder NH₂ steht,
bei dem man eine Verbindung der Formel (2)



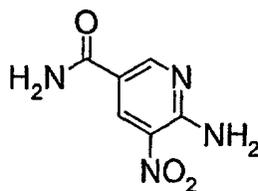
(2)

in Cyclohexanon mit einer 3-Halogen-2-butanon-Verbindung umgesetzt.

2. Verfahren nach Anspruch 1, bei dem es sich bei der 3-Halogen-2-butanon-Verbindung um 3-Brom-2-butanon oder 3-Chlor-2-butanon handelt.
3. Verfahren nach Anspruch 1 oder 2, bei dem die Menge der 3-Halogen-2-butanon-Verbindung sich auf 1,1 bis 5 Moläquivalente beläuft.

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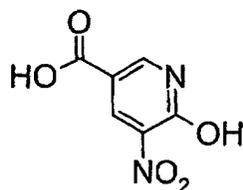
4. Verfahren nach Anspruch 1, bei dem die Reaktionstemperatur 80 bis 100°C beträgt.
5. Verfahren nach Anspruch 1, bei dem das Cyclohexanon mit einem inerten Lösungsmittel verdünnt wird.
- 5 6. Verfahren nach Anspruch 1, bei dem R¹ für C₁-C₆-Alkoxy steht.
7. Verfahren nach Anspruch 1, bei dem R¹ für NH₂ steht.
8. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** Verbindung (2) nach einem Verfahren hergestellt wird, bei dem man eine Verbindung der Formel (4)
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(4)

in wäßrig-alkoholischer Lösung unter Verwendung eines Katalysators hydriert.

- 25 9. Verfahren nach Anspruch 8, bei dem es sich bei dem Katalysator um eine Pd-Ru/C-Paste handelt.
10. Verfahren nach Anspruch 8 oder 9, **dadurch gekennzeichnet, daß** Verbindung (4) nach einem Verfahren hergestellt wird, bei dem man eine Verbindung der Formel (3)
- 30

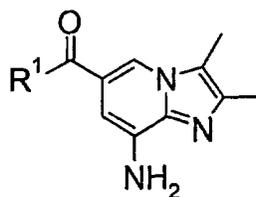


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(3)

mit Thiopnylchlorid zur entsprechenden Chloridverbindung umgesetzt und diese dann mit Ammoniak behandelt.

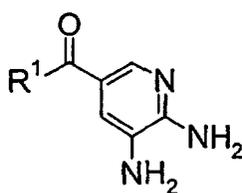
45 **Revendications**

1. Procédé de préparation d'un composé d'imidazopyridine substitué de formule (1)
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(1)

15 dans laquelle R¹ est alcoxy en C₁-C₆ ou NH₂,
comprenant l'étape de réaction d'un composé de formule (2)

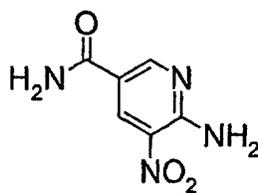


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(2)

avec un composé de 3-halogéno-2-butanone dans de la cyclohexanone.

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2. Procédé selon la revendication 1, dans lequel le composé de 3-halogéno-2-butanone est la 3-bromo-2-butanone ou la 3-chloro-2-butanone.
 3. Procédé selon la revendication 1 ou 2, dans lequel la quantité de composé de 3-halogéno-2-butanone est de 1,1 à 5 équivalents molaires.
 - 35
 4. Procédé selon la revendication 1, dans lequel la température réactionnelle est de 80°C à 100°C.
 5. Procédé selon la revendication 1, dans lequel la cyclohexanone est diluée avec un solvant inerte.
 - 40
 6. Procédé selon la revendication 1, dans lequel R¹ est alcoxy en C₁-C₆.
 7. Procédé selon la revendication 1, dans lequel R¹ est NH₂.
 8. Procédé selon la revendication 1, **caractérisé en ce que** le composé (2) est préparé par un procédé comprenant l'étape d'hydrogénation d'un composé de formule (4)

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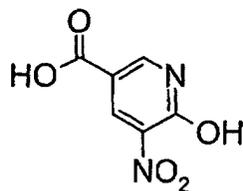
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(4)

dans une solution alcoolique aqueuse en utilisant un catalyseur.

9. Procédé selon la revendication 8, **caractérisé en ce que** le catalyseur est une pâte de Pd-Ru/C.

10. Procédé selon l'une ou l'autre des revendications 8 et 9, **caractérisé en ce que** le composé (4) est préparé par un procédé comprenant l'étape de réaction d'un composé de formule (3)

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(3)

avec du chlorure de thionyle pour donner le composé de chlorure correspondant, qui est ensuite traité avec de l'ammoniac.

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