

Description

The invention relates to a process for the preparation of optically active amino acid amide whereby a mixture of the L-amino and D-amino acid amides in the presence of an aldehyde and a suitable solvent is converted in whole or in part, by means of an optically active carboxylic acid, into the salt of the amino acid amide and the carboxylic acid, and a portion mainly consisting of one of the diastereoisomers of that salt is separated from the reaction mixture obtained.

Such a process - an asymmetric transformation, as described for instance in 'Enantiomers, Racemates and Resolutions', Jean Jacques, André Collet, Samuel H. Wilen; John Wiley & Sons, New York (1981), pp. 369 ff.- is known from US-A-4072698, in which a process is described whereby optically pure nitriles, amides or Schiff bases of nitriles or amides are prepared with an optically active acid in the presence of a ketone or an aldehyde. That publication is notably aimed at the preparation of optically pure nitriles, in particular 2-amino-2- (optionally p-substituted) phenyl acetone nitrile, using optically pure tartaric acid and a ketone.

The yield of salt of nitrile and tartaric acid in the examples described in said patent specification is relatively low, however, i.e. not higher than 85%. In respect of amino acid amides and Schiff bases, no experimental data are mentioned, nor are claims made for processes with such compounds as starting material.

The invention now aims to provide a process with which optically active amino acid amide is obtained with a high yield.

According to the invention this is achieved due to the addition of water to the reaction mixture and the quantity of aldehyde amounting to 0.5-4 equivalents relative to the quantity of amino acid amide, whereby the temperature during the conversion is between 70 and 120°C.

For it has appeared that also if an amino acid amide and an aldehyde are started from, poor efficiency rates are obtained if no water is added to the reaction mixture. Although the invention is not bound to any theoretical explanation, it seems that due to the presence of water, fewer side reactions occur, so that the losses are lower. The efficiency achieved for instance if no water is added to the reaction mixture, starting from p-hydroxyphenylglycine amide and benzaldehyde, is only 81.3%, while if 1 equivalent of water is added to the reaction mixture, an efficiency of 92.5% is obtained. Starting from phenylglycine amide and benzaldehyde, the efficiency achieved is 87.7% and 96.0%, respectively. This is surprising because it is to be expected a priori that the presence of water will have a negative effect on the efficiency, since the asymmetric transformation proceeds via the Schiff base, the formation of which is inhibited by the presence of water. After all, it is to be expected that the presence of water has a negative effect on the establishment of equilibrium in the formation of the Schiff base. Moreover, water enhances the solubility of the diastereoisomeric salt, which is recovered in solid form, which implies that a lower yield should be expected. An additional negative aspect of the addition of water is that in many cases a two-phase system is formed, which is difficult to filter and wash.

Aldehydes that can be used in the process according to the invention are for instance aromatic aldehydes, such as benzaldehyde, anisaldehyde, o-, p-, or m-nitrobenzaldehyde, o-, p- or m-chlorobenzaldehyde or aliphatic aldehydes, such as isobutyraldehyde or isovaleraldehyde. The quantity of aldehyde to be added is 0.5-4.0 equivalents relative to the quantity of amino acid amide, preferably 1-2 equivalents.

Instead of a mixture of L-amino and D-amino acid amides and an aldehyde, the starting material can also be a mixture of the Schiff bases (formed from aldehydes) of L-amino and D-amino acid amides. In that case it is not strictly necessary to add an extra quantity of aldehyde. In order to obtain an optimum yield of the diastereoisomeric salt of optically active amino acid amide and optically active carboxylic acid, at least an equimolar quantity of water relative to the quantity of Schiff base should be added. Application of less than an equimolar quantity of water results in a virtually proportional decrease in the yield. For instance, an efficiency of 99.0% is achieved when using 1.1 equivalents of water in the asymmetric transformation of the Schiff base of phenylglycine amide and benzaldehyde with optically active mandelic acid, against 45.7% when no water is added.

Since the addition of large quantities of water will in many cases lead to large quantities of dissolved diastereoisomeric salt and thus to a decrease in the quantity of diastereoisomeric salt that can be recovered in solid form, the quantity of water added in practice will be not be too great, for instance less than 20 equivalents of water relative to the quantity of amino acid amide or the Schiff base thereof. The optimum quantity of water to be used varies with the amino acid amide chosen and can be easily determined by a skilled person. In most cases the quantity of water will be between 0.1 and 4 equivalents relative to amino acid amide or the Schiff base thereof, preferably between 0.5 and 3 equivalents.

It is of no importance whether the water is added at the beginning of the reaction or in the course of the conversion process. The water can be added in any desired manner, for instance as diluent of the reactants or the solvent. Preferably, a sufficient quantity of water is added previously.

From US-A-4093653 a process is known for the preparation of optically active phenylglycine amide where-

by a mixture of L- and D-phenylglycine amide is treated with an optically active acid in the presence of ketones. The yield in this process is lower and the required reaction time longer than in the present invention.

In FR-A-2173231 the resolution of amino acid esters with an optically active acid in the presence of an aldehyde or ketone is described.

Mixtures of D,L-amino acid amides can be obtained in a manner known per se, for instance by reacting the corresponding ester with ammonia.

In the process according to the invention, optically active carboxylic acids are used. In general, the acid strength (pKa) will be 3 to 5. The quantity of optically active carboxylic acid used can be varied within wide limits and will in general be between 0.9 and 1.2 equivalents of carboxylic acid relative to amino acid amide. Preferably, an equivalent quantity of carboxylic acid is used.

An appropriate choice of the optically active carboxylic acid is determined by, among other things, the specific amino acid amide. In particular, the melting point of the diastereoisomeric salts should be sufficiently high, in order to enable separation to be effected by means of crystallization. In addition, there should be sufficient difference in solubility between the diastereoisomeric salts in the practically relevant solvents. For a technically/economically advantageous solution, the crystal form may also play a role, in connection with ease of filtration and purification by means of a washing liquid. For phenylglycine amide and p-hydroxyphenylglycine amide, for instance, good results are obtained with mandelic acid and 2-pyrrolidone-5-carboxylic acid. Moreover, these optically active carboxylic acids can be easily and almost quantitatively recovered through extraction by means of, for instance, methyl-t-butyl ether, methylisobutyl ketone, ethyl acetate, butyl acetate, amyl alcohol or by means of ion exchangers. The use of optically active mandelic acid gives the best results as regards the recoverability of the acid and the crystal form obtained.

The invention also relates to the new intermediate, diastereoisomeric LD and DL salts of L-, resp. D-mandelic acid and D resp. L phenylglycine amide or p-hydroxyphenylglycine amide, the DD and LL-salts of D-resp. L-methionine amide and D- resp. L-2-pyrrolidone-5-carboxylic acid, and the LD and DL-salts of L- resp. D-homophenylalanine amide and D- resp. L-Z-aspartic acid.

Suitable solvents for the asymmetric transformation are for instance hydrocarbons, such as cyclohexane, heptane and octane, aromatic hydrocarbons, such as toluene, xylene and benzene, ethers, such as methyl tertiary butyl ether, dioxane, tetrahydrofuran and anisole, esters, such as butyl acetate and ethyl acetate, ketones, such as acetone, butanone, methyl isobutyl ketone, carboxylic acids, aldehydes or mixtures of these substances. It will be clear that a solvent should be chosen which does not enter into irreversible chemical reactions with the amino acid amide, the optically active carboxylic acid or the aldehyde.

The pressure at which the process according to the invention is carried out is not critical and is for instance 0.01-1 MPa. The process is preferably carried out at atmospheric pressure. The temperature can be varied within wide limits and is in general 70-120°C, preferably 75-100°C. The reaction time is mostly 1-8 hours, preferably 1-4 hours.

The slurry concentration of the diastereoisomeric salts is about 5-30 wt.%, preferably 10-20 wt.%.

The optically active amino acid amide can be obtained from the separated diastereoisomeric salt by dissolving the salt in a mixture of water and a virtually equimolar quantity of mineral acid, such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid, and extracting the optically active carboxylic acid by means of an extraction agent. Suitable extraction agents are for instance ethers, alcohols, ketones or esters, such as methyl tertiary butyl ether, methyl isobutyl ketone, ethyl acetate, butyl acetate or amyl alcohol.

The optically active amino acid amide obtained can be converted into the corresponding amino acid in a known manner by hydrolysis with an excess of diluted mineral acids, such as hydrochloric acid, sulphuric acid, nitric acid or phosphoric acid. The hydrolysis is preferably carried out at 60-100°C, in particular at 85-95°C.

It is usual for the diastereoisomeric salt to be separated from the reaction mixture before the hydrolysis and further processing. Good results are also obtained, however, if the hydrolysis is carried out before filtering off the diastereoisomeric salt.

The invention will now be elucidated by means of the examples, without being restricted thereto. Each experiment is carried out in a nitrogen atmosphere.

The analysis method used is thin-layer chromatography (TLC), with: Merck 60 F 254 silicagel being used as carrier;

UV (short wave) and ninhydrine being used as detection methods.

The three TLC eluents and the proportions by volume in which they are used are:

A CHCl_3 - CH_3OH - NH_4OH (25 wt.%)
 60 45 20

B sec. butanol - formic acid - water
 75 15 10

C n-butanol - acetic acid - ethyl acetate - water
 1 1 1 1

The selectivity (enantiomeric purity) is defined as follows:

$$\text{selectivity} = 50 \% + \frac{50 \times [\alpha]_{\text{D}}^{20}}{\text{max. } [\alpha]_{\text{D}}^{20}} \%$$

The maximum specific rotations of a number of amino acid amides and/or their salts are given in Greenstein and Winitz, vol. 2, pp. 1196-2000, as well as in Beilstein 14 III, p. 1189.

The maximum specific rotations of some amino acid amides and/or their salts are also described in US-A-4 847 412:

D-phenylglycine amide.HCl: -100.8° ($c = 0.8$; water)

D-methionine amide.HCl: -18.2° ($c = 1.0$; water)

D-homophenylalanine amide. $1/2 \text{ H}_2\text{SO}_4$: -15.7° ($c = 1.0$; water)

L-phenylalanine amide. $1/2 \text{ H}_2\text{SO}_4$: $+17.8^\circ$ ($c = 1.0$; water)

From the applicant's own observations the maximum specific rotation of D-p-hydroxyphenylglycine amide is known: -121.5° ($c = 1.0$; 1.0 N acetic acid).

Comparative experiment A

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 23.8 g (0.10 mole) D,L-N-benzylidene phenylglycine amide, 15.2 g (0.10 mole) L-mandelic acid and 200 ml toluene are stirred for 2.5 hours at a temperature of 86°C .

After cooling to 30°C (1/4 hour) the salt of D-phenylglycine amide and L-mandelic acid (DL salt) is filtered and washed on the glass filter with 4 x 25 ml toluene. The yield of diastereoisomeric DL salt after drying amounts to 13.8 g, which corresponds to an efficiency of 45.7%.

1.0 g of the diastereoisomeric DL salt thus obtained is suspended in 10 ml water, to which subsequently 10 ml 12 N hydrochloric acid is added with stirring. After filtration and washing with 4 x 10 ml acetone on the glass filter of the D-phenylglycine amide.HCl crystals formed, the specific rotation of the D-phenylglycine amide.HCl salt obtained (yield = 0.55; efficiency = 88.7%):

$[\alpha]_{\text{D}}^{20} = -99.5^\circ$ ($c = 0.8$; water).

According to the literature (Beilstein, 14 III, p. 1189) the specific rotation of D-phenylglycine amide.HCl is:

$[\alpha]_{\text{D}}^{20} = -100.8^\circ$ ($c = 0.8$; water).

Example I

The procedure described in comparative experiment A is repeated, on the understanding that 2.0 g (0.11 mole) water is added to the mixture of D,L-N-benzylidene phenylglycine amide and L-mandelic acid.

Results:

Yield of diastereoisomeric DL salt: 29.9 g (efficiency = 99.0%).

Yield of D-phenylglycine amide.HCl: 0.55 g (efficiency = 88.7%).

Specific rotation:

$[\alpha]_{\text{D}}^{20} = -101.3^\circ$ ($c = 0.8$; water).

Comparative experiment B

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 23.8 g (0.10 mole) D,L-N-

benzylidene phenylglycine amide, 12.9 g (0.10 mole) L-2-pyrrolidone-5-carboxylic acid, 235 ml toluene and 15 ml (0.15 mole) benzaldehyde are stirred for 2.5 hours at a temperature of 84°C.

After cooling to 25°C (1/6 hour), the resulting diastereoisomeric salt of L-phenylglycine amide and L-2-pyrrolidone-5-carboxylic acid (LL salt) is filtered and washed on the glass filter with 4 x 25 ml toluene. The yield of filtered product after drying amounts to 12.8 g.

According to a thin-layer chromatographic analysis, the product obtained contains more than an equivalent quantity of L-2-pyrrolidone-5-carboxylic acid. 2.0 g of the diastereoisomeric LL salt is dissolved in 10 ml water, to which subsequently 10 ml 12 N hydrochloric acid is added. After filtration and washing on the glass filter of the resulting L-phenylglycine amide.HCl crystals with 4 x 10 ml acetone, the specific rotation of the L-phenylglycine amide.HCl obtained (yield = 0.1 g; overall efficiency = 7.5%) is:

$[\alpha]^{20}_D = +102.5^\circ$ (c = 0.8; water).

Literature value of L-phenylglycine amide.HCl (Beilstein, 14 III. p. 1189):

$[\alpha]^{20}_D = +100.8^\circ$ (c = 0.8; water).

Example II

Procedure as described in comparative experiment B, on the understanding that stirring takes place for 2.5 hours at 84°C in the presence of 2.7 g (0.15 mole) water.

Results:

Yield of diastereoisomeric LL salt: 25.4 g (efficiency = 91.0%).

Specific rotation of L-phenylglycine amide.HCl (yield = 1.2 g; efficiency = 89.8%):

$[\alpha]^{20}_D = +99.8^\circ$ (c = 0.8; water).

Example III

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 15.0 g (0.10 mole) D,L-phenylglycine amide, 15.2 g (0.10 mole) D-mandelic acid, 230 ml toluene, 20 ml benzaldehyde and 1.8 g (0.10 mole) water are stirred for 2 hours at a temperature of 88°C.

After cooling to 20°C (0.5 hour) the resulting diastereoisomeric salt of L-phenylglycine amide and D-mandelic acid (LD salt) is filtered and washed on the glass filter with 4 x 25 ml toluene. The yield of TLC pure LD salt after drying amounts to 29.3 g, which corresponds to an efficiency of 97.0%.

The specific rotation of the optically pure LD salt (recrystallization) amounts to:

$[\alpha]^{20}_D = +4.0^\circ$ (c = 1.0; water).

1.0 g of the diastereoisomeric LD salt obtained is suspended in 10 ml water, to which subsequently 10 ml 12 N hydrochloric acid is added with stirring. After filtration and washing with 4 x 10 ml acetone on the glass filter of the L-phenylglycine amide.HCl crystal mass obtained, the specific rotation of the TLC pure L-phenylglycine amide.HCl salt obtained (yield = 0.55 g; efficiency = 88.7%) is:

$[\alpha]^{20}_D = +101.7^\circ$ (c = 0.8; water).

The LD salt (22.7 g = 0.075 mole) is dissolved at 50°C in a mixture of 40 ml water and 2.7 ml 96 wt.% sulphuric acid (0.05 mole) and, after extraction with 5 x 50 ml methyl-b-butyl ether (removal of D-mandelic acid), hydrolyzed to L-phenylglycine at a temperature of 90°C by means of 10 ml 96 wt.% sulphuric acid (0.18 mole) with stirring for 3 hours. After neutralization of the sulphuric L-phenylglycine hydrolizate by means of 28 ml 25 wt.% ammonia to an acidity of pH=5 and cooling to 30°C, the L-phenylglycine thus obtained is filtered and then washed on the glass filter with 5 x 10 ml water.

The yield of L-phenylglycine after drying amounts to 10.5 g, which corresponds to an efficiency of 92.9%.

The specific rotation of the TLC pure L-phenylglycine is:

$[\alpha]^{20}_D = +157.7^\circ$ (c = 1.6; 2.6 wt.% hydrochloric acid).

Literature value of specific rotation of L-phenylglycine (Beilstein 14 III. p. 1188):

$[\alpha]^{20}_D = +157.5^\circ$ (c = 1.6; 2.6 wt.% hydrochloric acid).

Example IV

Procedure as described in example III, but with use of L-mandelic acid instead of D-mandelic acid.

Results:

Specific rotation and yield values:

Optically pure DL salt (recrystallization):

$[\alpha]^{20}_D = -4.1^\circ$ (c = 1.0; water); 29.0 g (efficiency = 96.3%)

TLC pure D-phenylglycine amide.HCl:

$[\alpha]^{20}_D = -101.9^\circ$ ($c = 0.8$; water); 0.55 g (efficiency = 88.7%)

TLC pure D-phenylglycine:

$[\alpha]^{20}_D = -157.4^\circ$ ($c = 1.6$; 2.6 wt.% hydrochloric acid); 10.4 g (efficiency = 92.0%).

Example V

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, a suspension of 30.0 g (0.20 mole) D,L-phenylglycine amide, 32.0 g (0.21 mole) L-mandelic acid, 400 ml toluene, 40 ml benzaldehyde and 5.4 g (0.30 mole) water is stirred for 2 hours at a temperature of 85°C. After cooling to 60°C the suspension is poured into a mixture of 120 ml water and 8.0 ml 96 wt.% sulphuric acid (0.144 mole). After separation of the organic phase at 50°C the acid aqueous phase is extracted at this temperature with 4 x 60 ml ethyl acetate (removal of L-mandelic acid).

After addition of 30 ml 96 wt.% sulphuric acid (0.54 mole) the sulphuric D-phenylglycine amide solution is hydrolyzed to D-phenylglycine with stirring for 4 hours at 85°C.

The yield of D-phenylglycine after, successively, neutralization to pH = 4 by means of 85 ml 25 wt.% ammonia, cooling to 20°C, filtration, washing on the glass filter with 5 x 30 ml water and drying, amounts to 27.2 g, which corresponds to an efficiency of 90.0%.

The specific rotation of the TLC pure D-phenylglycine is:

$[\alpha]^{20}_D = -153.4^\circ$ ($c = 1.6$; 2.6 wt.% hydrochloric acid)

Examples VI-XI

D,L-phenylglycine amide is contacted with 1 equivalent optically active D-mandelic acid and the TLC pure L-phenylglycine amide.HCl salt, recovered as in example III, the quantities of aldehyde and water added being varied. The results are given in table 1, which also shows the temperature (T) in °C and the retention time (t).

Comparative experiment C

A procedure analogous to example III is carried out up to the recovery of the TLC pure L-phenylglycine amide.HCl salt, but without addition of water, which results in a lower yield. The results and specific conditions are given in table 1.

Comparative experiment D

A procedure analogous to example III is carried out up to the recovery of the TLC pure L-phenylglycine amide.HCl salt, but with only 0.1 equivalent benzaldehyde, which results in a very low selectivity. The results and specific conditions are given in table 1.

Table 1 example	solvent	aldehyde (eq.)	water (eq.)	slurry concentr.	T	t	efficiency	selectivity*
VI	methylisobutyl ketone	1.0 BA	2.0	15%	85°C	3 h	90.1%	99.8%
VII	cyclohexane	2.0 BA	2.0	11%	77°C	3 h	96.0%	99.8%
VIII	butyl acetate	1.0 BA	1.5	12%	85°C	2 h	91.0%	99.4%
IX	ethyl acetate/ toluene: 1/3	2.0 BA	1.5	12%	86°C	2 h	96.0%	99.3%
X	ethyl acetate/ toluene: 1/3	1.5 AA	1.0	14%	84°C	3.5h	96.7%	99.8%
XI	ethyl acetate/ toluene: 1/4	2.0 IBA	1.0	11%	80°C	3 h	92.4%	99.8%
C	ethyl acetate: 1/3 toluene	2.0 BA	0	12%	86°C	3.5h	87.7%	99.8%
D	methylisobutyl ketone	0.1 BA	1.0	15%	70°C	2.5h	93.7%	50.5%

Abbreviations: AA = anisaldehyde

BA = benzaldehyde

IBA = isobutyraldehyde

* = optical purity of phenylglycine amide.HCl

Example XII

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 8.3 g (0.05 mole) D,L-p-hydroxyphenylglycine amide, 7.6 g (0.05 mole) L-mandelic acid, 150 ml toluene, 50 ml ethyl acetate, 6.0 ml (0.06 mole) benzaldehyde and 2.0 g (0.11 mole) water are stirred for 2.5 hours at a temperature of 85°C.

After cooling to 30°C (3/4 hour) the resulting diastereoisomeric salt of D-p-hydroxyphenylglycine amide and L-mandelic acid (DL salt) is filtered and washed on the glass filter with 5 x 20 ml ethyl acetate. The yield of TLC pure DL salt amounts to 14.5 g, which corresponds to an efficiency of 91.2%. The specific rotation of the optically pure DL salt, after recrystallization from water, is:

$[\alpha]^{20}_D = -8.1^\circ$ ($c = 1.0$; water)

1.6 g of the DL salt is dissolved in 20 ml water at 50°C , after which with stirring 1 ml 25 wt.% ammonia is added. After cooling to 20°C , filtration and washing of the resulting D-p-hydroxyphenylglycine amide crystals with, successively, 3 x 10 ml water and 3 x 10 ml methanol, the specific rotation of the TLC pure D-p-hydroxyphenylglycine amide (yield = 0.8 g; efficiency = 95.8%):

$[\alpha]^{20}_D = -121^\circ$ ($c = 1.0$; 1.0 N acetic acid)

The percentage of D-enantiomer is 99.8%.

Example XIII

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 33.2 g (0.20 mole) D,L-p-hydroxyphenylglycine amide, 30.5 g (0.20 mole) D-mandelic acid, 800 ml toluene, 200 ml ethyl acetate, 24 ml (0.24 mole) benzaldehyde and 8.0 g (0.44 mole) water are stirred for 2.5 hours at a temperature of 84°C .

After cooling to 25°C (1 hour) the resulting diastereoisomeric salt of L-p-hydroxyphenylglycine amide and D-mandelic acid (LD salt) is filtered and washed on the glass filter with 5 x 50 ml ethyl acetate. The yield of TLC pure Lb salt amounts to 57.8 g, which corresponds to an efficiency of 90.9%.

The specific rotation of the optically pure LD salt (recrystallization from water) is:

$[\alpha]^{20}_D = +8.0^\circ$ ($c = 1.0$; water)

50.9 g (0.16 mole) of the LD salt is dissolved at 50°C in 500 ml water, after which with stirring 25 ml (0.19 mole) 25 wt.% ammonia is added. After cooling to 30°C the L-p-hydroxyphenylglycine amide crystals obtained are filtered and washed on the glass filter with 5 x 25 ml water. The yield of pure L-p-hydroxyphenylglycine amide after drying amounts to 25.1 g, corresponding to an efficiency of 94.3%.

The specific rotation of the L-p-hydroxyphenylglycine amide thus obtained is:

$[\alpha]^{20}_D = +120.4^\circ$ ($c = 1.0$; 1.0 N acetic acid)

The L-p-hydroxyphenylglycine amide (24.9 g = 0.15 mole) is hydrolyzed to L-p-hydroxyphenylglycine with 33.3 ml 96 wt.% sulphuric acid (0.6 mole) in 57 ml water (3 hours; 90°C). After neutralization to $\text{pH} = 4$ by means of 90 ml 25 wt.% ammonia, the p-hydroxyphenylglycine is filtered at 20°C and washed on the glass filter with 3 x 20 ml water. The yield of TLC pure L-p-hydroxyphenylglycine after drying amounts to 21.6 g, corresponding to an efficiency of 86.2%.

The specific rotation of the L-p-hydroxyphenylglycine is:

$[\alpha]^{20}_D = +157.7^\circ$ ($c = 1.0$; 1.0 N hydrochloric acid).

Examples XIV-XVIII

In the same manner as in example XII, an asymmetric transformation of D,L-p-hydroxyphenylglycine amide is carried out with 1 equivalent D-mandelic acid. The results are given in table 2.

Table 2

example	solvent	aldehyde (eq.)	water (eq.)	slurry concentr.	T	t	efficiency	selectivity*
XIV	toluene/ethyl acetate = 3/1	0.5 BA	2.0	13%	85°C	2.5h	94.3%	78.8%
XV	toluene/ethyl acetate = 3/1	1.2 BA	2.2	8%	86°C	1.5h	91.1%	91.6%
XVI	toluene/tetra- hydrofuran = 2/1	1.2 BA	1.7	10%	80°C	5h	90.5%	99.2%
XVII	toluene/ dioxane = 2/1	1.0 BA	1.6	20%	90°C	4h	93.1%	98.5%
XVIII	toluene/ dioxane = 5/1	2.0 CBA	1.0	10%	86°C	2.5h	99.8%	

Abbreviations: BA = benzaldehyde

CBA = o-chlorobenzaldehyde

* = optical purity of p-hydroxyphenylglycine amide

Examples XIX and XX and comparative experiments E and F

In the same manner as in example XII, an asymmetric transformation of D,L-p-hydroxyphenylglycine amide is carried out with 1 equivalent L-mandelic acid, the quantities of water and benzaldehyde being varied. The results are given in table 3.

Owing to the absence of water or aldehyde, the yield is considerably lower.

Table 3 example	solvent	BA (eq.)	water (eq.)	slurry concentr.	T	t	efficiency
E	toluene/methyl tert.- butyl ether = 4/1	1.1	0	12%	84°C	3.5h	81.3%
XIX	toluene/methyl tert.- butyl ether = 4/1	1.1	1.1	12%	84°C	3.5h	92.5%
F	toluene/ethyl acetate = 4/1	0	1.1	6%	85°C	2h	81.8%
XX	toluene/ethyl acetate = 4/1	1.2	2.2	6%	85°C	2h	91.2%

abbreviation: BA = benzaldehyde

Example XXI

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 23.7 g (0.10 mole) D,L-N-benzylidene methionine amide (SB of methionine amide and benzaldehyde), 12.9 g (0.10 mole) L-2-pyrrolidone-5-carboxylic acid, 200 ml ethyl acetate and 2.7 ml (0.15 mole) water are stirred for 2.5 hours at a temperature of 75°C. After cooling to 20°C (0.5 hour) the resulting salt of L-methionine amide and L-2-pyrrolidone-5-carboxylic acid (LL salt) is filtered and washed on the glass filter with 4 x 25 ml ethyl acetate. The yield of TLC pure LL salt amounts to 21.2 g, which corresponds to an efficiency of 73.6%. 2.8 g (0.01 mole) of the LL salt is dissolved in a mixture of 3 ml water and 2 ml 12 N hydrochloric acid. After addition of 60 ml acetone to this solution, the L-methionine amide.HCl salt is isolated through filtration.

The specific rotation of the TLC pure L-methionine amide.HCl salt is:

$[\alpha]_D^{20} = +17.9^\circ$ (c = 1.0; water)

Selectivity: 99.2% L enantiomer

Example XXII

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 10.7 g (0.04 mole) D,L-benzylidene homophenylalanine amide, 10.7 g (0.04 mole) L-Z-aspartic acid (L-N-(carbobenzoxycarboxyl)aspartic acid) 110 ml MIBK and 1.5 g (0.08 mole) water are stirred for 5 hours at a temperature of 80°C. The resulting salt of D-homo-phenylalanine amide and L-Z-aspartic acid (DL-salt) is filtered and washed on the glass filter with 2 x 25 ml MIBK. The yield of TLC pure DL-salt amounts 9.46 g, which corresponds with a efficiency of 53%. 5 g (0.01 mole) of the DL-salt is splitted in a mixture of 100 ml water and 3.7 ml 6 N hydrochloric acid, in D-homophenylalanine amide.HCl salt L-Z-aspartic acid, which is extracted with ethylacetate. The D-homophenylalanine amide.HCl present in the water layer is hydrolysed with 6 N hydrochloric acid at 80°C into D-homophenylalanine. After neutralisation and filtration in order to remove the salts present, and after drying a specific rotation of the TLC pure D-homophenylalanine is measured.

$[\alpha]_D^{20} = -29.2^\circ$ (c = 1; 1N HCl)

$[\alpha]_D^{20} = -46.3^\circ$

Selectivity: 81.5% D enantiomer

Claims

1. Process for the preparation of optically active amino acid amide whereby a mixture of the L-amino and D-amino acid amides in a suitable solvent in the presence of an aldehyde is converted in whole or in part, by means of an optically active carboxylic acid, into the salt of the amino acid amide and the carboxylic acid, and a portion mainly consisting of one of the diastereoisomers of that salt is separated from the reaction mixture obtained, characterized in that water is added to the reaction mixture and that the quantity of aldehyde amounts to 0.5-4 equivalents relative to the quantity of amino acid amide, and that the temperature during the conversion is between 70 and 120°C.
2. Process according to claim 1, with the quantity of water amounting to 0.5 to 3 equivalents relative to the quantity of amino acid amide.
3. Process according to claim 1 or 2, characterized in that the quantity of aldehyde amounts to 1-2 equivalents relative to the quantity of amino acid amide.
4. Process for the preparation of optically active amino acid amide whereby a mixture of Schiff bases (formed from aldehydes) of the corresponding L-amino and D-amino acid amides in the presence of a suitable solvent is converted in whole or in part, by means of an optically active carboxylic acid, into the salt of the amino acid amide and the carboxylic acid, and a portion mainly consisting of one of the diastereoisomers of that salt is separated from the reaction mixture obtained, characterized in that in the conversion at least 1 equivalent of water is added relative to the quantity of Schiff base.
5. Process according to any one of the claims 1-4, with the quantity of water being added at the beginning of the reaction.
6. Process according to any one of the claims 1-5, with the amino acid amide being phenylglycine amide.
7. Process according to any one of the claims 1-5, with the amino acid amide being p-hydroxyphenylglycine amide.
8. Process according to any one of the claims 1-5, with the amino acid amide being methionine amide.
9. Process according to any one of the claims 1-8, with L- or D-mandelic acid being used as optically active carboxylic acid.
10. Process according to any one of the claims 1-8, with 2-pyrrolidone-5-carboxylic acid being used as optically active carboxylic acid.
11. Process according to any one of the claims 1-10, characterized in that the carboxylic acid is used in virtually equimolar quantities relative to the amino acid amide or the corresponding Schiff base.

**Example XXII**

In a reaction flask provided with a stirrer, a thermometer and a reflux cooler, 10.7 g (0.04 mole) D,L-benzylidene homophenylalanine amide, 10.7 g (0.04 mole) L-Z-aspartic acid (L-N-(carbobenzoxy)aspartic acid) 110 ml MIBK and 1.5 g (0.08 mole) water are stirred for 5 hours at a temperature of 80°C. The resulting salt of D-homo-phenylalanine amide and L-Z-aspartic acid (DL-salt) is filtered and washed on the glass filter with 2 x 25 ml MIBK. The yield of TLC pure DL-salt amounts 9.46 g, which corresponds with a efficiency of 53%. 5 g (0.01 mole) of the DL-salt is splitted in a mixture of 100 ml water and 3.7 ml 6 N hydrochloric acid, in D-homophenylalanine amide.HCl salt L-Z-aspartic acid, which is extracted with ethylacetate. The D-homophenylalanine amide.HCl present in the water layer is hydrolised with 6 N hydrochloric acid at 80°C into D-homophenylalanine. After neutralisation and filtration in order to remove the salts present, and after drying a specific rotation of the TLC pure D-homophenylalanine is measured.

$[\alpha]_D^{20} = -29.2^\circ$ (c = 1; 1N HCl)

$[\alpha]_D^{20} = -46.3^\circ$

Selectivity: 81.5% D enantiomer

Claims

1. Process for the preparation of optically active amino acid amide whereby a mixture of the L-amino and D-amino acid amides in a suitable solvent in the presence of an aldehyde is converted in whole or in part, by means of an optically active carboxylic acid, into the salt of the amino acid amide and the carboxylic acid, and a portion mainly consisting of one of the diastereoisomers of that salt is separated from the reaction mixture obtained, characterized in that water is added to the reaction mixture and that the quantity of aldehyde amounts to 0.5-4 equivalents relative to the quantity of amino acid amide, and that the temperature during the conversion is between 70 and 120°C.
2. Process according to claim 1, with the quantity of water amounting to 0.5 to 3 equivalents relative to the quantity of amino acid amide.
3. Process according to claim 1 or 2, characterized in that the quantity of aldehyde amounts to 1-2 equivalents relative to the quantity of amino acid amide.
4. Process for the preparation of optically active amino acid amide whereby a mixture of Schiff bases (formed from aldehydes) of the corresponding L-amino and D-amino acid amides in the presence of a suitable solvent is converted in whole or in part, by means of an optically active carboxylic acid, into the salt of the amino acid amide and the carboxylic acid, and a portion mainly consisting of one of the diastereoisomers of that salt is separated from the reaction mixture obtained, characterized in that in the conversion at least 1 equivalent of water is added relative to the quantity of Schiff base.
5. Process according to any one of the claims 1-4, with the quantity of water being added at the beginning of the reaction.
6. Process according to any one of the claims 1-5, with the amino acid amide being phenylglycine amide.
7. Process according to any one of the claims 1-5, with the amino acid amide being p-hydroxyphenylglycine amide.
8. Process according to any one of the claims 1-5, with the amino acid amide being methionine amide.
9. Process according to any one of the claims 1-8, with L- or D-mandelic acid being used as optically active carboxylic acid.
10. Process according to any one of the claims 1-8, with 2-pyrrolidone-5-carboxylic acid being used as optically active carboxylic acid.
11. Process according to any one of the claims 1-10, characterized in that the carboxylic acid is used in virtually equimolar quantities relative to the amino acid amide or the corresponding Schiff base.



12. Process according to any one of the claims 1-11, characterized in that the conversion takes place at a temperature between 75 and 100°C.
13. LD or DL salt of phenylglycine amide and mandelic acid.
14. LD or DL salt of p-hydroxyphenylglycine amide and mandelic acid.
15. LL or DD salt of methionine amide and 2-pyrrolidone-5-carboxylic acid.
16. LD or DL salt of homophenylalanine amide and L-Z-aspartic acid.
17. Process for the preparation of optically active amino acids in which the salt of an amino acid amide and an optically active carboxylic acid, obtained by the process according to any one of the claims 1-12, is treated with a mineral acid before separation from the reaction mixture.
18. Use of amino acid amides obtained according to any one of the claims 1-12 in the preparation of amino acids.

Patentansprüche

- Verfahren zur Herstellung von optisch aktivem Aminosäureamid, wobei eine Mischung der L-Amino- und D-Aminosäureamide in einem geeigneten Lösungsmittel in Anwesenheit eines Aldehyds zur Gänze oder zum Teil mittels einer optisch aktiven Carbonsäure in das Salz des Aminosäureamids und der Carbonsäure übergeführt und ein hauptsächlich aus einem der Diastereoisomere bestehender Teil dieses Salzes von der erhaltenen Reaktionsmischung abgetrennt wird, dadurch gekennzeichnet, daß Wasser zu der Reaktionsmischung zugesetzt wird und die Menge des Aldehyds bezogen auf die Menge des Aminosäureamids 0,5 bis 4 Äquivalente beträgt und daß die Temperatur während der Reaktion 70 bis 120°C ist.
- Verfahren nach Anspruch 1, wobei die Wassermenge 0,5 bis 3 Äquivalente bezogen auf die Menge des Aminosäureamids beträgt.
- Verfahren nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Aldehydmenge 1 bis 2 Äquivalente bezogen auf die Menge des Aminosäureamids beträgt.
- Verfahren zur Herstellung von optisch aktivem Aminosäureamid, wobei eine Mischung von Schiff'schen Basen (aus Aldehyden gebildet) der entsprechenden L-Amino- und D-Aminosäureamide in Anwesenheit eines geeigneten Lösungsmittels zur Gänze oder zum Teil mittels einer optisch aktiven Carbonsäure in das Salz des Aminosäureamids und der Carbonsäure übergeführt und ein hauptsächlich aus einem der Diastereoisomere bestehender Teil dieses Salzes von der erhaltenen Reaktionsmischung abgetrennt wird, dadurch gekennzeichnet, daß bei der Überführung mindestens 1 Äquivalent Wasser bezogen auf die Menge der Schiff'schen Base zugesetzt wird.
- Verfahren nach einem der Ansprüche 1 bis 4, wobei die Wassermenge am Beginn der Reaktion zugesetzt wird.
- Verfahren nach einem der Ansprüche 1 bis 5, wobei das Aminosäureamid Phenylglycinamid ist.
- Verfahren nach einem der Ansprüche 1 bis 5, wobei das Aminosäureamid p-Hydroxyphenylglycinamid ist.
- Verfahren nach einem der Ansprüche 1 bis 5, wobei das Aminosäureamid Methioninamid ist.
- Verfahren nach einem der Ansprüche 1 bis 8, wobei L- oder D-Mandelsäure als optisch aktive Carbonsäure verwendet wird.
- Verfahren nach einem der Ansprüche 1 bis 8, wobei 2-Pyrrolidon-5-carbonsäure als optisch aktive Carbonsäure verwendet wird.
- Verfahren nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß die Carbonsäure in faktisch äquimolaren Mengen bezogen auf das Aminosäureamid oder die entsprechende Schiff'sche Base ver-



wendet wird.

12. Verfahren nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß die Reaktion bei einer Temperatur von 75 bis 100°C stattfindet.
13. LD- oder DL-Salz von Phenylglycinamid und Mandelsäure.
14. LD- oder DL-Salz von p-Hydroxyphenylglycinamid und Mandelsäure.
15. LL- oder DD-Salz von Methioninamid und 2-Pyrrolidon-5-carbonsäure.
16. LD- oder DL-Salz von Homophenylalaninamid und L-Z-Asparaginsäure.
17. Verfahren zur Herstellung von optisch aktiven Aminosäuren, in dem das Salz eines Aminosäureamids und einer optisch aktiven Carbonsäure, erhalten durch das Verfahren nach einem der Ansprüche 1 bis 12, vor Abtrennung von der Reaktionsmischung mit einer Mineralsäure behandelt wird.
18. Verwendung von Aminosäureamiden, erhalten nach einem der Ansprüche 1 bis 12, bei der Herstellung von Aminosäuren.

Revendications

1. Procédé de préparation d'un amide d'acide aminé optiquement actif selon lequel on convertit en totalité ou en partie un mélange d'amides de L-amino et D-amino-acides au sein d'un solvant approprié en présence d'un aldéhyde, à l'aide d'un acide carboxylique optiquement actif, en sel d'amide d'acide aminé et d'acide carboxylique et on sépare du mélange de réaction obtenu une portion consistant principalement en l'un des diastéréoisomères de ce sel, caractérisé en ce qu'on ajoute de l'eau au mélange de réaction et en ce que la quantité d'aldéhyde représente de 0,5 à 4 équivalents par rapport à la quantité de l'amide d'acide aminé, et en ce que la température pendant la conversion est comprise entre 70 et 120°C.
2. Procédé selon la revendication 1, dans lequel la quantité d'eau représente de 0,5 à 3 équivalents par rapport à la quantité d'amide d'acide aminé.
3. Procédé selon la revendication 1 ou 2, caractérisé en ce que la quantité d'aldéhyde représente 1 à 2 équivalents par rapport à la quantité d'amide d'acide aminé.
4. Procédé de préparation d'un amide d'acide aminé optiquement actif par lequel on convertit en totalité ou en partie un mélange de bases de Schiff formé à partir des aldéhydes des amides de L-amino et D-amino-acides correspondants en présence d'un solvant convenable, à l'aide d'un acide carboxylique optiquement actif, en sel de l'amide d'acide aminé et d'acide carboxylique ; et on sépare du mélange de réaction obtenu une portion consistant principalement en l'un des diastéréoisomères de ce sel, caractérisé en ce qu'au cours de la conversion, au moins 1 équivalent d'eau est ajouté par rapport à la quantité de la base de Schiff.
5. Procédé selon l'une quelconque des revendications 1 à 4, la totalité de l'eau étant ajoutée au début de la réaction.
6. Procédé selon l'une quelconque des revendications 1 à 5, l'amide d'acide aminé étant l'amide de phénylglycine.
7. Procédé selon l'une quelconque des revendications 1 à 5, l'amide d'acide aminé étant l'amide de p-hydroxyphénylglycine.
8. Procédé selon l'une quelconque des revendications 1 à 5, l'amide d'acide aminé étant l'amide de méthionine.
9. Procédé selon l'une quelconque des revendications 1 à 8, l'acide L- ou D-mandélique étant utilisé en qualité d'acide carboxylique optiquement actif.



10. Procédé selon l'une quelconque des revendications 1 à 8, l'acide 2-pyrrolidone-5-carboxylique étant utilisé en qualité d'acide carboxylique optiquement actif.
- 5 11. Procédé selon l'une quelconque des revendications 1 à 10, caractérisé en ce qu'on utilise l'acide carboxylique en des quantités virtuellement équimolaires par rapport à l'amide d'acide aminé ou à la base de Schiff correspondante.
- 10 12. Procédé selon l'une quelconque des revendications 1 à 11, caractérisé en ce que la conversion a lieu à une température comprise entre 75 et 100°C.
13. Sel LD ou DL d'amide de phénylglycine et d'acide mandélique.
14. Sel LD ou DL de l'amide de p-hydroxyphénylglycine et d'acide mandélique.
- 15 15. Sel LL ou DD de l'amide de méthionine et d'acide 2-pyrrolidone-5-carboxylique.
16. Sel LD ou DL de l'amide d'homophénylalanine et d'acide L-Z-aspartique.
17. Procédé de préparation d'acides aminés optiquement actifs, selon lequel on traite le sel d'un amide d'acide aminé et d'un acide carboxylique optiquement actif qu'on obtient par le procédé selon l'une quelconque des revendications 1 à 12, avec un acide minéral avant de le séparer du mélange de réaction.
- 20 18. Utilisation d'amides d'acides aminés obtenus selon l'une quelconque des revendications 1 à 12 pour la préparation des acides aminés.
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