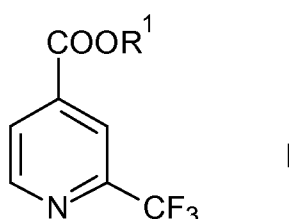


PROCESS FOR THE PREPARATION OF 2-TRIFLUORMETHYL ISONICOTINIC ACID AND ESTERS

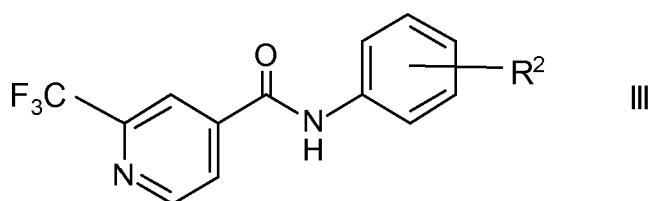
The invention relates to a novel process for the preparation of 2-trifluoromethyl isonicotinic acid and esters of the formula



5 wherein R¹ is hydrogen or C₁₋₆-alkyl.

The 2-trifluoromethyl isonicotinic acid and esters of the formula I are versatile intermediates for the preparation of active pharmaceutical and agrochemical agents (e.g. Manfred Schlosser et al., Eur. J. Org. Chem. 2003, 1559-1568).

10 The invention further relates to the use of the process of the present invention for a process for the preparation of TAAR1 agonists of the formula



wherein

R² is (CH₂)_n-(O)_o- heterocycloalkyl, optionally substituted by C₁₋₆-alkyl, hydroxy, halogen, or by -(CH₂)_p-aryl;

15 n is 0,1,2;

o is 0,1;

p is 0,1,2;

or a pharmaceutically suitable acid addition salt thereof.

TAAR agonists of the formula III have been disclosed in PCT Publ. WO 2012/016879.

Various syntheses are described in the art.

Chikara Fukaya et al., Chem. Pharm. Bull. 38(9) 2446-2458 (1990) for instance suggest to
5 first methylate 4-chloro-2-trifluoromethylpyridine with trimethylaluminium and to subsequently
oxidize the methyl group with KMnO_4 . The resulting yield is low and the process is not
applicable on technical scale.

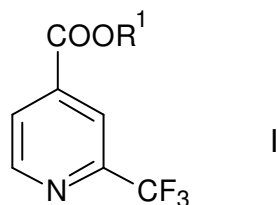
Manfred Schlosser et al., Eur. J. Org. Chem. 2003, 1559-1568) describe the preparation of
2-trifluoromethyl-4-pyridine carboxylic acid in an overall yield of 45% from 2-trifluoro pyridine
10 by initial deprotonation, subsequent iodination at the 3-position, followed by halogen migration
and final carboxylation. Also this synthesis is not applicable on technical scale.

Manfred Schlosser et al., Eur. J. Org. Chem. 2003, 1569-1575 describe a synthesis which
starts start from 2-trifluoromethylpyridine which is treated with the amide base LITMP (Li-
2,2,5,5-tetramethylpiperidine) at minus 70°C followed by a treatment with carbon dioxide. This
15 synthesis shows low selectivity towards the desired 2-trifluormethyl isonicotinic acid, applies an
expensive amide base and is as well difficult to handle on technical scale.

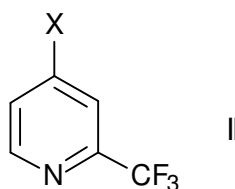
The object of the embodiments disclosed herein therefore was to find a process which is
able to overcome the drawbacks known from the processes known in the art and which is able to
be performed on technical scale.

20 It was found that the object could be reached with the process as outlined below.

The disclosure provides a process for the preparation of 2-trifluoromethyl isonicotinic acid and
esters of the formula

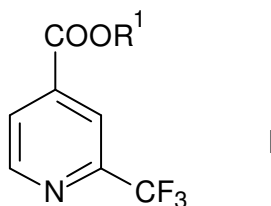


wherein R^1 is hydrogen or C_{1-6} -alkyl, comprises the conversion of a 2-trifluoromethyl
25 pyridine derivative of the formula

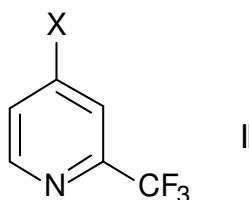


wherein X is halogen or -OSO₂CY₃, wherein Y is halogen, in the presence of a palladium complex catalyst.

In one aspect, there is provided a process for the preparation of 2-trifluoromethyl
5 isonicotinic acid and esters of the formula

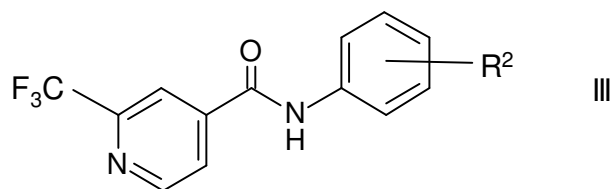


wherein R¹ is hydrogen or C₁₋₆-alkyl, comprising the conversion of a 2-trifluoromethyl pyridine derivative of the formula



10 wherein X is halogen or -OSO₂CY₃, wherein Y is halogen, with carbon monoxide (CO); in the presence of the reactant R¹OH, wherein R¹ is as above and in the presence of a palladium complex catalyst selected from Palladium(II)chloride with the ligand 1,1'-Bis-(diphenylphosphino)ferrocen (dppf).

In another aspect, there is provided use of the process as disclosed herein for a process for
15 the preparation of TAAR1 agonists of the formula



wherein

R^2 is $(CH_2)_n-(O)_o$ - heterocycloalkyl, optionally substituted by C_{1-6} -alkyl, hydroxy, halogen, or by $-(CH_2)_p$ -aryl;

5 n is 0,1,2;

 o is 0,1;

 p is 0,1,2;

or a pharmaceutically suitable acid addition salt thereof

10 The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term " C_{1-6} -alkyl" relates to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to six carbon atoms, preferably one to four, more preferably one to two carbon atoms. This term is further exemplified by radicals as methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl, pentyl and its isomers and hexyl and its isomers.

15 The term "halogen" refers to fluorine, chlorine, bromine or iodine, but particularly to chlorine.

The term "aryl", relates to an aromatic carbon ring such as to the phenyl or naphthyl ring, preferably the phenyl ring.

20 The term "heterocycloalkyl" refers to a non-aromatic 5 to 6 membered monocyclic ring which can comprise 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and/or sulphur, such as piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl or thiomorpholinyl.

25 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.

The 2-trifluoromethyl pyridine derivatives of the formula II are commercially available. They can alternatively be synthesized according to the teaching of the PCT Int. Publication WO 2011/161612 or the literature cited therein.

Suitable 2-trifluoromethyl pyridine derivatives of the formula II are those, wherein X is
5 fluorine, chlorine, bromine, iodine or trifluoromethanesulfonyl. 4-chloro-2-trifluoro pyridine (X=chlorine) is particularly used.

Suitable palladium complex catalysts are either commercially available or can be prepared in situ following methods known to the skilled in the art.

They can be selected from Bis(benzonitrile)palladium(II)-chloride (CAS No.14220-64-5), Tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3), (Palladium(II)acetate (CAS No.3375-31-3) or Palladium(II)chloride CAS No. 7647-10-1 with the ligands selected from 1,1-Bis(diphenylphosphino)ethane (dppe), 1,1'-Bis(diphenylphosphino)ferrocene (dppf),
5 Bis(diphenylphosphino)methane (dppm), 1,3-Bis(diphenylphosphino)propane (dppp), 4,5-Bis(diphenylphosphino) 9,9-dimethylxanthene or from triphenylphosphane.

In one embodiment the conversion comprises the reaction of the 2-trifluoromethyl pyridine derivative of the formula II with carbon monoxide (CO) in the presence of the reactant R^1OH , wherein R^1 is as above.

10 Particularly selected palladium complex catalysts for this conversion is Palladium(II)chloride with the ligands 1,1'-Bis(diphenylphosphino)ferrocene (dppf) or 1,3-Bis(diphenylphosphino)propane (dppp) preferably in their commercially available form 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct (CAS No.95464-05-4) and (1,3-Bis
15 (diphenylphosphino) propane)- palladium(II)chloride (CAS No.59831-02-6).

The conversion can be performed under a CO pressure of 5 bar to 100 bar, more particularly of 60 bar to 70 bar.

The reaction temperature is as a rule selected between 50°C and 170°C, particularly between 120°C and 140°C.

20 Advantageously a base is present which can either be selected from an organic base, like a tertiary amine or from an inorganic base, like an alkali hydrogen carbonate or an alkali phosphate. A suitable representative for an organic base is a tri-alkylamine, like triethylamine and suitable representatives for inorganic bases are for instance sodium hydrogen carbonate or tri-potassium phosphate.

25 The reactant R^1OH is either water ($R^1 = H$) affording the 2-trifluoromethyl isonicotinic acid or a C_{1-6} -alcohol ($R^1 = C_{1-6}$ -alkyl) affording the respective 2-trifluoromethyl isonicotinic acid esters.

Particularly C_{1-4} -alcohols such as methanol, ethanol, n-propanol, i-propanol, n-butanol, s-butanol or t-butanol, more particularly methanol, ethanol, or i-propanol and even more
30 particularly methanol are used.

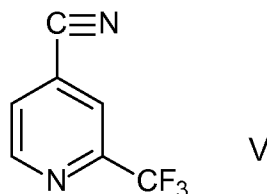
In case of the conversion with water an organic solvent selected from ethers like dioxane or tetrahydrofuran or lower alcohols like methanol, ethanol or i-propanol can be added. Tetrahydrofuran was found to be particularly suitable.

In the case of the conversion with a C₁₋₆-alcohol the initial conversion with carbon monoxide can be followed by a treatment with a hydrogen chloride producing agent to foster complete ester formation.

Suitable hydrogen chloride producing agents can be selected from inorganic acid chlorides, like hydrogen chloride or from organic acid chlorides such as thionyl chloride or acetylchloride. Thionyl chloride was found to be most suitable.

The treatment with the hydrogen producing agent is usually performed at reflux conditions of the reaction mixture.

In a further embodiment the conversion comprises the reaction of the 2-trifluoromethyl pyridine derivative of the formula I with a metal cyanide MCN, wherein M stands for a metal ion to form a nitrile of formula IV



and the further hydrolysis or esterification to form the 2-trifluoromethyl isonicotinic acid and esters of the formula I.

The palladium complex catalyst selected for this conversion as a rule is Pd(PPh₃)₄(0), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct (CAS No.95464-05-4), Pd(P-tert.-Bu₃)₂, Tris(dibenzylideneacetone)dipalladium(0) or Pd(TFA)₂ with the ligands 1,1'-Bis(diphenylphosphino)ferrocene (dppf) or rac-2-(di-tert.-butylphosphino)-1,1'-binaphthyl.

Suitable metal cyanides MCN are zinc cyanide, or zinc cyanide with a mixture with sodium cyanide or potassium cyanide, but particularly is zinc cyanide.

The reaction temperature is usually selected between 50°C and 120°C.

The reaction takes place in a suitable organic solvent such as in N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone, N-ethyl-2-pyrrolidone, but preferred in N,N-dimethyl formamide.

The nitrile of formula IV can be isolated from the reaction mixture for instance by way of extraction with a suitable solvent such as with tert. methyl butyl ether and evaporation of the solvent. Vacuum distillation of the crude nitrile can afford the nitrile in high purity.

5 The hydrolysis of the nitrile of formula IV to the 2-trifluoromethyl isonicotinic acid of formula I with $R^1 = \text{hydrogen}$ is performed with a suitable base which can be selected from an alkali hydroxide such as sodium-, potassium- or lithium hydroxide.

As a rule the reaction takes place in a suitable solvent such as in lower alcohols like methanol, ethanol, 1-propanol, 2-propanol at reflux conditions.

10 Isolation of the product can happen after acidification with aqueous hydrochloric acid by filtration.

The esterification of the nitrile of formula IV to the 2-trifluoromethyl isonicotinic acid ester of formula I with $R^1 = C_{1-6}\text{-alkyl}$ is performed with an alcohol $R^1\text{OH}$, wherein R^1 is $C_{1-6}\text{-alkyl}$ in the presence of hydrogen chloride gas or a hydrogen chloride producing agent.

15 Particularly $C_{1-4}\text{-alcohols}$ such as methanol, ethanol, n-propanol, i-propanol, n-butanol, s-butanol or t-butanol, more particularly methanol, ethanol, or i-propanol and even more particularly methanol are used.

Suitable hydrogen chloride producing agents can be selected from inorganic acid chlorides, like hydrogen chloride or from organic acid chlorides such as thionyl chloride or acetyl chloride. Acetyl chloride was found to be most suitable.

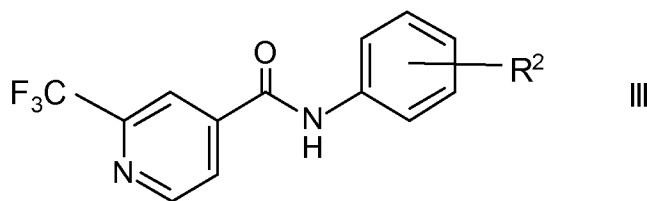
20 The reaction as a rule takes place under reflux conditions of the respective alcohol.

Isolation of the respective ester can happen by way of extraction with a suitable solvent such as with tert. methyl butyl ether out of the neutralized reaction mixture and by subsequent evaporation of the organic solvent.

25 The embodiment comprising the conversion of the 2-trifluoromethyl pyridine derivative of the formula II with carbon monoxide (CO) in the presence of the reactant $R^1\text{OH}$, wherein R^1 is as above is preferred.

As indicated above the invention further comprises the use of the process of the present invention in a process for the preparation of TAAR1 agonists of the formula

-7-



wherein

R^2 is $(CH_2)_n$ -(O)_o- heterocycloalkyl, optionally substituted by C₁₋₆-alkyl, hydroxy, halogen, or by $-(CH_2)_p$ -aryl;

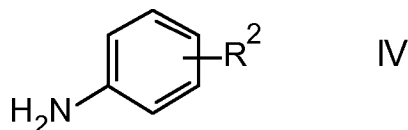
5 n is 0,1,2;

 o is 0,1;

 p is 0,1,2;

or a pharmaceutically suitable acid addition salt thereof.

10 The compounds of formula III can for instance be prepared according to the PCT Publ. WO 2012/016879 by reacting the 2-trifluoromethyl isonicotinic acid and esters of the formula I with an optionally protected arylamine of formula IV



15 Optionally protected in this context means that the nitrogen heteroatom of the heterocycloalkyl moiety R^2 is protected with a common amino protecting group such as for instance with Boc. In that case the process further comprises the removal of the amino protecting group for instance under acidic conditions.

Examples

Abbreviations:

DMF	N,N'-dimethylformamide
MTBE	Methyl tert. butyl ether
PdCl ₂ (dppp)	dichloro(diphenylphosphine-propane)palladium(II)
r.t.	Room temperature
THF	tetrahydrofuran

Example 1

5 Preparation of 4-Chloro-2-trifluoromethyl-pyridine

In a 25 ml round bottom flask equipped with a reflux condenser, magnetic stirrer and a inert gas supply 1.63 g (10.0 mmol) 4-Hydroxy-2-trifluoromethyl-pyridine was treated with 4.9 ml cyclohexane and 0.077 ml DMF, at room temperature 2.19 ml (25.0 mmol) oxalyl chloride was added, the mixture was heated to reflux for 3 hours, cooled to room temperature, slowly (gas evolution) 18 ml water was added dropwise, the mixture was extracted with 18 ml MTBE, the separated organic layer was washed with 1M NaHCO₃ and the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated at reduced pressure, the crude black liquid was treated with 12 ml n-hexane, stirred for 5min at rt, filtered and evaporated under reduced pressure to obtain 0.9 g 4-Chloro-2-trifluoromethyl pyridine as yellow liquid.

15 GC-EI-MS: M 181⁺/M 183⁺.

Example 2

Preparation of 2-Trifluoromethyl-isonicotinic acid methyl ester from 4-Chloro-2-trifluoromethylpyridine

A mixture of 76.8 g (423 mmol) 4-Chloro-2-trifluoromethyl-pyridine, 7.67 g (7.67 mmol) 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct and 88.4 ml (635 mmol) triethylamine in 792 ml methanol was stirred under 70 bar CO for 18 hour at 130°C. The crude mixture (contain ~30% acid), was concentrated under reduced pressure to a ~20% mixture, treated slowly with 30.9 ml (423 mmol) thionyl chloride and refluxed for one hour. The mixture was evaporated under reduced pressure, the residue was treated with 450 ml

water and 450 ml MTBE, and the formed suspension was filtered. From the filtrate, the organic layer was separated and extracted with 225 ml 1M NaHCO₃, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to obtain crude 2-trifluoromethyl-isonicotinic acid methyl ester which was distilled at ~20mmbar/bp 97-99°C, to
5 obtain 80.7 g 2-trifluoromethyl-isonicotinic acid methyl ester as colorless liquid.
GC-EI-MS: M 205⁺.

Example 3

Preparation of 2-Trifluoromethyl-isonicotinic acid ethyl ester from 4-Chloro-2-trifluoromethyl pyridine

10 A mixture of 182 mg (1.0 mmol) 4-Chloro-2-trifluoromethyl pyridine, 18.2 mg (0.022 mmol) 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct and 0.21 ml (1.50 mmol) triethylamine in 3.0 ml ethanol was stirred under 70 bar CO for 18 hour at 130°C, the crude mixture was evaporated under reduced pressure, the residue was treated with 4.0 ml 0.5M HCl and 4.0 ml MTBE, the formed suspension was filtered, the organic layer was
15 separated and extracted with 2.0 ml 1M NaHCO₃, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to obtain crude 2-trifluoromethyl-isonicotinic acid ethyl ester which was stirred with 2.0 ml cyclohexane for 10 min at room temperature, the light cloudy brown solution was filtered and the filtrate was evaporated under reduced pressure to obtain 113 mg 2-trifluoromethyl-isonicotinic acid ethyl
20 ester as light brown liquid.
GC-EI-MS: M 219⁺.

Example 4

Preparation of 2-Trifluoromethyl-isonicotinic acid isopropyl ester from 4-Chloro-2-trifluoromethyl pyridine

25 A mixture of 182 mg (1.0 mmol) 4-Chloro-2-trifluoromethyl pyridine, 18.2 mg (0.022 mmol) 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct and 0.21 ml (1.5 mmol) triethylamine in 3.0 ml 2-propanol was stirred under 70 bar CO for 18 hour at 130°C, the crude mixture was evaporated under reduced pressure, the residue was treated with 4.0 ml 0.5M HCl and 4.0 ml MTBE, the formed suspension was filtered, the organic
30 layer was separated and extracted with 2.0 ml 1M NaHCO₃, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to obtain crude 2-trifluoromethyl-isonicotinic acid ethyl ester which was stirred with 2.0 ml cyclohexane for 10 min at room temperature, the light cloudy brown solution was filtered and the filtrate was evaporated under reduced pressure to obtain 134 mg 2-trifluoromethyl-isonicotinic acid

isopropyl ester as light brown liquid.

GC-EI-MS: M 233⁺.

Example 5

Preparation of trifluoro-methanesulfonic acid 2-trifluoromethyl-pyridin-4-yl ester

- 5 In a 25 ml round bottom flask equipped with a magnetic stirrer and a inert gas supply 1.63 g (10.0 mmol) 2-Trifluoromethyl-pyridin-4-ol was dissolved 8.15 ml dichloromethane, 2.04 ml (12.0 mmol) N-ethyl-diisopropylamine was added and the solution was cooled to 0-5°C and 1.86 ml (11.0 mmol) Trifluoromethanesulfonic anhydride was added dropwise, the mixture was stirred at 0-5°C for 1 hour, the mixture was extracted with 10 ml 0.5M HCl, the separated
10 organic layer was dried with anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified over 15 g silica with cyclohexane/MTBE to obtain 1.58 g trifluoro-methanesulfonic acid 2-trifluoromethyl-pyridin-4-yl ester as light yellow oil.
GC-EI-MS: M 295⁺.

Example 6

- 15 **Preparation of 2-Trifluoromethyl-isonicotinic acid methyl ester from trifluoro-methanesulfonic acid 2-trifluoromethyl-pyridin-4-yl ester**

- A mixture of 295 mg (1.0 mmol) trifluoro-methanesulfonic acid 2-trifluoromethyl-pyridin-4-yl ester 18.1 mg (0.022 mmol) 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct and 0.21 ml (1.5 mmol) triethylamine in 4.0 ml methanol was stirred
20 under 70 bar CO for 18 hour at 130°C, the crude mixture (contain ~30% acid) was treated with 0.073 ml (1.0 mmol) thionyl chloride refluxed for one hour, the mixture was evaporated under reduced pressure, the residue was treated with 4.0 ml water and 4.0 ml MTBE, the formed suspension was filtered the separated organic layer was extracted with 4.0 ml 1M NaHCO₃, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced
25 pressure to obtain crude 2-trifluoromethyl-isonicotinic acid methyl ester which was treated with 2.0 ml cyclohexane, the mixture was filtered and evaporated under reduced pressure to obtain 136 mg 2-trifluoromethyl-isonicotinic acid methyl ester as light yellow liquid.
GC-EI-MS: M 205⁺.

Example 7

- 30 **Preparation of 2-Trifluoromethyl-isonicotinic acid methyl ester from 4-Bromo-2-trifluoromethyl pyridine hydrobromide**

A mixture of 307 mg (1.0 mmol) 4-Bromo-2-trifluoromethyl pyridine hydrobromide, 18.1 mg (0.022 mmol) 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct and 0.35 ml (2.5 mmol) triethylamine in 4.0 ml methanol was stirred under 70 bar CO for 18 hour at 130°C, the crude mixture (contain ~30% acid) was treated with 0.073 ml (1.0 mmol) thionyl chloride refluxed for one hour, the mixture was evaporated under reduced pressure, the residue was treated with 4.0 ml water and 4.0 ml MTBE, the formed suspension was filtered, the separated organic layer was extracted with 2.0 ml 1M NaHCO₃, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to obtain crude 2-trifluoromethyl-isonicotinic acid methyl ester which was stirred with 2.0 ml cyclohexane for 15 min, filtered and evaporated under reduced pressure to obtain 112 mg 2-trifluoromethyl-isonicotinic acid methyl ester as colorless liquid.
GC-EI-MS: M 205⁺.

Example 8

Preparation of 2-Trifluoromethyl-isonicotinic acid methyl ester from 4-Iodo-2-trifluoromethyl pyridine

A mixture of 165 mg (0.60 mmol) 4-Iodo-2-trifluoromethyl pyridine, 16.5 mg (0.020 mmol) 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane adduct and 0.126 ml (0.907 mmol) triethylamine in 3.0 ml methanol was stirred under 70 bar CO for 18 hour at 130°C, the crude mixture was treated with 0.044 ml (1.0 mmol) thionyl chloride and refluxed for one hour, evaporated under reduced pressure, the residue was treated with 2.0 ml water and 2.0 ml MTBE, the formed suspension was filtered, the organic layer was separated and extracted with 2.0 ml 1M NaHCO₃, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to obtain crude 2-trifluoromethyl-isonicotinic acid ethyl ester which was stirred with 2.0 ml cyclohexane for 10 min at room temperature, the light brown suspension was filtered and the filtrate was evaporated under reduced pressure to obtain 104 mg 2-trifluoromethyl-isonicotinic acid methyl ester as light brown liquid. GC-EI-MS: M 205⁺.

Example 9

Preparation of 2-Trifluoromethyl-isonicotinic acid from 4-Chloro-2-trifluoromethyl pyridine

A mixture of 182 mg (1.0 mmol) 4-Chloro-2-trifluoromethyl pyridine, 18.0 mg PdCl₂(dppp) and 210 mg sodium hydrogencarbonate in 1.5 ml THF and 1.5 ml water was stirred under 70 bar CO for 20 hour at 120°C, THF was removed under reduced pressure, 0.5 ml 2M NaOH was added and the suspension was filtered. The clear solution was treated with 0.52 ml

hydrochloric acid 25 %, stirred for 1h at rt, filtered and the white crystals were dried at 40°C, to obtain 146 mg 2-trifluoromethyl-isonicotinic acid. GC-EI-MS: M 191⁺.

Example 10

Preparation of 2-(Trifluoromethyl)pyridine-4-carbonitrile from 4-Chloro-2-trifluoromethyl pyridine

A mixture of 4.0g (22.0 mmol) 4-Chloro-2-trifluoromethyl pyridine in 40.0 ml DMF was flushed with argon, 0.98 g (1.76 mmol) 1,1'-Bis(diphenylphosphino)ferrocene (CAS: 12150-46-8), 1.01 g (1.10 mmol) Tris(dibenzylideneacetone)dipalladium(0) (CAS: 51364-51-3) and 2.59 g (22.0 mmol) zinc cyanide was added. The mixture was flushed with argon and stirred for 15 hour at 85-90°C, the black mixture was cooled to 5-10°C, 110 ml water and 110 ml MTBE was added, stirred for a half hour at r.t. then filtered over a glass fibre filter, the filter cake was washed with 15 ml MTBE, the organic layer from the filtrate was separated, and washed twice with 110 ml water, the separated organic layer was dried with anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to obtain crude 4.20 g 2-(trifluoromethyl)pyridine-4-carbonitrile which contain dibenzylideneacetone as impurity. The crude product was treated with 8.40 ml MTBE, and the formed suspension was stirred for 15 min at r.t., then filtered and the filter cake was washed with 4.0 ml MTBE. The brown filtrate was evaporated under reduced pressure to obtain 3.60 g of the title product as brown oil, which was distilled at 10 mbar/b.p. 58-60°C to obtain 2.75 g 2-(trifluoromethyl)pyridine-4-carbonitrile as colorless liquide GC-EI-MS: M 172⁺.

Example 11

Preparation of 2-Trifluoromethyl-isonicotinic acid from 2-(Trifluoromethyl)pyridine-4-carbonitrile

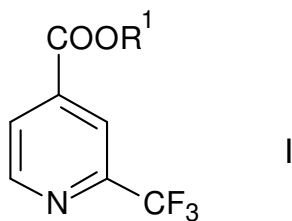
A mixture of 172 mg (1.0 mmol) 2-(trifluoromethyl)pyridine-4-carbonitrile in 0.86 ml ethanol was treated with , 0.20 g (5.0 mmol) sodium hydroxide. The mixture was refluxed for 1.5 hours, cooled to r.t. and the yellow suspension was cooled to r.t., 3.0 ml water and 0.65 ml hydrochloric acid was added. The suspension was cooled to 0-5°C for 30 min., filtered and washed with 2.0 ml water. The beige crystals were dried at 40°C/15mbar/2hour to obtain 0.15 g 2-trifluoromethyl-isonicotinic acid. GC-EI-MS: M 191⁺.

Example 12**Preparation of 2-Trifluoromethyl-isonicotinic acid methyl ester from 2-(Trifluoromethyl)pyridine-4-carbonitrile**

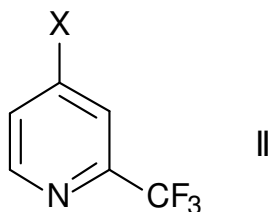
- A mixture of 172 mg (1.0 mmol) 2-(trifluoromethyl)pyridine-4-carbonitrile in 1.70 ml
- 5 methanol was treated with under ice cooling with 0.71 ml acetyl chloride (in situ generation of hydrogen chloride), the solution was refluxed for 4 hour, cooled to r.t. and evaporated under reduced pressure, the residue was treated with 1.0 ml MTBE and extracted with 1.0 ml 1M NaHCO₃, the separated organic layer was dried with Na₂SO₄, filtered and evaporated under reduced pressure to obtain 0.16 g 2-trifluoromethyl-isonicotinic acid methyl ester.
- 10 GC-EI-MS: M 205⁺.

Claims

1. Process for the preparation of 2-trifluoromethyl isonicotinic acid and esters of the formula



5 wherein R^1 is hydrogen or C_{1-6} -alkyl, comprising the conversion of a 2-trifluoromethyl pyridine derivative of the formula



10 wherein X is halogen or $-\text{OSO}_2\text{CY}_3$, wherein Y is halogen, with carbon monoxide (CO); in the presence of the reactant R^1OH , wherein R^1 is as above and in the presence of a palladium complex catalyst selected from Palladium(II)chloride with the ligand 1,1'-Bis-(diphenylphosphino)ferrocen (dppf).

2. Process of claim 1, wherein the conversion is performed under a CO pressure of 5 bar to 100 bar.

3. Process of any one of the claims 1 or 2, wherein the conversion is performed in the presence of a base.

5 4. Process of any one of claims 1 to 3, wherein the conversion is performed at a reaction temperature between 50°C and 170°C.

5. Process of any one of the claims 1 to 4, wherein in the case of the conversion with reactant R¹OH, wherein R¹ is C₁₋₆-alkyl the conversion with carbon monoxide is followed by a treatment with a hydrogen chloride producing agent.

10 6. Process of claim 5, wherein the hydrogen chloride producing agent is selected from thionyl chloride or acetyl chloride

7. Process of claims 5 or 6, wherein the treatment with the hydrogen chloride producing agent is performed at reflux conditions of the reaction mixture.

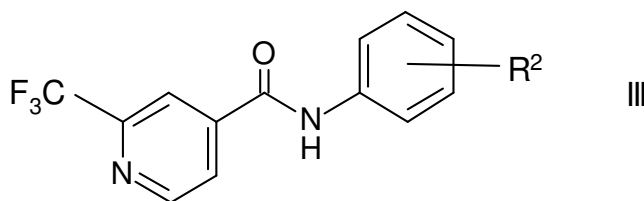
8. Process of any one of claims 1 to 7, wherein R^1 is hydrogen, methyl, ethyl or i-propyl.

9. Process of any one of claims 1 to 8, wherein R^1 is hydrogen or methyl.

10. Process of any one of claims 1 to 9, wherein X is fluorine, chlorine, bromine, iodine or trifluoromethanesulfonyl.

5 11. Process of any one of claims 1 to 10, wherein X is chlorine.

12. Use of the process of any of claims 1 to 11 for the preparation of TAAR1 agonists of the formula



wherein

10 R^2 is $(CH_2)_n-(O)_o$ - heterocycloalkyl, optionally substituted by C_{1-6} -alkyl, hydroxy, halogen, or by $-(CH_2)_p$ -aryl;

n is 0,1,2;

o is 0,1;

p is 0,1,2;

or a pharmaceutically suitable acid addition salt thereof.