(19) DANMARK

(10) DK/EP 2509937 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 C 231/06 (2006.01)* *C 07 C 209/62 (2006.01)* *C 07 C 211/15 (2006.01)* *C 07 C 233/13 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2014-12-15**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2014-10-08**

(86) Europæisk ansøgning nr.: **10798990.7**

(86) Europæisk indleveringsdag: **2010-12-07**

(87) Den europæiske ansøgnings publiceringsdag: **2012-10-17**

(86) International ansøgning nr.: **EP2010069036**

(87) Internationalt publikationsnr.: **WO2011069994**

(30) Prioritet: **2009-12-11 EP 09178860** **2009-12-15 US 286607 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF 2,2-DIFLUORETHYLAMIN SAMT SALTE HERAF GÅENDE UD FRA DIFLUORACETONITRIL**

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Description

The present invention relates to a process for preparing 2,2-difluoroethylamine of the formula (I) and salts thereof, for example sulphates, hydrochlorides or acetates, which proceeds from difluoroacetonitrile.

2,2-Difluoroethylamines and salts thereof are important intermediates for preparation of active ingredients, especially active agrochemical ingredients. Various preparation methods for 2,2-difluoroethylamine are known.

Donetti et al. (*J. Med. Chem.* **1989**, *32*, 957-961) describe, for example, the synthesis of 2,2-difluoroethylamine hydrochloride proceeding from 2,2-difluoroacetamide, in which the corresponding amide is reduced with a diboran solution in tetrahydrofuran (THF). Kluger et al. describe, in *JACS* **1982**, *104*, 10, 2891-2897, the reduction of 2,2-difluoroacetamide with sodium boranate and boron trifluoride etherate to give 2,2-difluoroethylamine.

Wodzinska et al., "pKa-dependent formation of amides in water from an acyl phosphate monoester and amines", Journal of Organic Chemistry, Vol. 73 No. 12 (2008), pp. 4753-4754, describe a process for preparing amides through reaction of an acyl phosphate monoester and an amine. Not disclosed, however, is the process of the invention, in which 2,2-difluoroethylamine is prepared by catalytic hydrogenation of difluoroacetonitrile to difluoroethylamide and subsequent dissociation of the difluoroethylamide in the presence of an acid.

Dickey et al., "Fluorinated Aminoanthraquinone dyes", Industrial and Engineering Chemistry, Vol. 48 No. 2 (1956), 209-213, disclose a process for preparing difluoro-ethylamine by nucleophilic substitution. Not disclosed, however, is the process of the invention, in which 2,2-difluoroethylamine is prepared by catalytic hydrogenation of difluoroacetonitrile to

difluoroethylamide and subsequent dissociation of the difluoroethylamide in the presence of an acid.

US-A-4,030,994 discloses a process for preparing difluoroethylamine by direct fluorination of ethylamine with fluorooxytrifluoromethane. Not disclosed, however, is the process of the invention, in which 2,2-difluoroethylamine is prepared by catalytic hydrogenation of difluoroacetonitrile to difluoroethylamide and subsequent dissociation of the difluoroethylamide in the presence of an acid.

Nor do any of the stated documents disclose the difluoroethylamide intermediates of the formula (III) that are produced in the process of the invention.

The low yield and the use of expensive and hazardous chemicals, for example sodium boranate/BF_3 or diborane, prevent the processes according to Donetti et al. and Kluger et al. from being suitable for the industrial scale preparation of 2,2-difluoroethylamine. All these processes are uneconomic, and industrial scale implementation is associated with high costs.

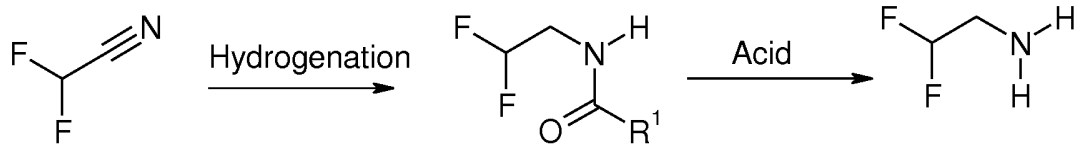
An inexpensive preparation process consists in the hydrogenation of difluoroacetonitrile, which is readily available as a starting material. It can be prepared, for example, from difluoroacetamide (Swarts et al., *Bulletin des Societes Chimiques Belges* **1922**, *31*, 364-5), Grunewald et al., *J. Med. Chem.* **2006**, *49 (10)*, 2939-2952). The catalytic hydrogenation of trifluoroacetonitrile using PtO_2 has been described by Gilman et al. (*JACS* **1943**, *65 (8)*, 1458 – 1460), to obtain trifluoroethylamine hydrochloride.

The inventors have now found that the process described for trifluoroacetonitrile by Gilman et al. is unsuitable for the hydrogenation of difluoroacetonitrile. When the hydrogenation of difluoroacetonitrile is performed under the conditions described, 2,2-difluoroethylamine is obtained only in traces,

whereas a multitude of more highly alkylated reaction products is otherwise obtained.

In addition, it has been found that the catalytic hydrogenation of difluoroacetonitrile in pure glacial acetic acid or in toluene does afford difluoroethylamine, but the conversions were unselective and the product was not isolable from the reaction mixture owing to the low boiling point.

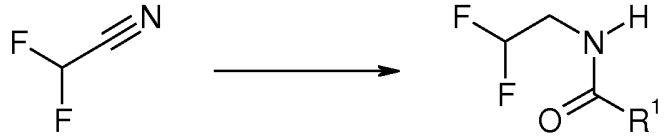
It is therefore an object of the present invention to provide a process with which difluoroacetonitrile can be converted to 2,2-difluoroethylamine selectively and in good yields. It has now been found that 2,2-difluoroethylamine of the formula (I) can be obtained by first reducing difluoroacetonitrile of the formula (II) in a first step by catalytic hydrogenation to the N(2,2-difluoroethyl)amide of the formula (III), and then converting the N(2,2-difluoroethyl)amide thus obtained to 2,2-difluoroethylamine by treatment with acid. The reaction is illustrated in the reaction scheme below, where R^1 may be as defined below.



(II) (III) (I)

The present invention thus relates to a process for preparing 2,2-dfluoroethylamine of the formula (I), comprising the following reaction steps:

(a) catalytically hydrogenating difluoroacetonitrile of the formula (II) to the corresponding amide of the formula (III)



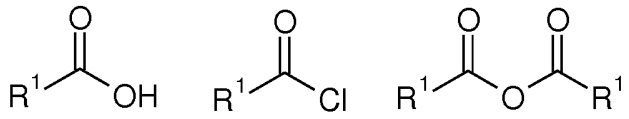
(II) (III)

where

R^1 is H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{1-12}-haloalkyl, aryl (e.g. phenyl), C_{1-12}-alkyl-C_{6-10}-aryl, wherein R^1 is preferably H,

methyl, trifluoromethyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, phenyl or benzyl, more preferably H, methyl, t-butyl or phenyl.

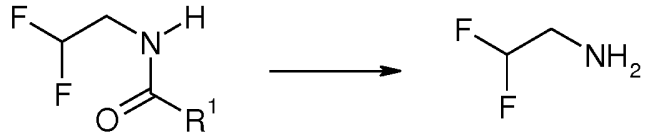
in the presence of an organic acid of the general formula (IVa), of an acid chloride of the general formula (IVb) or acid anhydride of the general formula (IVc)



(IVa) (IVb) (IVc)

or a mixture thereof, where R^1 is as defined above, preferably in the presence of CF_3COOH, CH_3COOH, CH_3COCl, benzoyl chloride, acetic anhydride, pivalic anhydride, t-butylacetic anhydride, trifluoroacetic anhydride or benzoic anhydride, or mixtures thereof, more preferably in the presence of CH_3COOH, CH_3COCl or acetic anhydride or a mixture thereof; and

(b) converting the difluoroethylamide of the formula (III) to 2,2-difluoroethylamine of the formula (I) by adding an acid which is suitable for cleaving the difluoroethylamide



(III) (I)

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The invention further relates to the difluoroethylamide intermediate of the general formula (III), where R^1 is H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{1-12}-haloalkyl, C_{1-12}-alkyl- C_{6-10}-aryl, which is obtained by the process according to the invention.

The inventive catalytic hydrogenation in step (a) takes place in the presence of a catalyst, with gaseous hydrogen being introduced into the reaction vessel or being generated *in situ* in the reaction vessel by the use of formic acid or hydrazine and the derivatives or salts thereof.

For the inventive catalytic hydrogenation in reaction step

(a), the catalyst used may be any catalyst which is suitable for catalytic hydrogenation and is known to those skilled in the art. Useful examples include palladium catalysts, platinum catalysts, Raney nickel catalysts, Lindlar catalysts, ruthenium catalysts and rhodium catalysts. In addition to these heterogeneous catalysts, it is also possible to use homogeneous catalysts. Suitable catalysts preferably contain one or more metals of groups 8 - 10 of the Periodic Table, especially one or more metals selected from iron, ruthenium, osmium, cobalt, rhodium, iridium, nickel, palladium and platinum. The metals may be present in any chemical form, for example in elemental, colloidal, salt or oxide form, together with complexing agents as chelates, or as alloys, in which case the alloys may also include other metals, for example aluminium, as well as the metals listed above. The metals may be present in supported form, i.e. applied to any support, preferably an inorganic support. Examples of suitable supports are carbon (charcoal or activated carbon), aluminium oxide, silicon dioxide, zirconium dioxide or titanium dioxide. Catalysts preferred in accordance with the invention contain one or more metals of groups 8 - 10 of the Periodic Table on an inorganic support. Particular preference is given in accordance with the invention to catalysts which include platinum and/or palladium, and are optionally applied to an inorganic support. Such catalysts are, for example, PtO_2, $Pd(OH)_2$ on activated carbon (Pearlman catalyst), Raney nickel and Lindlar catalysts.

In the process according to the invention, the catalyst is used, based on the difluoroacetonitrile used, in a concentration of about 0.01 to about 30% by weight. The catalyst is preferably used in a concentration of about 0.1 to about 12% by weight, more preferably of about 0.1 to about 2% by weight.

In step (a) of the process according to the invention, it is usual to initially charge difluoroacetonitrile and the catalyst with the organic acid, acid chloride, acid anhydride

or mixture thereof in a first step (i), and to introduce hydrogen or produce it *in situ* in a second step (ii). The reversal of steps (i) and (ii) is possible. It is also possible to hydrogenate continuously or batchwise.

The catalytic hydrogenation can be performed under elevated pressure (i.e. up to about 200 bar) in an autoclave, or at standard pressure in a hydrogen gas atmosphere. Especially at high reaction temperatures, it may be helpful to work at elevated pressure. The (additional) pressure increase can be brought about by supply of an inert gas, such as nitrogen or argon. The inventive hydrogenation is effected preferably at a pressure in the range from about 1 to about 100 bar, more preferably at a pressure in the range from about 5 to about 25 bar.

The organic acid, acid chloride or acid anhydride, or mixture thereof, present in reaction step (a) causes the difluoroethylamine formed to be removed from the hydrogenation process, rather than reacting to give $(CF_2HCH_2)_2NH$.

The necessary amount of the organic acid, acid chloride or acid anhydride present in reaction step (a), based on difluoroacetonitrile, can be determined by the person skilled in the art in a simple manner by routine tests. The molar ratio of difluoroacetonitrile to the organic acid, acid chloride or acid anhydride used, or mixture thereof, may, for example, be about 0.5 to 10, or about 0.9 to 2. A ratio of about 1 to 1.1 is preferred. The use of greater amounts of organic acid, acid chloride or acid anhydride or a mixture thereof is possible in principle, but is disadvantageous for economic reasons.

Preferred reaction temperatures for the hydrogenation in reaction step (a) range from -20°C to 100°C, preference being given to temperatures of 0°C to 40°C.

The reaction time of the hydrogenation is generally 30 minutes

to 24 hours, though shorter or longer reaction times do not have an adverse effect.

In the inventive reaction step (b), the amide of the formula (III) is reacted with a suitable acid to give the 2,2-difluoroamine.

After reaction step (a), the amide of the formula (III) can also be isolated by removing the catalyst and the solvent, if present, and sent to reaction step (b).

The acids useable in reaction step (b) are selected from phosphoric acid (H_3PO_4), sulphuric acid (H_2SO_4), hydrochloric acid (HCl), hydrobromic acid (HBr), hydrofluoric acid (HF), potassium hydrogensulphate ($KHSO_4$), CF_3COOH, CF_3SO_3H, CH_3COOH, and p-toluenesulphonic acid.

Preferred reaction temperatures for the cleavage of the difluoroamide of the formula (III) in reaction step (b) range from about 0°C to about 100°C.

It is generally advantageous to perform the process according to the invention in the presence of solvents (diluents). However, the catalytic hydrogenation can also be performed without a solvent. Solvents are advantageously used in such an amount that the reaction mixture remains efficiently stirrable over the entire process. Advantageously, based on the difluoroacetonitrile used, 1 to 50 times the amount of solvent, preferably 2 to 40 times the amount of solvent and more preferably 2 to 30 times the amount of solvent is used.

Useful solvents for performance of the process according to the invention include all organic solvents which are inert under the reaction conditions, the type of solvent used depending on the type of reaction procedure, more particularly on the type of catalyst used and/or the hydrogen source (introduction of gaseous hydrogen or generation *in situ*). Solvents are also understood in accordance with the invention

to mean mixtures of pure solvents.

Solvents suitable in accordance with the invention are especially ethers, such as ethyl propyl ether, n-butyl ether, anisol, phenetol, cyclohexyl methyl ether, dimethyl ether, diethyl ether, dimethylglycol diphenyl ether, dipropyl ether, diisopropyl ether, di-n-butyl ether, diisobutyl ether, diisoamyl ether, ethylene glycol dimethyl ether, isopropyl ethyl ether, methyl tert-butyl ether, tetrahydrofuran, methyltetrahydrofuran, dioxane, dichlorodiethyl ether, and polyethers of ethylene oxide and/or propylene oxide; aliphatic, cycloaliphatic or aromatic hydrocarbons such as pentane, hexane, heptane, octane, nonane, and technical-grade hydrocarbons which may be substituted by fluorine and chlorine atoms, such as methylene chloride, dichloromethane, trichloromethane, carbon tetrachloride, fluorobenzene, chlorobenzene or dichlorobenzene; for example white spirits having components with boiling points in the range, for example, from 40°C to 250°C, cymene, petroleum fractions within a boiling range from 70°C to 190°C, cyclohexane, methylcyclohexane, petroleum ether, ligroin, octane, benzene, toluene, chlorobenzene, bromobenzene, xylene; esters such as methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, and also dimethylcarbonate, dibutylcarbonate or ethylenecarbonate. Organic acids such as formic acid or acetic acid. The inventive solvent used may also be water. In reaction step (a), the organic acid, the acid chloride or anhydride, or mixtures thereof, present in the reaction, may also be used as the solvent.

Solvents preferred in accordance with the invention in reaction step (a) are toluene, tetrahydrofuran, methyltetrahydrofuran or mixtures thereof.

In reaction step (b), water is preferred as the inventive solvent.

The workup and purification can be effected via the free amine

or via salts thereof. When the 2,2-difluoroethylamine is present in free form after the process according to the invention, it is purified by distillation if necessary. When 2,2-difluoroethylamine is present as a salt, it is then purified if necessary, preferably by crystallization. Preferred salts are, for example, sulphates, hydrochlorides or acetates.

Water-soluble salts of 2,2-difluoroethylamine are generally purified by extraction from an aqueous solution. The free 2,2-difluoroethylamine is released by reacting the corresponding salt with organic or inorganic bases (e.g. $NaHCO_3$, Na_2CO_3 or NaOH). Subsequently, the difluoroethylamine is distilled directly out of the aqueous solution or extracted into an organic solvent.

The present invention is illustrated in detail by the examples which follow, though the examples should not be interpreted so as to restrict the invention.

Preparation examples:

Synthesis of N-(2,2-difluoroethyl)acetamide

20 g (0.259 mol) of difluoroacetonitrile and 26.5 g (0.259 mol) of acetic anhydride are dissolved in 242 ml of tetrahydrofuran and hydrogenated over 0.66 g (0.31 mmol) of palladium on activated carbon (5% Pd) with 50 bar of hydrogen until the pressure is constant. The autoclave is cooled, such that the reaction temperature does not rise above 20°C. The reaction mixture is filtered through kieselguhr. After the solvent has been removed 34.9 g (GC-MS purity 75.5%) of N-(2,2-difluoroethyl)acetamide are obtained.

^{1}H NMR (400 MHz, d_6-DMSO): 8.24 (1H, sb, NH), 5.98 (1H, dt, $^3J_{HF}$ = 60 Hz; $^3J_{HH}$ = 3.9 Hz), 3.56-3.49 (2H, m), 1.87 (3H, s).

^{13}C NMR (600 MHz, d_6-THF): 171.7 (CO), 115.3 (CHF_2), 42.5 (CH_2), 22.3 (CH_3).

^{19}F NMR (376 MHz, D_2O, $CFCl_3$ internal standard): -121.3 (dt, $^2J_{FH}$

= 56.1 Hz; $^{3}J_{FH}$ = 16.1 Hz).

Synthesis of 2,2-difluoroethylamine hydrochloride

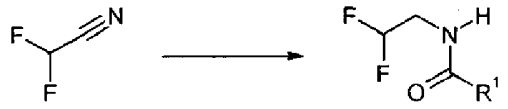
10 g (81.23 mmol) of N-(2,2-difluoroethyl)acetamide are initially charged in 16 g of water and admixed with 18.5 g (162.5 mmol, 32%) of hydrochloric acid. The reaction mixture is stirred at 90°C for 1 hour and cooled to room temperature, and then the solvent is removed. The residue is azeotroped with toluene. This gives 8.70 g of 2,2-difluoroethylamine hydrochloride (91.1% yield based on N-(2,2-difluoroethyl)acetamide).

^{1}H NMR (400 MHz, D_2O): 6.31 (1H, dt, $^{3}J_{HF}$ = 53.34 Hz; $^{3}J_{HH}$ = 2.6 Hz), 3.52 (2H, dt, $^{3}J_{HF}$ = 16.32 Hz; $^{3}J_{HH}$ = 2.6 Hz).

Patentkrav

1. Fremgangsmåde til fremstilling af 2,2-difluorethylamin med formel (I) omfattende de følgende reaktionstrin

(a) katalytisk hydrering af difluoracetonitril med formel (II) til difluorethylamid med formel (III)

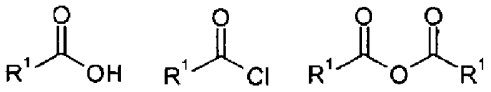


(II) (III)

hvor

R^1 står for H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{1-12}-haloalkyl, aryl, C_{1-12}-alkyl-C_{6-10}-aryl,

i nærvær af en organisk syre med den almene formel (IVa), af en syrechlorid med den almene formel (IVb) eller syreanhydrid med den almene formel (IVc) eller blandinger heraf



(IVa) (IVb) (IVc)

hvor R^1 har den ovenfor anførte betegnelse; og

(b) omsætning af difluorethylamiden med formel (III) til 2,2-difluorethylamin ved hjælp af tilsætning af en syre, som er egnet til at spalte difluorethylamiden

(III) (I)

2. Fremgangsmåde ifølge krav 1, idet R^1 står for H, methyl, trifluormethyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl- og t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, phenyl eller benzyl.

3. Fremgangsmåde ifølge krav 1 eller 2, idet den i reaktionstrinnet (a) forekommende syre foreligger i et molært forhold mellem difluoracetonitril og syre på 0,5 til 10.

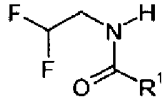
4. Fremgangsmåde ifølge et af kravene 1 til 3, idet fremgangsmådetrinnene (a) og (b) gennemføres uden isolering af difluorethylamid med formel (III).

5. Fremgangsmåde ifølge et af kravene 1 til 4, idet den i den katalytiske hydrering i reaktionstrinnet (a) anvendte katalysator indeholder palladium, platin, Raney-nikkel eller rhodium.

6. Fremgangsmåde ifølge et af kravene 1 til 5, idet der ved den katalytiske hydrering ledes gasformet hydrogen ind i reaktionskarret, eller denne frembringes *in situ*.

7. Fremgangsmåde ifølge et af kravene 1 til 6, idet den syre, der skal tilsættes i reaktionstrin (b), og som er egent til at spalte difluorethylamiden, er udvalgt blandt H_3PO_4, H_2SO_4, HCl, HBr, HF, $KHSO_4$, CF_3COOH, CF_3SO_3H, CH_3COOH og p-tolylsulfonsyre.

8. Difluorethylamid med formel (III) til anvendelse i fremgangsmåden som defineret i et af kravene 1 til 7



(III)

hvor

R^1 står for H, C_{1-12}-alkyl, C_{3-8}-cycloalkyl, C_{1-12}-haloalkyl, C_{1-12}-alkyl-C_{6-10}-aryl.

9. Difluorethylamid med formel (III) ifølge krav 8, hvor R^1 står for H, methyl, trifluormethyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl- og t-butyl, n-pentyl, n-hexyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, eller benzyl.