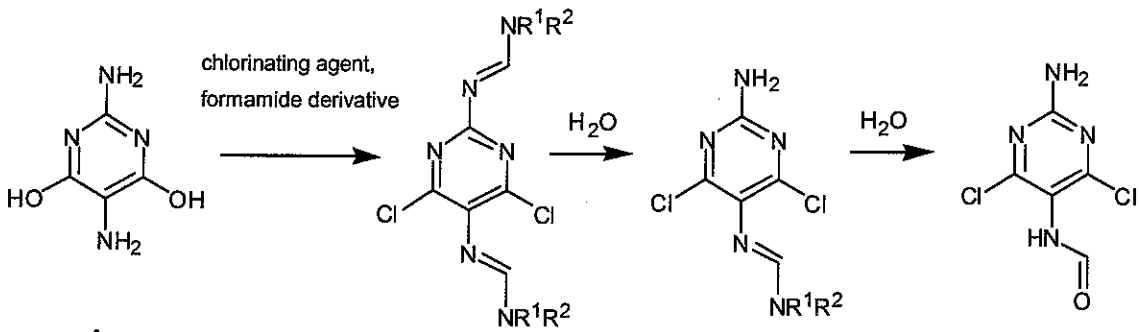
Method for producing 2-amino-4,6-dichloro-5-formamidopyrimidine

Description

2-Amino-4,6-dichloro-5-formamidopyrimidine is a valuable intermediate for the preparation of purine derivatives, as find use, for example, as active pharmaceutical ingredients in the treatment of viral diseases, for example in the treatment of AIDS. Such a medicament and routes to its preparation have been described in detail (cf. Susan M. Daluge et. al., Nucleosides, Nucleotides & Nucleic Acids, 19(1&2), 297-327 (2000)).

Routes for the synthesis of 2-amino-4,6-dichloro-5-formamidopyrimidine have already been described in accordance with the prior art. The known processes are based on the principle that 2,5-diamino-4,6-dihydroxy-pyrimidine (or a salt thereof) is reacted with a chlorinating agent and a formamide and/or a Vilsmeyer-type reagent. In this process, the amino groups, which tend to side reactions in unprotected form, are protected as formamidines, the hydroxyl groups are chlorinated and the protecting groups are removed again partially of fully in subsequent steps. The overall synthesis sequence can be illustrated with the following scheme:



This reaction has already been considered in detail in the patent literature. For example, US 6,552,193 describes the reaction of 2,5-diamino-4,6-dihydroxypyrimidine hemisulfate A with chloromethylenedimethyl-ammonium chloride (Vilsmeyer reagent) in chloroform to give B (R^1, R^2 = CH_3) in 81% yield, the hydrolysis thereof to give C in 95% yield and the further reaction of C to give 2-amino-4,6-dichloro-5-formamidopyrimidine

D in a phosphate buffer with 68% yield. The overall yield over all 3 stages is 52%. According to the teaching from US 6,552,193, an inert solvent, for example dichloromethane, chloroform or dichloroethane, is required for the first reaction step (the chlorination).

US 5,663,340 and EP 684 236 describe the chlorination of A with phosphorus oxychloride in the presence of dimethylformamide using an inert solvent (examples include toluene, xylene, chloroform, dichloromethane, dichloroethane, chlorobenzene) to form B (R^1, R^2 = CH_3) and further reaction to give C (without isolation of B) in 85% yield. The conversion of C to D is effected in the presence of aqueous propionic acid in 64% yield. The overall yield is thus 54%.

Although these prior art processes mentioned fulfill their purpose of providing 2-amino-4,6-dichloro-5-formamidopyrimidine D as an intermediate for preparing antiviral pharmaceuticals, they display significant disadvantages. For the chlorination step a), considerable amounts of chlorinated and/or aromatic solvents are used. This gives rise to an unfavorable space-time yield and considerable environmental pollution. The salt-containing wastewaters obtained from the chlorination step have to be disposed of, but a reagent (phosphate buffer or propionic acid) again has to be used for the subsequent hydrolysis step from C to D.

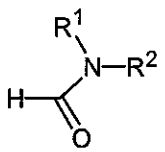
In addition, it is not evident from the prior art - in spite of some experiments with "one-pot variants" - that a direct process for preparing D from A without isolating the intermediates might be possible. All of these factors increase the amount of the raw materials used and the residual materials to be disposed of, worsen the space-time yield in the production and lead additionally to considerable environmental pollution.

It was therefore an object of the invention to provide a simple and environmentally friendly process for preparing 2-amino-4,6-dichloro-5-formamidopyrimidine from 2,5-diamino-4,6-dihydroxypyrimidine or a salt

thereof with high space-time yields. In addition, the process should be simplified such that the isolation of intermediates can be dispensed with (one-pot reaction).

The object of the invention is achieved by

a) reacting the 2,5-diamino-4,6-dihydroxypyrimidine or salt or tautomeric forms thereof with a chlorinating agent and a formamide of the formula (I)



(I)

where

R^1 and R^2 are each independently a C_1-C_4-alkyl radical, or $-R^1-R^2-$ is $-(CH_2)_n-$ where n = from 4 to 6 or $-(CH_2)_2-O-(CH_2)_2-$, without addition of a solvent at from 50 to 130°C,

b) reacting the reaction product from stage a) at from 0 to 100°C with water and adjusting to a pH of from 1.0 to 6.0 with an inorganic base and

c) reacting the aqueous reaction mixture from stage b) at from 70 to 120°C with hydrolysis to give 2-amino-4,6-dichloro-5-formamidopyrimidine.

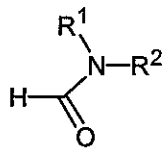
Surprisingly, it has been found that, in a suitable reaction, the reaction mixture in the chlorination step is better stirrable without solvent than when a solvent is used, and that, owing to the solubility conditions of product and by-products, 2-amino-4,6-dichloro-5-formamidopyrimidine can be obtained in high purity from the complex reaction mixture.

The raw material used for the process according to the invention is 2,5-diamino-4,6-dihydroxypyrimidine or salt or tautomeric forms thereof.

Owing to the easy oxidizability of the free base, especially the hemisulfate, the hydrochloride monohydrate and the anhydrous hydrochloride are particularly suitable. In order to avoid unnecessary reagent consumption and undesired sulfate ions, particular preference is given to using anhydrous 2,5-diamino-4,6-dihydroxypyrimidine hydrochloride.

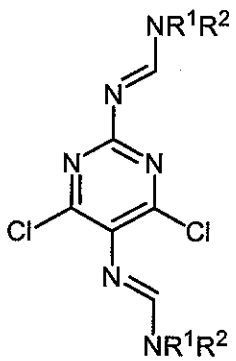
The chlorinating agents used may be various inorganic and organic reagents having the functionality of an acid chloride. Examples include phosgene, oxalyl chloride, chloromethylenedimethylammonium chloride (Vilsmeyer reagent), thionyl chloride, sulfuryl chloride, phosphorus trichloride, phosphorus pentachloride or phosphorus oxychloride. Particular preference is given to using phosphorus oxychloride.

The formamide of the formula (I) serves to formylate the amino groups of the starting material and to protect them as the formamidine.



(I),

The intermediates obtained in stage a) are the 2,5-diformamidino-4,6-dichloropyrimidines of the formula (II):



(II)

The particular R^1 and R^2 radicals are detached again in the further reaction to give the end product, so that, irrespective of the amide of the formula I used, the same end product is always obtained. The R^1 and R^2 radicals are each independently a C_1 to C_4-alkyl radical and in particular methyl, ethyl, n-propyl or/and n-butyl. Alternatively, the R^1 and R^2 radicals can be joined via a single bond and can assume the definition $-(CH_2)_n-$ where n = from 4 to 6 or $-(CH_2)_2-O-(CH_2)_2-$. Preferred amides of the formula (I) are N,N-dimethylformamide, N-formylpyrrolidine, N-formylpiperidine and N-formylmorpholine. Particular preference is given to N,N-dimethylformamide.

The molar ratios of the reactants in the chlorination step can be varied within wide limits. Preference is given to using from 1 to 5 mol of formamide of the formula (I) per 1 mol of 2,5-diamino-4,6-dihydroxypyrimidine. Preference is further given to using from 3 to 7 mol of chlorinating agent per 1 mol of 2,5-diamino-4,6-dihydroxypyrimidine. For the special case of use of phosphorus oxychloride and N,N-dimethylformamide, preference is given to using from 3 to 5 mol of phosphorus oxychloride and from 1 to 3 mol of N,N-dimethylformamide per mole of 2,5-diamino-4,6-dihydroxypyrimidine.

In a preferred embodiment, the chlorinating agent is first mixed with the formamide and only in a second step is the 2,5-diamino-4,6-dihydroxypyrimidine, as the case may be, metered in slowly or added in portions. In this way, it is ensured that the insoluble 2,5-diamino-4,6-dihydroxypyrimidine added is reacted continually to give soluble subsequent products of the structure (II), so that stirrability remains ensured.

In a preferred embodiment, the chlorinating agent is initially charged. The N,N-dialkylformamide is then added at a temperature of from 20 to 100°C, preferably from 40 to 70°C, and the reaction mixture is allowed to react at this temperature for a period of from 5 to 180 minutes. The 2,5-diamino-4,6-dihydroxypyrimidine is metered in at a temperature of from 50 to 130°C, preferably from 50 to 100°C, over the course of from 15 minutes to 5 hours.

Subsequently, continued reaction is effected over from 1 to 30 hours at a temperature of from 50 to 130°C, preferably from 70 to 110°C.

In a preferred embodiment, reaction step a) is effected within a temperature range from 70 to 110°C.

The subsequent hydrolysis step can in principle be carried out in two different ways. One is to meter the amount of water required directly into the chlorination mixture. This is advantageous since no further reaction vessel is required, but has the disadvantage of a metering time which is longer owing to the high heat production. Alternatively, with the same result, the chlorination mixture can be metered into initially charged water.

The added or initially charged water should be sufficient, after the end of the hydrolysis, to obtain a readily stirrable reaction mixture. According to the invention, from 2 to 5 liters of water per 1 mol of 2,5-diamino-4,6-dihydroxypyrimidine used are sufficient for this purpose.

The hydrolysis step b) should be effected within the temperature range from 0 to 100°C. The range from 20 to 60°C is considered to be preferable.

Subsequently, the resulting reaction mixture is adjusted to a certain pH with an inorganic base and partially hydrolyzed in this way.

Suitable inorganic bases are in principle all bases which form soluble chloride salts. Preference is given to sodium hydroxide solution, sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide solution, potassium hydroxide, potassium carbonate and potassium hydrogencarbonate. Particular preference is given to sodium hydroxide solution. The amount of base added depends upon the pH to be established and it is typically from 2 to 3 mol per mole of chlorinating agent used.

The pH is crucial, since it controls the selective reaction of B via C to D. In the case of incorrectly selected pH, a reduced yield and/or undesired by-products in the product are obtained. According to the invention, the pH is adjusted at a defined value in the range between pH 1.0 and 6.0, preferably from pH 2.0 to 5.0, more preferably from 3.0 to 4.0, the pH being measured by means of a glass electrode at a temperature of 20°C. If appropriate, the pH can be readjusted continuously in the course of the reaction which follows by adding further base under pH control.

The further reaction is carried out by heating the aqueous mixture to a temperature of from 70 to 120°C, preferably from 80 to 100°C. In the course of a reaction time of from 1 to 20 hours, the unisolated intermediates form the desired target product 2-amino-4,6-dichloro-5-formamidopyrimidine. This is insoluble in the reaction mixture and can be removed, washed and dried by means of process steps familiar to those skilled in the art.

It is considered to be essential to the invention that this last reaction step is effected in the absence - even of traces - of a solvent. This is because it has been found to be capable of starting to dissolve the water-insoluble 2-amino-4,6-dichloro-5-formamidopyrimidine in the reaction mixture, which makes the pyrimidine more vulnerable to a further hydrolysis, so that the ultimate result is reduced yields and/or contamination of the product with 2,5-diamino-4,6-dichloropyrimidine, the subsequent product of the hydrolysis.

The process according to the invention affords satisfactory yields which are only slightly below the yields of the prior art processes. On the other hand, it offers the advantage of higher purity of the end products. The considerably reduced reaction volumes, the savings of solvents, assistants and residual substances, and the considerably simplified process in process technology terms, give rise to distinctly more favorable preparation costs for 2-amino-4,6-dichloro-5-formylaminopyrimidine.

A further aspect of the invention relates to the use of the 2-amino-

4,6-dichloro-5-formylaminopyrimidine prepared by the process according to the invention for preparing purine derivatives. The invention further relates to the use of the 2-amino-4,6-dichloro-5-formylaminopyrimidine prepared by the process according to the invention for preparing active pharmaceutical ingredients, in particular for antiviral medicaments, for example for the treatment of AIDS.

The examples which follow serve to illustrate the process found without restricting the scope of the invention.

Examples

Example 1

61.33 g (0.40 mol) of phosphorus oxychloride were initially charged. At 50°C, 18.27 g (0.25 mol) of dimethylformamide were added dropwise within 45 minutes. The mixture was then heated to 70°C and 17.86 g (0.10 mol) of 2,5-diamino-4,6-dihydroxypyrimidine hydrochloride were added by spatula within 45 minutes. Subsequently, the mixture was heated to 90°C and stirred for 20 hours. A dark, moderately viscous, but homogeneous and readily stirrable mixture formed. It was cooled to 20°C and admixed with 200 g of water with external cooling. Addition of 82.03 g of 50% sodium hydroxide solution adjusted the pH from -0.6 to 4.0, and the reaction mixture was heated to 90°C and stirred for 8 hours. The mixture was cooled to 18°C, and the precipitated product was filtered off with suction, washed with water and dried under reduced pressure.

8.28 g of pure 2-amino-4,6-dichloro-5-formamidopyrimidine were obtained with a content of 98.7%. The yield based on 2,5-diamino-4,6-dihydroxy-pyrimidine used was 39.5%.

Example 2

61.33 g (0.40 mol) of phosphorus oxychloride were initially charged and heated to 50°C. Within 45 minutes, 29.24 g (0.40 mol) of dimethylformamide were added dropwise. The mixture was then heated to 72°C and 17.86 g (0.10 mol) of 2,5-diamino-4,6-dihydroxypyrimidine hydrochloride were added within 45 minutes. The mixture was heated to 90°C and stirred for 17 hours. The mixture was then cooled to 20°C and admixed with 200 g of water with external cooling. Addition of 88.35 g of 50% sodium hydroxide solution adjusted the pH from -0.5 to 3.6, and the reaction mixture was heated to 97°C and stirred for 4 hours. The mixture was cooled to 18°C, and the precipitated product was filtered off with suction, washed with water and

dried under reduced pressure.

7.92 g of pure 2-amino-4,6-dichloro-5-formamidopyrimidine were obtained with a content of 97.6%. The yield based on 2,5-diamino-4,6-dihydroxy-pyrimidine used was 37.4%.

Example 3 (comparative)

180 ml of toluene and 76.7 g (0.5 mol) of phosphorus oxychloride were initially charged. At 50°C, 29.2 g of dimethylformamide were added dropwise within 45 minutes. At 70°C, 17.86 g (0.1 mol) of 2,5-diamino-4,6-dihydroxy-pyrimidine hydrochloride were then added in portions. Subsequently, the mixture was stirred at 90°C for 20 hours. A viscous mass formed, which adhered to stirrer and flask wall and was only partially soluble in toluene.

After cooling, 300 g of water were metered into the mixture, the pH was adjusted to 5.0 by adding 89.6 g of 50% sodium hydroxide solution and the toluene phase was removed. An interface layer which was difficult to remove formed. After the toluene phase had been evaporated, 15.9 g of crude 2,5-bis(dimethylaminomethyleneamino)-4,6-dichloropyrimidine remained.

The water phase was extracted 3 times with 200 ml each time of ethyl acetate, and the organic phases were concentrated by evaporation. 9.8 g of a second, less pure fraction of 2,5-bis(dimethylaminomethyleneamino)-4,6-dichloropyrimidine remained.

250 g of water and 5.7 g of 85% phosphoric acid were initially charged, and adjusted to pH 4.0 with 3.7 g of sodium hydroxide solution, and the mixture of the two crude products was added. The mixture was again adjusted to pH 4.0 with 10.5 g of phosphoric acid. The mixture was stirred at 100°C for 4 hours. After cooling, the precipitated product was filtered off, washed and dried. 11.3 g of 2-amino-4,6-dichloro-5-formamidopyrimidine were obtained with a content of 83.8%. The pure yield based on 2,5-diamino-

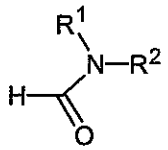
4,6-dihydroxypyrimidine used was 45.7%.

An experiment carried out analogously using chlorobenzene instead of toluene lead to better stirrability of the reaction mixture. After extracting 3 times with chlorobenzene and analogous reaction in a phosphate buffer, 12.4 g of 2-amino-4,6-dichloro-5-formamidopyrimidine were obtained with a content of 78.3%. It was found that chlorobenzene distilled off incompletely had brought about partial further hydrolysis to 2,5-diamino-4,6-dichloropyrimidine.

What is claimed is:

1. A process for preparing 2-amino-4,6-dichloro-5-formamidopyrimidine from 2,5-diamino-4,6-dihydroxypyrimidine or a salt thereof, characterized in that

a) the 2,5-diamino-4,6-dihydroxypyrimidine or salt or tautomeric forms thereof is reacted with a chlorinating agent and a formamide of the formula (I)



(I),

where

R^1 and R^2 are each independently a C_1-C_4-alkyl radical, or $-R^1-R^2-$ is $-(CH_2)_n-$ where n = from 4 to 6 or $-(CH_2)_2-O-(CH_2)_2-$, without addition of a solvent at from 50 to 130°C,

b) the reaction product from stage a) is reacted at from 0 to 100°C with water and adjusted to a pH of from 1.0 to 6.0 with an inorganic base and

c) the aqueous reaction mixture from stage b) is reacted at from 70 to 120°C with hydrolysis to give 2-amino-4,6-dichloro-5-formamido-pyrimidine.

2. The process as claimed in claim 1, characterized in that the starting material used is 2,5-diamino-4,6-dihydroxypyrimidine as the hemisulfate, hydrochloride monohydrate or as the anhydrous hydrochloride, preferably anhydrous 2,5-diamino-4,6-dihydroxypyrimidine hydrochloride as the raw material.

3. The process as claimed in claim 1 or 2,
characterized in that
the chlorinating agent used is a reagent having the functionality of an acid chloride, preferably phosgene, oxalyl chloride, chloromethylene-dimethylammonium chloride, thionyl chloride, sulfuryl chloride, phosphorus trichloride, phosphorus pentachloride or phosphorus oxychloride, more preferably phosphorus oxychloride.

4. The process as claimed in one of claims 1 to 3,
characterized in that
the amide of the formula (I) is reacted with the chlorinating agent in a preceding step and the 2,5-diamino-4,6-dihydroxypyrimidine is only then added in portions.

5. The process as claimed in one of claims 1 to 4,
characterized in that
N,N-dimethylformamide, N-formylpyrrolidine, N-formylpiperidine or N-formylmorpholine, preferably N,N-dimethylformamide, is used.

6. The process as claimed in one of claims 1 to 5,
characterized in that
from 1.0 to 5.0 mol of amide of the formula (I) per mole of 2,5-diamino-4,6-dihydroxypyrimidine are used.

7. The process as claimed in one of claims 1 to 6,
characterized in that
from 3.0 to 7.0 mol of chlorinating agent per mole of 2,5-diamino-4,6-dihydroxypyrimidine are used.

8. The process as claimed in one of claims 1 to 7,
characterized in that
reaction step a) is effected within a temperature range from 70 to 110°C.

9. The process as claimed in one of claims 1 to 8, characterized in that the inorganic base used in step b) is a base which forms soluble chloride salts, preferably one or more compounds which are selected from the group of sodium hydroxide solution, sodium hydroxide, sodium carbonate, sodium hydrogencarbonate, potassium hydroxide solution, potassium hydroxide, potassium carbonate and potassium hydrogencarbonate.

10. The process as claimed in one of claims 1 to 9, characterized in that the base used is sodium hydroxide solution.

11. The process as claimed in one of claims 1 to 10, characterized in that from 2 to 3 mol of the inorganic base are used per mole of chlorinating agent.

12. The process as claimed in one of claims 1 to 11, characterized in that the partial neutralization in step b) is effected up to a pH of from 2.0 to 5.0, preferably from 3.0 to 4.0.

13. The process as claimed in one of claims 1 to 12, characterized in that the reaction product from stage a) is reacted at from 20 to 60°C.

14. The process as claimed in one of claims 1 to 13, characterized in that the hydrolysis in step c) is effected at a temperature of 70-120°C, preferably from 80 to 100°C.

15. The process as claimed in one of claims 1 to 13,

characterized in that
step c) is effected in the absence of a solvent.

16. The process as claimed in one of claims 1 to 15,
characterized in that
the claimed reaction is effected without isolation of intermediates, i.e. as a one-pot reaction.

17. The use of the 2-amino-4,6-dichloro-5-formamidopyrimidine prepared according to one of claims 1 to 15 for preparing purine derivatives, in particular for preparing active pharmaceutical ingredients.

18. The use of the 2-amino-4,6-dichloro-5-formamidopyrimidine prepared according to one of claims 1 to 15 for preparing active pharmaceutical ingredients, in particular for antiviral medicaments.

19. The use as claimed in claim 18 for preparing active pharmaceutical ingredients for the treatment of AIDS.