T601027-7 IPOS

The title of the invention is:

Reductive amination of an amino acid or an amino acid derivative with an alpha-keto acid or an alpha-keto acid derivative

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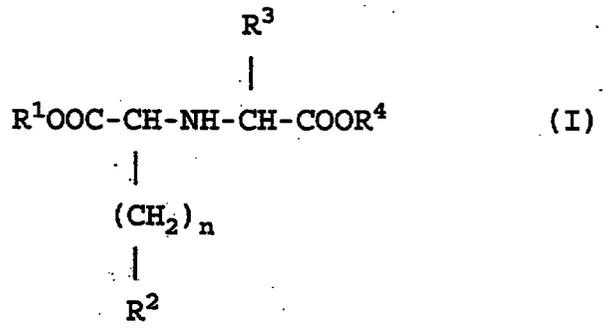
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Reductive amination of an amino acid or an amino acid derivative with an α-keto acid or an α-keto acid derivative

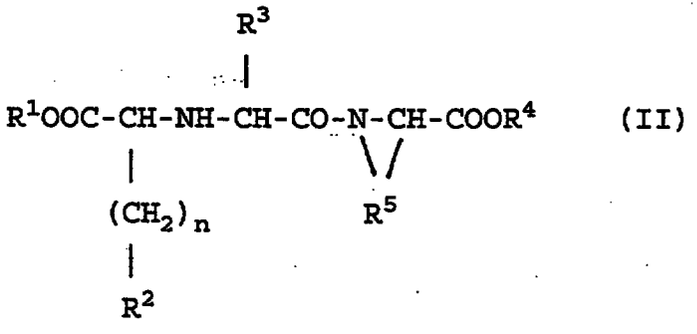
Description

The invention relates to a reductive amination of an amino acid or an amino acid derivative with an α-keto acid or an α-keto acid derivative in an inert solvent in the presence of a hydrogenation catalyst and a hydrogenating agent, and optionally with the removal of water, and in particular to a process for the preparation of compounds of the formula



(I)

or of the formula



(II)

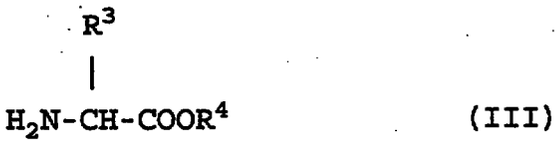
in which

R^1 is hydrogen, methyl, ethyl or benzyl,
R^2 is hydrogen, C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],

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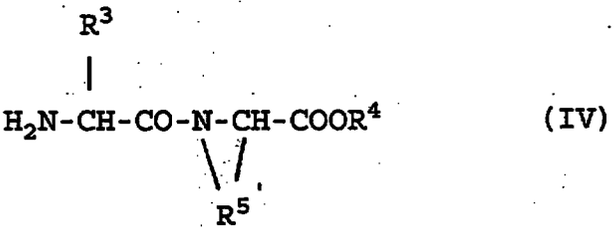
R^3 is hydrogen, heteroalkyl (*e.g.* the radical of a natural amino acid) or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert-butoxycarbonylamino-[C_1- C_5]-alkyl or benzyloxycarbonylamino-[C_1-C_5]-alkyl,
R^4 is H or an ester protecting group,
R^5 together with the atoms by which it is carried is a heterocyclic mono- or bicyclic ring system with 5 to 10 ring members, and
n is 0, 1 or 2,

by the hydrogenolytic reaction of a compound of the formula



(III)

in which R^3 and R^4 are as already defined,
for the preparation of compounds of formula (I), or of a compound of the formula



(IV)

in which R^3 to R^5 are as already defined,
for the preparation of compounds of formula (II), with a compound of the formula



(V)

in which R^1, R^2 and n are as already defined, in the presence of an inert solvent, a hydrogenation catalyst and a hydrogenating agent, and optionally with the removal of water.
In principle, "alkyl", "acyl", "aromatic" *etc.* for the

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radicals R also include corresponding radicals with typical substituents, *e.g.* 4-(trifluoroacetylamino)butyl for R^3.

N-Substituted α-amino acids (such as I) and dipeptides containing them (such as II) are valuable intermediates for the preparation of inhibitors of angiotensin converting enzyme (ACE), which are of great interest as blood pressure regulators. Some of said N-substituted dipeptides are already commercially available as drugs or are at the licensing stage, examples being enalapril (N^{α}-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline), lisinopril (N^{α}-[(S)-1-carboxy-3-phenylpropyl]-L-lysyl-L-proline) or ramipril (2-[N^{α}-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L- alanyl]-(1S,3S,5S)-2-azabicyclo[3,3,0]octane-3-carboxylic acid).

A process of this type, for the preparation of compounds of formula (II), is described in J. Org. Chem. 1988, 53, 836-844. Absolute ethanol is used as the inert solvent, a molecular sieve is used for removal of the water and Raney nickel is used as the hydrogenation catalyst. The products formed here are obtained in 42 - 80% yield according to the literature. However, these yields cannot easily be reproduced; furthermore, the products generally still contain considerable amounts of by-products, which make the purification to pharmaceutically useful products difficult.

A reductive amination of an amino acid ester with pyruvic acid is described in J. Med. Chem. 28 (1985), 1596 - 1602. The amino acid ester is used as the hydrochloride. A small amount of NaOH is dissolved in the solvent in order to free the amine from the amino acid ester hydrochloride and partially neutralize the pyruvic acid. Due to the pyruvic acid, there is an overall excess of acid in the reaction mixture.

Further reductive aminations of dipeptides with α-keto acids are known from US-PS 4,474,692, especially Examples 2, 7 - 14 and 21. The reaction mixture contains a sodium acetate/

acetic acid buffer in which the acetic acid is in approximately twofold molar excess.

The object of the invention is to modify the known process to give high yields and less by-products without introducing high additional costs. Moreover, it should be possible - if desired - to influence the reaction in respect of the formation of the diastereoisomers.

This object is achieved in the process according to the invention by carrying out the hydrogenolysis reaction in the presence of an excess of an organic or inorganic base.

Excess base is applicable when the educts used are adjusted to their isoelectric point and the system then also contains one or more compounds which, in water, reduce the hydrogen ion concentration of the water or abstract protons from water molecules, thereby forming hydroxide ions or, if the pK of the educts used (their isoelectric point) is below pH 7, raising the pH, in water, above the pK of the educts.

The pH of the system (based on the corresponding aqueous concentration) is preferably at least 5.0 and advantageously at least 6.0. Values of 6.2 and above are particularly suitable, advantageous upper values being 11 or especially 10.

Surprisingly, this addition markedly increases the chemical yield of the reaction, even though the first step of the reaction, namely the imine formation (Roberts J.D., Caserio M.C.; Basic Principles of Organic Chemistry, 2nd ed., W.A. Benjamin Inc., Philippines, 1977, pp. 697, 1154), proceeds under acid catalysis. Weak bases are particularly suitable, examples being organic bases such as mono-, di- or tri- ethanolamine, trimethylamine, triethylamine, tripropylamine, tributylamine or N-methylmorpholine.

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Examples of suitable inorganic bases are salts of weak acids, such as NaOAc, K_2CO_3, $KHCO_3$, Na_2CO_3, $NaHCO_3$ and, particularly preferably, basic aluminium oxide.

Strong bases can also support the reaction, especially in very dilute concentration. Preferably, the (theoretical) pH of the reaction system is raised only slightly above the pK of the educts by the excess base. It is conventionally increased by 0.1 to 3 pH units, preferably 0.3 to 2 pH units.

The base is conveniently added in an amount of 0.01 to 5 mol equivalents, preferably of 0.05 to 2 mol equivalents, based in each case on the compound of formula (III) or (IV) used. When organic bases are used, amounts less than the stoichiometric amounts, especially 0.08 - 0.6 mol equivalent, are particularly preferred.

During the reaction, the amino group of the amino acids or amino acid derivatives used must be at least partially in the form of a primary amine; this is also applicable in the process according to the invention if this compound are used as an internal salt or as some other salt, *e.g.* the hydrochloride.

The amino acid derivative is preferably an ester of the amino acid or an amide of the acid group, the amide bond preferably being formed with another amino acid or derivative so that the amino acid derivative is a di- or oligo-peptide. It is preferable on the whole to use α-amino acids or derivatives thereof.

Particularly preferred α-keto acids or derivatives thereof are compounds of formula V, pyruvic acid being the simplest representative.

The reaction generally requires removal of the water formed, the water binding agent used preferably being inert or basic.

Examples of suitable water binding agents are molecular sieves and aluminium oxides. Removal of the water is particularly advantageous in the reaction of the keto group with the amine to give the imine and is especially indicated when using α-keto esters, as otherwise reduction of the keto group also takes place more extensively as a secondary reaction under certain circumstances.

The addition of the organic base frequently makes it possible markedly to reduce the amount of molecular sieve used as the water binding agent, and the addition of a basic aluminium oxide makes the molecular sieve totally unnecessary under certain circumstances because it simultaneously acts as a water binding agent itself. Apart from saving costs, this results in particular in less waste products.

If an inorganic base, *e.g.* a basic aluminium oxide, is used as an additive, the amount added is conveniently 50 g/mol to 500 g/mol, based on the compound of formula (III) or (IV) used, if the water of reaction formed is to be simultaneously bound with this base; otherwise the amounts added are 2 to 400 g/mol.

The solvents used should preferably be anhydrous. Inert solvents suitable for the process according to the invention are alcohols such as methanol, ethanol, propanol or butanol; ethers such as ethylene glycol dimethyl ether, diethylene glycol dimethyl ether or tetrahydrofuran; and carboxylic acid dialkylamides such as dimethylformamide or dimethylacetamide. It is also possible to use mixtures of such solvents. It is advantageous to use at least one protic solvent.

Raney nickel, palladium or palladium-on-activated charcoal and platinum or platinum-on-activated charcoal are preferably used as hydrogenation catalysts and H_2 is preferably used as hydrogenating agent. If stereoselectivity is not desired, it is also possible to use hydrides as hydrogenation catalysts

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and hydrogenating agents. Raney nickel is particularly preferred because it gives the best diastereoselectivity.

Of the diastereoisomers formed in the reaction, the product with the S configuration is generally preferred. The diastereoselectivity of the reaction which is required for preparation of the preferred enantiomer can be further increased in many cases by using a chiral organic base. Examples of such bases are L- or D-prolinol, L- or D-valinol, (-)- or (+)-ephedrine and (-)- or (+)-norephedrine, which often promote the formation of one enantiomer, depending on the compounds involved.

The compounds of formula (III) which are preferably used in the preparation of compounds of formula (I) are the naturally occurring α-amino acids or their optical antipodes, if appropriate in protected form. Examples are alanine, valine, methionine, cysteine, serine, tryptophan, asparagine, glutamine, aspartic acid, glutamic acid, phenylalanine, tyrosine, leucine, isoleucine or glycine, and their esters, for example the benzyl, tert-butyl or ethyl esters (ester protecting groups). If lysine or ornithine is used as the compound of formula (III), the amino group on the side chain must be protected, for example by a trifluoroacetyl, carbobenzoxy or tert-butoxycarbonyl group.

In the reaction of compounds of formula (III) with a compound of formula (V), it can be advantageous if they are first brought together and heated with the aid of a suitable water-entraining solvent, for example cyclohexane, methyl tert-butyl ether or toluene, with separation of the water, and are thus azeotropically dehydrated. If appropriate, the compounds of formula (III) as well as those of formula (II) can also be used here in the form of salts, for example as paratoluene-sulphonates or hydrochlorides, if R^4 is not H. For conversion of the salts to their free amines, the base should already be present in a molar proportion of up to 100 mol% in

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the azeotropic dehydration. Weak bases such as N-methylmorpholine are preferred here. In this procedure, care must be taken to avoid the formation of lactones or dimerization products of the compound (V); high temperature (especially above 100°C) should accordingly be avoided. The solvent is then changed, if appropriate, and the hydrogenolysis reaction is carried out, *i.e.* the base and the hydrogenation catalyst are added.

The compounds of formula (IV) which are preferably used in the preparation of compounds of formula (II) are dipeptides consisting of a naturally occurring α-amino acid or antipodes thereof, if appropriate protected in one of the possible side-chain functional groupings, in the N-terminal position, and of a cyclic α-amino acid in the C-terminal position. Examples are alanyl-proline, N^{ϵ}-trifluoroacetyl-lysyl-proline, N^{ϵ}-carbobenzoxy-lysyl-proline, N^{ϵ}-tert-butoxycarbonyl-lysyl-proline, N^{δ}-trifluoroacetyl-ornithyl-proline, N^{δ}-carbobenzoxy-ornithyl-proline or N^{δ}-tert-butoxycarbonyl-ornithyl-proline.

Ethyl 2-oxo-4-phenylbutyrate is preferably used as the compound of formula (V). The compounds of formula (V) are conveniently used in a 0.05- to 1-fold molar excess relative to the particular compound of formula (III) or (IV).

When the process according to the invention is carried out in practice, a compound of formula (V) and a compound of formula (III) or (IV) are dissolved or suspended in the inert solvent. After the addition, if necessary, of a molecular sieve or aluminium oxide as a water binding agent, the organic or inorganic base is added (if still required). The reaction mixture is then conveniently stirred for some time so that any water still contained therein binds onto the molecular sieve or the basic aluminium oxide. Here the Schiff base is formed too, the water produced also being bound. After this preactivation, the previously dehydrated hydrogenation catalyst is added and the hydrogenolysis reaction is carried

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out under a hydrogen atmosphere, a hydrogen overpressure of between 1 and 8 bar being particularly favourable.

The process according to the invention is particularly advantageous in the case of reductive aminations which, under acid catalysis (with excess acid) or at the isoelectric point (pK) of the educts, proceed only with small yields, if at all.

The process according to the invention will be illustrated in greater detail by the following Examples:

Example 1:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline

50 mmol (9.3 g) of Ala-Pro were suspended in 100 ml of ethanol; 10 mmol (1 g) of triethylamine, 75 mmol (15.5 g) of ethyl 2-oxo-4-phenylbutyrate and 18 g of 3 Å molecular sieve were added and the mixture was stirred for 2 hours with the exclusion of water. A teaspoon of dehydrated Raney nickel and 15 g of 3 Å molecular sieve were then added and the mixture was stirred briefly and then hydrogenated for 22 hours under an H_2 atmosphere of 4 bar. The reaction mixture was filtered and concentrated.
Conversion (according to HPLC) based on Ala-Pro used: 95.6%.
Product yield (according to HPLC): 95%.
The residue was taken up in 250 ml of ethanol and adjusted to pH 4.25 with concentrated HCl (this was done by removing an aliquot, diluting it with water and adjusting the pH and then calculating on the basis of the total amount). The solution was concentrated to 50 g under reduced pressure at 40°C, filtered through Célite and diluted with ethyl acetate to a total volume of 100 ml. 5.2 g of maleic acid dissolved in ethyl acetate + ethanol were added and the mixture was seeded with enalapril maleate. The crystals formed were separated off and dried.
Yield: 20.9 g = 85% of theory.

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>99% of SSS diastereoisomer, melting point: 145-146°C.
$[\alpha]_D^{25}$: 42° (c = 1 in MeOH).

Comparative experiment:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline

50 mmol (9.3 g) of Ala-Pro were suspended in 100 ml of ethanol; 75 mmol (15.5 g) of ethyl 2-oxo-4-phenylbutyrate and 18 g of 3 Å molecular sieve were added and the mixture was stirred for 2 hours with the exclusion of water. A teaspoon of dehydrated Raney nickel and 15 g of 3 Å molecular sieve were then added and the mixture was stirred briefly and then hydrogenated for 22 hours under an H_2 atmosphere of 4 bar. The reaction mixture was filtered and concentrated.
Conversion (according to HPLC) based on Ala-Pro used: 76.7%.
Product yield (according to HPLC): 35%.
The residue was taken up in 250 ml of ethanol and adjusted to pH 4.25 with concentrated HCl (this was done by removing an aliquot, diluting it with water and adjusting the pH and then calculating on the basis of the total amount). The solution was concentrated to 50 g under reduced pressure at 40°C, filtered through Célite and diluted with ethyl acetate to a total volume of 100 ml. 5.2 g of maleic acid dissolved in ethyl acetate + ethanol were added and the mixture was seeded with enalapril maleate. The crystals formed were separated off and dried.
Yield: 7.4 g = 30% of theory.
>99% of SSS diastereoisomer, melting point: 145-146°C.
$[\alpha]_D^{25}$: 42° (c = 1 in MeOH).

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Example 2:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline

The procedure of Example 1 was followed except that 0.8 mol equivalent of ethanolamine was used as the base in place of triethylamine.
Conversion (according to HPLC) based on Ala-Pro: 85%.
Product yield (according to HPLC): 85%.
Ratio of diastereoisomers before crystallization: SSS:RSS isomer = 88:12.

Example 3:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ϵ}-trifluoroacetyl-L-lysyl-L-proline

150 mmol of H-N^{ϵ}-TFA-Lys-Pro-OH (50.9 g) were taken up in 120 ml of n-butanol, and *ca.* 50 ml of n-butanol were distilled off under vacuum. The solution was diluted with 600 ml of ethanol. 22.5 g of 3 Å molecular sieve, 34 g of ethyl 2-oxo-4-phenylbutyrate and 30 mmol of triethylamine (4.2 ml) were added and the mixture was stirred for 2 hours with the exclusion of water. Three teaspoons of dehydrated Raney nickel were then added and the mixture was stirred for 4 hours under an H_2 atmosphere of 4 bar. After this time, the pressure was released, a further 12.4 g of ethyl 2-oxo-4-phenylbutyrate were added and the mixture was subsequently stirred for 2 hours. A pressure of 4 bar of H_2 was then applied again and hydrogenation was carried out for a further 4 hours at this pressure. The catalyst was separated off (it can be re-used directly) and the solution was evaporated.
Conversion (according to HPLC) based on N^{ϵ}-TFA-Lys-Pro: *ca.*. 95%.
Product yield (according to HPLC): 90%.
Ratio of diastereoisomers: SSS:RSS isomer = 95:5.

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The residue was suspended in 450 ml of water and 450 ml of 1,1,1-trichloroethane at 5°C, the pH in the water phase was adjusted to 9.6 with 50% NaOH and the phases were mixed thoroughly. The organic phase was separated off and the aqueous product phase was re-extracted with 100 ml of 1,1,1-trichloroethane. The pH in the aqueous phase was then adjusted to 4.6 at 5°C and this phase was extracted 2x with 400 ml of 1,1,1-trichloroethane. The organic phase was evaporated and taken up in 250 ml of methyl tert-butyl ether. The solution was cooled to 0°C and seeded.
Yield: 48 g (60% of theory).
Content of SSS diastereoisomer: >99%.
$[\alpha]_D^{20}$: -25.5° [c = 1 in MeOH/.1 N HCl (1:1)].

Example 4:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ϵ}-trifluoroacetyl-L-lysyl-L-proline

The procedure of Example 4 was followed except that 0.2 mol equivalent of tributylamine was used as the base in place of triethylamine.
Conversion (according to HPLC) based on N^{ϵ}-TFA-Lys-Pro: 85%.
Product yield (according to HPLC): 75%.
Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 96.4:3.6.

Example 5:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ϵ}-trifluoroacetyl- L-lysyl-L-proline

The procedure of Example 4 was followed except that 0.8 mol equivalent of ethanolamine was used as the base in place of triethylamine.
Conversion (according to HPLC) based on N^{ϵ}-TFA-Lys-Pro: 75%.
Product yield (according to HPLC): 65%.

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Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 93:7.

Example 6:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ϵ}-trifluoroacetyl-L-lysyl-L-proline

The procedure of Example 4 was followed except that 0.2 mol equivalent of L-prolinol was used as the base in place of triethylamine.
Conversion (HPLC) based on N^{ϵ}-TFA-Lys-Pro: 85%.
Product yield (HPLC): 65%.
Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 95:5.

Example 7:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ϵ}-trifluoroacetyl-L-lysyl-L-proline

The procedure of Example 4 was followed except that 0.2 mol equivalent of (1R,2S)-(-)-ephedrine was used as the base in place of triethylamine.
Conversion (according to HPLC) based on N^{ϵ}-TFA-Lys-Pro: 84%.
Product yield (according to HPLC): 70%.
Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 96.7:3.3.

Example 8:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ϵ}-trifluoroacetyl-L-lysyl-L-proline

The procedure of Example 4 was followed except that 0.1 mol equivalent of triethylamine was used as the base.
Conversion (according to HPLC) based on N^{ϵ}-TFA-Lys-Pro: 75%.

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Product yield (HPLC): 60%.
Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 97.7:2.3.

Example 9:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ε}-trifluoroacetyl-L-lysyl-L-proline

The procedure of Example 4 was followed except that 25 g of basic activated aluminium oxide were used in place of the molecular sieve and the base.
Conversion (according to HPLC) based on N^{ε}-TFA-Lys-Pro: 95%.
Product yield (HPLC): 80%.
Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 95.5:4.5.

Example 10:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-N^{ε}-trifluoroacetyl-L-lysyl-L-proline

The procedure of Example 4 was followed except that 1% palladium-on-charcoal was used as the catalyst in place of Raney nickel.
Conversion (according to HPLC) based on N^{ε}-TFA-Lys-Pro: 90%.
Product yield (according to HPLC): 80%.
Ratio of diastereoisomers before crystallization: SSS:RSS diastereoisomer = 62:38.

Example 11:

N^{α}-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine

250 mmol of benzyl L-alaninate p-toluenesulphonate (88 g) and 312.5 mmol of ethyl 2-oxo-4-phenylbutyrate (65 g) were suspended in 500 ml of cyclohexane. After the addition of

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250 mmol of N-methylmorpholine (25.3 g), azeotropic distillation was carried out with separation of the water until the reaction had ended. After cooling, the salts were filtered off and the filtrate was evaporated and taken up in 400 ml of anhydrous methanol. After the addition of 25 mmol of N-methylmorpholine (1 g) and 3 teaspoons of dehydrated Raney nickel, hydrogenation was carried out at a hydrogen overpressure of 4 bar and at room temperature until the uptake of hydrogen had ended. The catalyst was filtered off and washed with warm methanol and the filtrate was evaporated. The residue was partitioned between water and 1,1,1-trichloroethane at 5°C and pH 9.6. The water phase was then extracted with 1,1,1-trichloroethane at pH 3 and 5°C and the organic phase was evaporated. The residue was crystallized in the cold from ethanol or acetone.
Yield: 1st fraction: 35 g; 2nd fraction: 12 g.
Melting point: 143-145°C.

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Claims

1. A reductive amination of an amino acid or an amino acid derivative with an α-keto acid or an α-keto acid derivative in an inert solvent in the presence of a hydrogenation catalyst and a hydrogenating agent, and optionally with the removal of water, characterized in that the reductive amination is carried out in the presence of excess base.

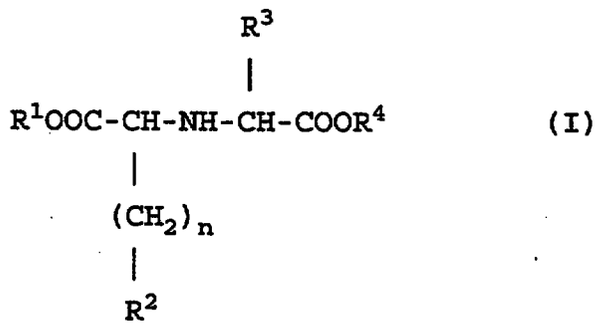
2. A reductive amination according to Claim 1, characterized in that the amino acid is an α-amino acid.

3. A reductive amination according to Claim 1 or 2, characterized in that the amino acid derivative is an ester.

4. A reductive amination according to Claim 1 or 2, characterized in that the amino acid derivative is an amide.

5. A reductive amination according to Claim 4, characterized in that the amide is a peptide.

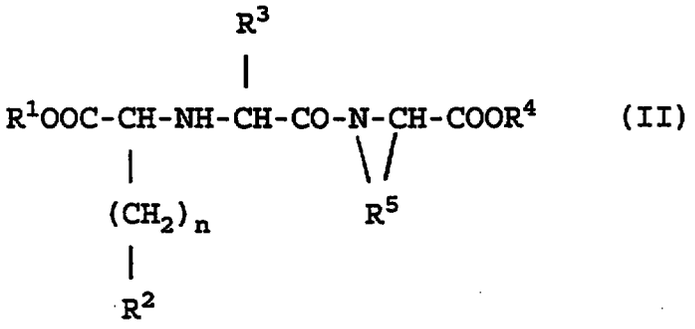
6. A reductive amination according to Claim 3 or 5, characterized in that a compound of the formula



(I)

or of the formula

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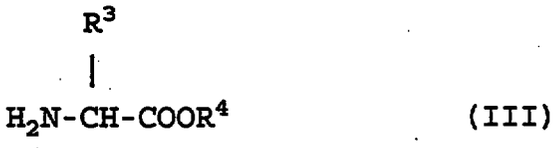


(II)

in which

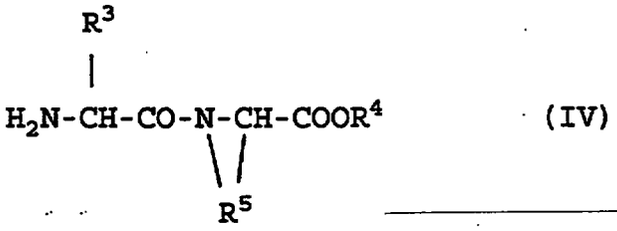
R^1 is hydrogen, methyl, ethyl or benzyl,
R^2 is hydrogen, C_1-C_4-alkyl, phenyl or phenyl-[C_1-C_4-alkyl],
R^3 is hydrogen, heteroalkyl or C_1-C_4-alkyl, benzyl, 4'-hydroxybenzyl, acylamino-[C_1-C_5]-alkyl, tert-butoxycarbonylamino-[C_1-C_5]-alkyl or benzyloxycarbonylamino- [C_1-C_5]-alkyl,
R^4 is H or an ester protecting group,
R^5 together with the atoms by which it is carried is a heterocyclic mono- or bi-cyclic ring system with 5 to 10 ring members, and
n is 0, 1 or 2,

is converted, by hydrogenolytic reaction with a compound of the formula



(III)

in which R^3 and R^4 are as already defined,
to a compound of formula (I) or a compound of the formula



(IV)

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in which R^3 to R^5 are as already defined,
for the preparation of compounds of formula (II), with a compound of the formula

$$R^2\text{-}(CH_2)_n\text{-}CO\text{-}COOR^1 \qquad (V)$$

in which R^1, R^2 and n are as already defined.

7. A process according to one of the preceding claims, characterized in that the organic base used is mono-, di- or tri-ethanolamine, trimethylamine, triethylamine, tripropylamine, tributylamine, N-methylmorpholine, L- or D-prolinol, L- or D-valinol, (-)- or (+)-ephedrine or (-)- or (+)- norephedrine.

8. A process according to one of Claims 1 - 6, characterized in that the inorganic base used is K_2CO_3, Na_2CO_3, $KHCO_3$, NaOAc, $NaHCO_3$ or basic aluminium oxide.

9. A process according to one of the preceding claims, characterized in that the base is used in an amount of 0.01 to 5, preferably 0.05 - 2 and, especially in the case of organic bases, particularly preferably 0.08 - 0.6 mol equivalents, based in each case on the compound of formula (III) or (IV) used.

10. A process according to Claim 8 or 9, characterized in that the basic aluminium oxide is used in an amount of 2 g/mol to 400 g/mol, based on the compound of formula (III) or (IV) used.

11. A process according to one of Claims 1 - 6, characterized in that basic aluminium oxide is used as a water binding agent for the removal of water.

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12. A process according to Claim 11, characterized in that the basic aluminium oxide is used in an amount of 50 g/mol to 500 g/mol, based on the compound of formula (III) or (IV) used.

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