

The invention relates to a process for the manufacture of 5H-dibenz[b,f]azepine-5-carboxamide, which is characterised in that 5H-dibenz[b,f]azepine (iminostilbene) is reacted with cyanic acid in an organic solvent or solvent mixture and in the presence of an acidic agent.

5H-Dibenz[b,f]azepine-5-carboxamide, known by the generic name carbamazepine as an active ingredient in medications, is, in accordance with US-PS 2 948 718, usually manufactured by reacting 5H-dibenz[b,f]azepine with phosgene to form 5H-dibenz[b,f]azepine-5-carboxylic acid chloride and by further reaction of the same with ammonia. In accordance with a more recent process according to DE-A1 2 307 174, 5H-dibenz[b,f]azepine is reacted with an acyl isocyanate and the resulting 5H-dibenz[b,f]azepine-5-(N-acyl)carboxamide is subjected to basic hydrolysis. The known processes have decided disadvantages. Two separate reaction steps must always be carried out, and in the first step of the process according to the US-PS the use of an equimolar amount of highly toxic phosgene is unavoidable.

The object of the invention was accordingly to address the hitherto unsolved problem of developing a manufacturing process that in one step results directly in 5H-dibenz[b,f]azepine-5-carboxamide.

The proposed solution according to the invention is surprising in as much as it is known that when 5H-dibenz[b,f]azepine is reacted with alkyl isocyanates it does not form corresponding 5H-dibenz[b,f]azepine-5-(N-alkyl)carboxamides (DE-A1 2 307 174) and the reaction of N,N-diarylamines with sodium cyanate and trifluoroacetic acid in benzene could not be used in the case of benzimidazole and carbazole (Chem. and Ind. 1965, pages 1428-9).

The cyanic acid used in accordance with the invention to introduce the 5-carbamoyl group is usually produced by pyrolysis of cyanuric acid, by oxidation of formamide with oxygen with silver or copper contact or by treating a solution and/or suspension of one of its salts, preferably sodium or potassium cyanate, with an acid. Cyanic acid is not stable in free form. It enters into a large number of polymerisation and autocondensation reactions and in addition readily adds water, alcohols, amines and the like. Solutions thereof in suitable organic solvents are, however, adequately stable for the purpose of the invention.

The reaction according to the invention is therefore carried out in organic solution, that is to say in an organic solvent or a mixture of organic solvents, cyanic acid preferably being blown into the reaction system in a gaseous state, advantageously with an inert gas such as nitrogen or argon, or being freed with the aid of an acid by treating a solution and/or suspension of one of its salts, preferably sodium or potassium cyanate.

Suitable organic solvents are those that do not react with isocyanic acid or that react with isocyanic acid only so slowly that the reaction according to the invention is not impaired by the formation of undesirable intermediates. The following, for example, are suitable: aromatic or araliphatic hydrocarbons, such as benzene or toluene, haloaliphatic compounds, such as 1,2-dichloroethane, aliphatic carboxylic acids and the aliphatic esters thereof, such as lower alkanecarboxylic acids, for example acetic acid, or lower alkanecarboxylic acid lower alkyl esters, for example ethyl acetate, and also aliphatic ethers, such as diethyl ether, dioxane, tetrahydrofuran and the like, as well as mixtures of the

same. Since cyanic acid enters into undesirable secondary reactions with water, alcohols, amines and the like, the reaction according to the invention is advantageously carried out under essentially aprotic conditions, that is to say, in essentially water-, alcohol- and amine-free organic solution and with the exclusion of water vapour. These precautionary measures can be dispensed with completely, however, when working up the reaction mixture and isolating the addition product formed.

An amount of cyanic acid that is at least equimolar to the amount of 5H-dibenz[b,f]azepine used is necessary for the reaction according to the invention. To achieve a better reaction yield, however, advantageously from 1.05 to 2.5 times the molar amount, preferably from 1.25 to 2.25 times the molar amount, for example from 1.3 to double the molar amount, of cyanic acid is used, that is to say, a 5 % to 150 %, preferably 25 % to 125 %, for example 30 % to 100 %, excess of cyanic acid is used.

To free cyanic acid from one of its salts, which is an especially preferred embodiment of the invention, in general any protonic acid with an acidic strength sufficient to free cyanic acid from its salts is suitable. The following, for example, are suitable: mineral acids, for example hydrochloric acid or sulphuric acid, organic sulphonic acids, such as C₁-C₇alkanesulphonic acids or unsubstituted or halo- or C₁-C₄alkyl-substituted benzenesulphonic acids, for example methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulphonic acid, or organic carboxylic acids of which the acidic strength in the solvent used corresponds in practice at least to that of formic acid, such as 2-mono-, 2,2-di- or 2,2,2-tri-halo-C₂-C₇alkanoic acids, for example trichloroacetic acid.

The reaction of the 5H-dibenz[b,f]azepine component with cyanic acid is spontaneous and slightly exothermic. The parameters of the reaction are not critical. The reaction can be carried out, for example, in a temperature range of from 0°C to 120°C and homogeneously or, preferably, heterogeneously. The reaction is, however, accelerated, and the reaction speed increased, by heating gently and/or by the presence of an acidic agent. The reaction is therefore carried out in the presence of an acidic agent and preferably in a temperature range of from 20°C to 120°C, preferably 100°C. Since the participation of the acidic agent in the reaction is only catalytic, in principle catalytic amounts of acid are sufficient. In general, from 0.01 to 0.15, for example from 0.04 to 0.05, of an equivalent of acidic agent per mol of 5H-dibenz[b,f]azepine is entirely adequate. Only when using polybasic acids of distinctly different acidity stages is it necessary to note in the case of heterogeneous reaction that acidic salts may be precipitated, blocking some of the acid used. When using sulphuric acid, for example, it is therefore necessary to use per mol of 5H-dibenz[b,f]azepine up to 1.5 mol equivalents, for example from 1.05 to 1.4 mol equivalents, of sulphuric acid, corresponding to 0.525 to 0.7 mol, that is to say 5 % to 40 % excess, if using the variant in which cyanic acid is freed from one of its salts and the reaction is carried out heterogeneously. Obviously, the catalytic acidic agent may alternatively be present or be added in the form of an ammonium salt derived from 5H-dibenz[b,f]-azepine.

Suitable acidic agents are, for example, the protonic acids indicated above as being suitable for freeing cyanic acid, and also aliphatic carboxylic acids, such as C₁-C₇alkanoic acids, for example acetic acid, especially if these also act as solvents. If the variant in which

cyanic acid is freed in situ from one of its salts is used, then it is generally advantageous to employ a small excess, that is an excess of from 0.5 % to 10 %, for example from 1 % to 5 %, of the acid used for freeing cyanic acid but if, for example, sulphuric acid is used, then, for the reasons mentioned, it is advantageous to employ a 5 % to 40 % excess, for example a 32 % excess.

In a preferred embodiment there is added to a suspension of 5H-dibenz[b,f]azepine and of 1.75 to 2.25 times the molar amount, for example approximately double the molar amount, of sodium cyanate in toluene, at from 20°C to 30°C, for example at from 20°C to 25 °C, per mol of sodium cyanate, from 1.005 to 1.05 mol, for example 1.02 mol, of trichloroacetic acid, that is to say a 0.5 % to 5 %, for example a 2 %, excess of trichloroacetic acid, and the whole is heated to from 40°C to 80°C, for example to from 50°C to 65°C; or there is added to a suspension of 5H-dibenz[b,f]azepine in acetic acid from 1.05 to 1.40 mol equivalents of sulphuric acid, corresponding to from 0.525 mol to 0.7 mol, that is to say a 5 % to 40 % excess, of sulphuric acid, and there is then added an amount of sodium cyanate that is at least equimolar to the amount of 5H-dibenz[b,f]azepine used, for example from 1.25 to 1.75 mol, for example 1.6 mol, of sodium cyanate per mol of 5H-dibenz[b,f]azepine, the operation being carried out at from 10°C to 120°C; or there is introduced into a suspension of sodium isocyanate in ethyl acetate from 1.02 to 1.10 times the molar amount, for example 1.05, that is to say from 1.04 to 1.06, times the molar amount of hydrogen chloride, that is an excess of from 2 % to 10 %, for example 5 %, that is to say from 4 % to 6 %, of hydrogen chloride, and there is then added an amount of 5H-dibenz[b,f]azepine that is at most equimolar to the amount of sodium cyanate used, for example a 5 % to 50 % molar deficit, for

example from 0.6 to 0.9 mol, for example 0.75 mol, of 5H-dibenz[b,f]azepine per mol of sodium cyanate, the operation being carried out at from 0°C to 80°C, for example with heating to from 40°C to 70°C after the addition of the amine component.

In another preferred embodiment, there is introduced into a suspension of 5H-dibenz[b,f]azepine in acetic acid, from 1.25 to 1.75 times the molar amount, preferably from 1.4 to 1.6 times the molar amount, that is to say a 25 % to 75 %, preferably 40 % to 60 %, excess of cyanic acid and the whole is heated, if necessary, to from 25°C to 50°C; or there is introduced into a suspension of 5H-dibenz[b,f]azepine in toluene, xylene, 1,2-dichloroethane or ethyl acetate, first of all from 0.01 to 0.15 times the molar amount, for example from 0.01 to 0.12 times the molar amount, that is to say from 1 to 15 mol %, for example from 1 to 12 mol %, of hydrogen chloride and then from 1.25 to 1.75 times the molar amount, preferably from 1.4 to 1.6 times the molar amount, that is to say a, for example, 25 % to 75 %, preferably 40 % to 60 %, excess of cyanic acid, and the whole is heated, if necessary, to from 50°C to 125°C, for example to from 75°C to 100°C. In a modification of this variant, there is introduced into a suspension of a mixture of 5H-dibenz[b,f]azepine and its hydrochloride, for example from 0.8 to 0.96, preferably from 0.85 to 0.95, molar proportions of 5H-dibenz[b,f]azepine and from 0.04 to 0.2, preferably from 0.05 to 0.15, molar proportions of 5H-dibenz[b,f]azepine* (total of molar proportions = 1), from 1.25 to 1.75 times the molar amount, preferably from 1.4 to 1.6 times the molar amount, that is to say a, for example, 25 % to 75 %, preferably 40 % to 60 %, excess of cyanic acid, and

*Translator's note: Presumably "hydrochloride" has been omitted in error from the German text.

the whole is heated, if necessary, to from 60°C to 100°C.

The invention is described in detail in the following Examples. Temperatures are given in degrees Celsius.

Example 1: 723 g of trichloroacetic acid are dissolved in 600 ml of toluene and, in the course of 1 1/2 hours, this solution is added to a suspension of 407 g of 5H-dibenz-[b,f]azepine and 290 g of sodium cyanate in 600 ml of toluene, the temperature being maintained at 25°C by cooling.

The whole is then allowed to react for 1/2 hour at 25°C and for 1 hour at 50°C, and 1300 ml of water are subsequently slowly added. The mixture is then cooled to 20°C and the product is filtered off, washed with toluene and water and dried at 85-90°C in vacuo. Yield: 475 g of 5H-dibenz[b,f]azepine-5-carboxamide.

Example 2: 25 g of 5H-dibenz[b,f]azepine are suspended in 180 ml of acetic acid and 14 g of 96 % sulphuric acid are slowly added. 13.5 g of sodium cyanate are added in portions at 30°C while stirring well.

The whole is stirred for 3 hours at 30°C, and the product is filtered off and washed with acetic acid and then with water.

29.5 g of 5H-dibenz[b,f]azepine-5-carboxamide are obtained after drying at 80°C in vacuo.

Example 3: 68 g of sodium cyanate are suspended in 1000 ml of ethyl acetate and, while stirring at room temperature, 40 g of hydrogen chloride in gaseous form are introduced. After 4 hours, the sodium chloride that has formed is filtered off and 155 g of 5H-dibenz[b,f]-

azepine are added to the clear filtrate. The reaction mixture is maintained at 50°C for from 4 to 5 hours, cooled to 0°C and the product is filtered off, washed with a small amount of ethyl acetate and dried at 80°C in vacuo to yield 177 g of 5H-dibenz[b,f]azepine-5-carboxamide.

Example 4: 17.4 g of 5H-dibenz[b,f]azepine and 2.3 g of 5H-dibenz[b,f]azepine hydrochloride are suspended in 250 ml of toluene. The suspension is heated to 80° and, in the course of 1 1/2 hours, 6.5 g of monomeric cyanic acid are introduced in a stream of nitrogen and the whole is then heated for a further 1/2 hour at 100°C.

After cooling to 5°, the product is filtered off, washed four times with cold toluene and dried in vacuo at 60°. 18.5 g of 5H-dibenz[b,f]azepine-5-carboxamide are obtained.

Example 5: 17.4 g of 5H-dibenz[b,f]azepine and 2.3 g of 5H-dibenz[b,f]azepine hydrochloride are suspended in 250 ml of xylene (isomeric mixture). At 20°C, 6.5 g of monomeric cyanic acid are introduced in a stream of nitrogen and the whole is then allowed to react for 4 hours at 30°.

Subsequently, the whole is cooled to 0°, and the product is filtered off, washed with xylene and dried in vacuo at 80° to yield 22.1 g of 5H-dibenz[b,f]azepine-5-carboxamide.

Example 6: 19.3* of 5H-dibenz[b,f]azepine are suspended in 200 ml of 1,2-dichloroethane. At 25°, first of all 4.5 g of hydrogen chloride and then 6.5 g of cyanic acid

*Translator's note: No unit appears in the German text.

in gaseous form (in a stream of nitrogen) are introduced. The introduction is carried out for a period of 5 hours and is in several portions. The whole is subsequently allowed to react for 1 hour, and the product is filtered off and washed with 1,2-dichloroethane and then with water.

After drying at 60° in vacuo, 16.0 g of 5H-dibenz[b,f]-azepine-5-carboxamide are obtained.

A batch treated in a similar manner was concentrated by evaporation when the reaction was complete and the residue was digested cold with toluene and filtered off. After washing with toluene and water and drying in vacuo at 60°, 22.5 g of 5H-dibenz[b,f]azepine-5-carboxamide were obtained.

Example 7: 29.0 g of 5H-dibenz[b,f]azepine are suspended in 150 ml of ethyl acetate at 20°. First of all 0.6 g of hydrogen chloride and then 9.7 g of cyanic acid in gaseous form (in a stream of nitrogen) are introduced.

After stirring for 15 hours at 20°, the product is filtered off, washed with ethyl acetate and then dried in vacuo at 60°. 32.0 g of 5H-dibenz[b,f]azepine-5-carboxamide are obtained.

An analogous test at 50° reaction temperature yielded 29.4 g of 5H-dibenz[b,f]azepine-5-carboxamide.

Example 8: 19.3 g of 5H-dibenz[b,f]azepine are suspended in 200 ml of ethyl acetate and 1.0 ml of sulphuric acid (98 %) is added.

At 25°, 6.5 g of monomeric cyanic acid (in a stream of nitrogen) are introduced. The whole is left to stand

overnight, then concentrated to dryness by evaporation in vacuo, and the residue is taken up with toluene. After filtration, washing with toluene and water and drying at 80° in vacuo, 19.7 g of 5H-dibenz[b,f]azepine-5-carboxamide are obtained.

Example 9: 19.3 g of 5H-dibenz[b,f]azepine are heated to 45° with 100 ml of acetic acid. In the course of 1 1/2 hours, 6.5 g of monomeric cyanic acid (in a stream of nitrogen) are introduced and the whole is left to react for 12 hours at 40°. After cooling to 15°, filtration is carried out followed by washing cold with acetic acid and drying in vacuo at 60°.

The resulting crude product is recrystallised from methanol/water (7:3) and yields 19.1 g of 5H-dibenz[b,f]azepine-5-carboxamide.

Example 10: 29.0 g of 5H-dibenz[b,f]azepine are heated to 45° in 150 ml of acetic acid. In the course of 1 1/2 hours, 9.7 g of monomeric cyanic acid (in a stream of nitrogen) are introduced and the whole is then allowed to react for 2 hours at 40° and for 12 hours at 20°.

After the addition of 15 ml of water, the whole is cooled to 0° and, after 1 hour, the product is filtered off and washed twice with 15 ml of acetic acid and water to give a crude product which, after recrystallisation from methanol/water (7:3), yields 29.1 g of 5H-dibenz[b,f]azepine-5-carboxamide.



Patent Claims

1. A process for the manufacture of 5H-dibenz[b,f]-azepine-5-carboxamide, characterised in that 5H-dibenz[b,f]azepine is reacted with cyanic acid in an organic solvent or solvent mixture and in the presence of an acidic agent.
2. A process according to claim 1, characterised in that the organic solvent used is an aliphatic carboxylic acid or an aliphatic ester of such an acid, an aromatic or araliphatic hydrocarbon, a haloaliphatic compound or an aliphatic ether.
3. A process according to either claim 1 or claim 2, characterised in that the organic solvent used is toluene, xylene, 1,2-dichloroethane, acetic acid or ethyl acetate.
4. A process according to either claim 1 or claim 2, characterised in that cyanic acid is freed by acid treatment of a solution and/or suspension of a cyanic acid salt in an organic solvent and is used without being isolated.
5. A process according to claim 3, characterised in that cyanic acid is freed by acid treatment of a solution and/or suspension of a cyanic acid salt in an organic solvent and is used without being isolated.
6. A process according to any one of claims 1, 2 and 4, characterised in that the organic solvent used is acetic acid, ethyl acetate or toluene.
7. A process according to either claim 3 or claim 5, characterised in that the acidic agent used is a mineral



acid, an organic sulphonic acid, an aliphatic carboxylic acid, or a 2-mono-, 2,2-di- or 2,2,2-tri-halo-C₂-C₇-alkanoic acid.

8. A process according to any one of claims 1, 2, 4 and 6, characterised in that the acidic agent used is a mineral acid, an organic sulphonic acid, or a 2-mono-, 2,2-di- or 2,2,2-tri-halo-C₂-C₇alkanoic acid.

9. A process according to any one of claims 1, 2, 4 and 6, characterised in that the acidic agent used is a mineral acid.

10. A process according to any one of claims 3, 5, 7 and 8, characterised in that the acidic agent used is trichloroacetic acid, hydrochloric acid or sulphuric acid.

11. A process according to any one of claims 1, 2, 4, 6 and 9, characterised in that the acidic agent used is hydrochloric acid or sulphuric acid.

12. A process according to any one of claims 3, 5, 7, 8 and 10, characterised in that the acidic agent used is trichloroacetic acid.

13. A process according to any one of claims 1, 2, 6 and 8, characterised in that acetic acid is used as acidic agent and simultaneously as solvent.

14. A process according to any one of claims 3, 5, 7, 10 and 12, characterised in that the reaction is carried out in a temperature range of from 0°C to 120°C.

15. A process according to any one of claims 1, 2, 4, 6, 8, 9, 11 and 13, characterised in that the reaction is



carried out in a temperature range of from 0°C to 120°C.

16. A process according to any one of claims 1 to 8, 10, 12, 14 and 15, characterised in that a 0.5 % to 5 % excess of trichloroacetic acid is added, at from 20°C to 30°C, to a suspension of 5H-dibenz[b,f]azepine and 1.75 to 2.25 times the molar amount of sodium cyanate in toluene, and the whole is heated to from 40°C to 80°C.

17. A process according to any one of claims 1 to 8, 10, 12, 14 and 15, characterised in that a 2 % excess of trichloroacetic acid is added at from 20°C to 25°C to a suspension of 5H-dibenz[b,f]azepine and approximately double the molar amount of sodium cyanate in toluene, and the whole is then heated to from 50°C to 65°C.

18. A process according to any one of claims 1 to 10, 14 and 15, characterised in that a 2 % to 10 % excess of hydrogen chloride is introduced into a suspension of sodium isocyanate in ethyl acetate, and then from 0.6 to 0.9 times the molar amount of 5H-dibenz[b,f]azepine related to the amount of sodium cyanate used is added, and the whole is heated to from 40°C to 70°C.

19. A process according to any one of claims 1, 2, 4, 6, 8, 11 and 15, characterised in that, at from 0°C to +80°C, a 4 % to 6 % excess of hydrogen chloride is introduced into a suspension of sodium isocyanate in ethyl acetate and then an amount of 5H-dibenz[b,f]azepine that is at most equimolar to the amount of sodium cyanate used is added.

20. A process according to any one of claims 1, 2, 4, 6, 8, 9, 11 and 14, characterised in that, at from +10°C to +120°C, a 5 % to 40 % excess of sulphuric acid is added to a suspension of 5H-dibenz[b,f]azepine in acetic acid



and then an amount of sodium isocyanate that is at least equimolar to the amount of 5H-dibenz[b,f]azepine used is added.

21. A process according to any one of claims 1 to 11 and 14, characterised in that a 5 % to 40 % excess of sulphuric acid is added to a suspension of 5H-dibenz[b,f]azepine in acetic acid and then from 1.25 to 1.75 mol of sodium isocyanate are added per mol of 5H-dibenz[b,f]azepine.

22. A process according to any one of claims 1 to 11 and 14, characterised in that, at from +10°C to +120°C, a 5 % to 40 % excess of sulphuric acid is added to a suspension of 5H-dibenz[b,f]azepine in acetic acid and then 1.6 mol of sodium isocyanate are added per mol of 5H-dibenz[b,f]azepine.

23. A process according to any one of claims 1 to 3, 6, 7, 13 and 14, characterised in that a 25 % to 75 % excess of cyanic acid is introduced into a suspension of 5H-dibenz[b,f]azepine in acetic acid.

24. A process according to any one of claims 1 to 3, 6, 7, 8 to 11 and 14, characterised in that first of all from 1 to 15 mol % of hydrogen chloride and then a 25 % to 75 % excess of cyanic acid are introduced into a suspension of 5H-dibenz[b,f]azepine in toluene, xylene, 1,2-dichloroethane or ethyl acetate.

25. A process according to any one of claims 1 to 3, 6, 7, 8 to 11 and 14, characterised in that a 25 % to 75 % excess of cyanic acid is introduced into a suspension of a mixture of from 0.8 to 0.96 molar proportion of 5H-dibenz[b,f]azepine and from 0.04 to 0.2 molar proportion of 5H-dibenz[b,f]azepine hydrochloride (total of molar



proportions = 1) in an araliphatic hydrocarbon.