

PREPARATION OF α -AMINO CARBOXYLIC ACID AMIDESBACKGROUND OF THE INVENTION

The present invention relates to a process for producing α -amino carboxylic acid amides. Such amides are useful as intermediates for N-substituted heterocyclic pharmaceutical compositions useful in the treatment of cardiovascular diseases including hypertension, as well as glaucoma, diabetic retinopathy and renal insufficiency. In particular, the pharmaceutical compositions demonstrate antagonistic action against angiotensin II, a potent vasopressor.

Conventional processes for the preparation of α -amino carboxylic acid amides suffer from various disadvantages, including low yields, low purity, the requirement of many steps in the synthetic route, and complex isolation schemes. One route to the amides is disclosed in Abramov, et al., Zhurnal Organ. Khimii, 20(7), p. 1243-1247 (1984) where the preparation of α -aminoamides and α -amino acids from the corresponding α -aminonitriles using manganese (IV) in the form of manganese oxide is taught. Reaction times are critical, as longer reaction times lead to the amino acid. In addition, reversion to the starting cyanohydrin and ketone can occur.

Another somewhat analogous synthetic scheme is disclosed in Johnson, et al., J. Org. Chem. 27, p.798-802 (1962). This method involves the reaction of an aminonitrile with anhydrous HCl in the presence of an alcohol. The aminonitrile is dissolved in n-butanol and is then treated with anhydrous HCl and stirred at room temperature for 24 hours. The reaction mixture is then refluxed for one hour. The imidate ester hydrochloride is formed as an intermediate, and decomposes upon the application of heat to the corresponding amide and an alkyl chloride. Alkyl chloride is formed as a by-product of the reaction.

U.S. Patent No. 5,352,788 discloses a synthesis that involves the hydrolysis of the oxalate salt of the aminonitrile using concentrated sulfuric acid, followed by treatment with ammonia and then extraction with chloroform containing 5% methanol. However, this method has many disadvantages.

It is therefore an object of the present invention to provide a method of producing aminoamides directly from the corresponding aminonitrile.

It is a further object of the present invention to provide a method of producing aminoamides from aminonitriles in high yield and without the concomitant production of potentially hazardous by-products.

It is a still further object of the present invention to provide a method of producing aminoamides from aminonitriles without requiring complex isolation steps.

SUMMARY OF THE INVENTION

The problems of the prior art have been overcome by the present invention, which provides a method of preparing α -amino carboxylic acid amides directly from aminonitriles in high yield and purity by acid hydrolysis. The method involves preparing the amide hydrochloride directly from the corresponding aminonitrile in the presence of water, a strong mineral acid such as HCl, and an organic solvent in which the resulting salt of the aminonitrile is insoluble or substantially insoluble. For example, in the case of HCl, the hydrochloride salt readily precipitates from the solvent, and can be isolated by filtration in high purity. The solvent and excess HCl can be recycled with no significant color build-up or product quality deterioration.

DETAILED DESCRIPTION OF THE INVENTION

The present invention can be used in connection with any α -amino carboxylic acid, provided that the corresponding salt is insoluble in the solvent employed. Suitable α -amino carboxylic acids include valine, glycine, alanine and leucine, with glycine, leucine and cycloleucine being particularly preferred.

The amino nitrile can be virtually any α -aminonitrile corresponding to the α -amino carboxylic acid desired, and can be prepared from the corresponding ketone by conventional means well known to those skilled in the art. For example, the

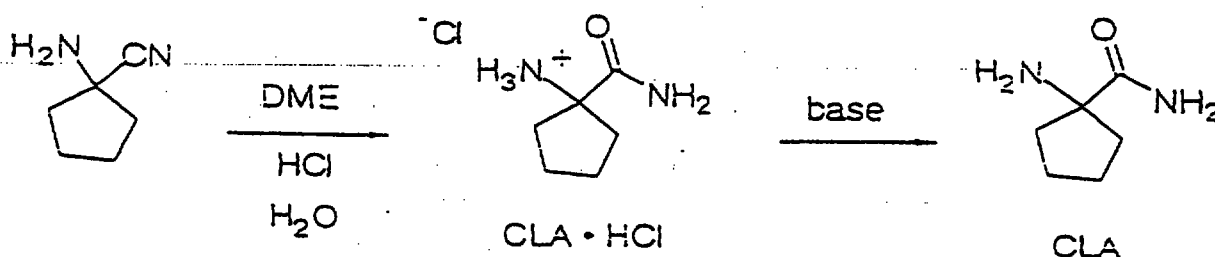
ketone in a suitable solvent such as methanol can be reacted with an ammonia source (such as ammonia and ammonium chloride) and a cyanide source (such as alkali metal cyanide), and the resulting amino nitrile can be recovered by extraction with methylene chloride and dried.

In accordance with the present invention, the amino nitrile is dissolved in a solvent in which the amino carboxylic acid amide salt readily precipitates. Suitable solvents include dialkyl ethers such as diethyl ether, and dialkyl ethylene glycols such as ethylene glycol dimethyl, diethyl, dibutyl, butyl methyl and propyl ethyl ether; secondary alcohols such as isopropanol (preferably anhydrous); hydrocarbons such as heptane and hexane; and ketones such as acetone. The particular solvent should be chosen such that it is a solvent in which the amino nitrile has sufficient solubility to be acid hydrolyzed, and in which the salt formed by the reaction is at least substantially insoluble, ensuring that it can be easily isolated from the reaction medium. As the solubility of the salt in the solvent increases, the yield will decrease. Ether solvents are preferred, with dimethoxyethane being an especially preferred solvent.

Water is added to the reaction medium, preferably in an amount of about 0.5 to 4 equivalents based upon the amount of amino nitrile employed, most preferably one equivalent based upon the amount of amino nitrile employed. High excesses of water lead to the production of the amino acid rather than the desired amide. The reaction mixture is then cooled to a temperature in the range of 0-50°C, preferably below about 30°, most preferably to about 10°C, and a suitably strong mineral acid is added while keeping the reaction temperature within the aforementioned range and preferably below about 30°C. Higher temperatures tend to result in undesirable side reactions. Suitable mineral acids include HCl, HBr, H₂SO₄, toluene sulfonic acid, methane sulfonic acid and trifluoro acetic acid. Since excess water is deleterious to the reaction, leading to the generation of alkyl chloride, for example, it is preferred that the strong mineral acid be added in anhydrous form, especially

once the appropriate amount of water is already in the system. Suitable amounts of mineral acid range from about 1 to about 6 equivalents, with 3-4 equivalents being preferred in order to reduce reaction times. Preferably the acid is added over time, such as 60 minutes. Once the addition of the acid is complete, the reaction mixture is sealed, warmed to a temperature of about 40°C or higher to effect conversion to the α -amino carboxylic amide salt, allowed to react to completion (about 4-20 hours), and cooled. Preferably a closed system is used, since at temperatures higher than 40°C, the loss of acid gas to the atmosphere becomes problematic. At temperatures below 40°C, the reaction is very sluggish. The resulting amide salt readily precipitates, which allows for easy isolation and purification. The salt can be collected by filtration and washed with additional solvent. The thus produced amide salt can be easily converted to the free amide acid by the addition of a suitable alkaline reagent, such as ammonium hydroxide or alkali metal hydroxide, preferably sodium or potassium hydroxide.

The theoretical reaction mechanism can be illustrated as follows for the preparation of cycloleucine amide:



EXAMPLE 1

The amino nitrile of cyclopentanone was prepared using methods commonly found in the literature. The amino nitrile of cyclopentanone (40.00g, 0.36 mole) was added to a 500 ml round bottom flask equipped with a mechanical stirrer, a thermocouple, and a gas inlet tube. Following the addition of 131g of dimethoxyethane (DME) and 6.55g (0.36 mole) of water, the reaction was cooled to <10°C. Anhydrous HCl (53.14g, 1.46 moles) was bubbled into the reaction mixture keeping the reaction temperature below 30°C. The HCl was added over a 60.

minute period. The reaction mixture was sealed and warmed to 40°C for eight hours and then cooled to 10°C. Cycloleucine amide hydrochloride (49.40g, 0.30 mole, 83.3%) was collected by filtration as a white solid and washed with an additional 26g of DME. Additional product can be isolated from the filtrate. The hydrochloride salt can be easily converted to the acid with an alkaline reagent.

EXAMPLE 2

2.8 g (0.05 mol) of anhydrous, liquid glycinonitrile was dissolved in 1,2-dimethoxyethane in a 125 ml Erlenmeyer flask. 9.2 g of anhydrous HCl was bubbled into the flask with cooling to the desired weight. 0.9 g (0.05 mol) of water was added, and the reaction mixture was stirred at the desired temperature for 6 hours. The product was filtered off, washed with additional solvent, and dried under vacuum. The yield of amide was 92.0%.

EXAMPLE 3

Isopropanol was placed in a 5 liter flask equipped with a stirrer, thermometer, gas inlet tube and condenser. The flask was cooled in an ice-salt bath and HCl was added from a cylinder until saturated - 600 grams absorbed. Glycinonitrile hydrochloride was added in one portion and the cooling bath was removed. The connecting tube and flask were attached to a condenser, and the flask was cooled in the ice bath to collect isopropyl chloride. The reaction mixture was heated slowly to about 60°C when the isopropyl chloride started to collect. The temperature was raised to 78-92°C and held there for 3.5 - 4 hours. After cooling overnight, the resulting solid was collected and air dried. 309 g of crude product were obtained, resulting in a yield of 93%. 37% of the isopropyl chloride was recovered.



What is claimed is:

1. A process of preparing an α -amino carboxylic acid amide, comprising reacting an α -amino nitrile with a strong mineral acid in the presence of water and an organic solvent in which the resulting salt of said amide precipitates.

2. The process of claim 1, wherein said organic solvent is selected from the group consisting of dialkyl ethers, dialkyl ethylene glycol ethers and secondary alcohols.

3. The process of claim 1, wherein said organic solvent is dimethoxyethane.

4. The process of claim 1, wherein said reaction is conducted in a closed system.

5. The process of claim 1 wherein said strong mineral acid is hydrochloric acid.

6. The process of claim 1 wherein said strong mineral acid is anhydrous hydrochloric acid.

7. The process of claim 1, further comprising contacting said salt of said amide with an alkaline reagent.

8. The process of claim 7, wherein said alkaline reagent is alkali metal hydroxide.

9. The process of claim 1 wherein said α -amino carboxylic acid amide is glycine amide.

10. The process of claim 2 wherein said α -amino carboxylic acid amide is glycine amide.

11. The process of claim 5 wherein said α -amino carboxylic acid amide is glycine amide.

12. The process of claim 1 wherein said α -amino carboxylic acid amide is leucine amide.

13. The process of claim 2 wherein said α -amino carboxylic acid amide is leucine amide.

14. The process of claim 5 wherein said α -amino carboxylic acid amide is leucine amide.

15. The process of claim 1 wherein said α -amino carboxylic acid amide is cycloleucine amide.

16. The process of claim 2 wherein said α -amino carboxylic acid amide is cycloleucine amide.

17. The process of claim 5 wherein said α -amino



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carboxylic acid amide is cycloleucine amide.

18. The process of claim 1, wherein 1-6 equivalents of acid are added based upon said nitrile.

~~19. The process of claim 1, wherein one equivalent of~~
~~5 water is present based upon said nitrile.~~