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 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.

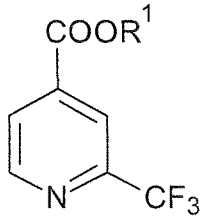
Manfred Schlosser et al., Eur. J. Org. Chem. 2003, 1559-1568) describe the preparation of 2-trifluoromethyl-4-pyridne carboxylic acid in an overall yield of 45% from 2-trifluoro pyridine by initial deprotonation, subsequent iodination at the 3-position, followed by halogen migration and final carboxylation. 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 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 ~~present invention~~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.

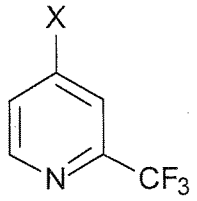
It was found that the object could be reached with the process as outlined below.

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



I

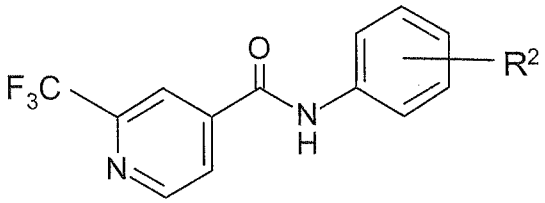
wherein R^1 is hydrogen or C_{1-6}-alkyl, comprises the conversion of a 2-trifluoromethyl pyridine derivative of the formula



II

wherein X is halogen or $-OSO_2CY_3$, wherein Y is halogen, in the presence of a palladium complex catalyst.

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



III

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;

n is 0,1,2;

o is 0,1;

p is 0,1,2;

or a pharmaceutically suitable acid addition salt thereof

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.

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.

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.

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 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.